

Pilot Study Investigating the Effect of Tai Chi as Treatment for IBS-C

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Principal/Overall Investigator:
Kyle Staller, MD, MPH

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I. Background and Significance

a.) Historical background

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder (FGID) characterized by abdominal pain and altered bowel habits. IBS is chronic and relapsing, causing significant reductions in health-related quality of life and work productivity.¹ As the most commonly diagnosed gastrointestinal disorder, IBS affects between 4%-22% of the general population worldwide.² In the United States, the distribution is approximately equal among IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), and IBS with a mixed bowel pattern (IBS-M).³ IBS is diagnosed in the absence of other medical causes with a pathogenesis mainly focused on abnormalities in gastrointestinal motility, visceral sensation, brain-gut interaction, and psychosocial distress.¹ Therefore, treatment options for IBS are aimed at various action sites of the brain-gut axis through the use of pharmacotherapy and dietary/lifestyle changes. In the case of IBS-C, strong methodological evidence for various types of conventional pharmacotherapy, such as bulking agents, prokinetics, and antispasmodics, is lacking.⁴ With inadequate relief from IBS symptoms, many patients seek out complementary and alternative medicine (CAM) therapies which are medical practices that are not considered to be a part of conventional medicine.⁵ A subset of CAM therapies focuses on mind-body interventions.⁶ In recognition of the communication between brain and gut, one such mind-body practice that may be beneficial for patients with IBS-C is the ancient practice of Tai Chi.

Tai Chi Chuan (taijiquan) or Tai Chi is a mind-body practice borne of Chinese philosophy and martial arts which has been practiced for centuries to promote deep relaxation, strengthened health, and to prevent injuries and illness. The principle behind the practice is that Tai Chi improves the circulation of blood and *Qi* (energy) throughout the body which enhances the body's natural healing capabilities. Tai Chi achieves this through gentle moving meditation and focusing on five building blocks: body, breath, mind, energy, and spirit. Through this method, Tai Chi practitioners exercise a balance between strength and flexibility, condition muscles, increase bone density, and massage their internal organs.⁷

b.) Previous studies supporting the proposed research

The practice of Tai Chi as a CAM therapy has already proven successful in the therapeutic arenas of other chronic conditions including anxiety, depression, PTSD, multiple sclerosis, fibromyalgia, rheumatoid arthritis, and osteoarthritis.^{8, 9, 10, 11, 12, 13} Tai Chi has even been shown to improve self-esteem, sleep quality, and immune response, and reduce declines related to aging and inactivity.^{14, 15, 16, 8}

In a recent randomized, controlled trial investigating the effect of Tai Chi compared to moderate aerobic exercise on symptoms associated with fibromyalgia, Tai Chi resulted in similar or greater improvement in symptoms than aerobic exercise. Fibromyalgia is a chronic condition characterized by musculoskeletal pain, fatigue, and sleep disturbance for which there is no cure. Although aerobic exercise is the most commonly prescribed non-pharmacological treatment for fibromyalgia patients, this study demonstrated that the mind-body approach of Tai Chi may be just as, if not more, effective in treating a complex pain condition.¹¹ The findings from this study may have applications for the treatment of IBS-C, which is also a chronic condition with a primary symptom of pain.

While there have been some investigations of other mind-body modalities, such as meditation, hypnosis, and yoga, and their effect of IBS symptoms, Tai Chi as a mind-body intervention for the treatment of IBS-C has not yet been explored in scientific literature.¹⁷ Tai Chi differs from other mind-body therapies through the combination of gentle movements, meditation, and focus on flow of energy through the body. Both Tai Chi and Yoga philosophies involve meditation and movement in their practices, but the focus in Yoga is on *asanas*, or standing postures, and breathing with meditation. In comparison to stationary postures in Yoga, the gentle movements in Tai Chi have the effect of massaging internal organs. Another important difference between Yoga and Tai Chi is that Tai Chi emphasizes five building blocks: the body, breath, mind, energy, and spirit; whereas Yoga mainly concentrates on just three elements: the body, breath, and spirit. With its specific focus on the mind and its relation to the body as well as the breath, energy, and spirit, Tai Chi may see different effects as a mind-body intervention for IBS compared to medication alone or Yoga.

c.) Rationale behind the proposed research

Through reinforcement of the mind-body connection, Tai Chi may be helpful in relieving chronic abdominal pain associated with IBS-C. The gentle moving meditation involved in Tai Chi practice may influence proper breathing and abdominal wall control in addition to massaging internal organs through movement.

Previous research has suggested that therapies engaging the mind-body connection may have promising effects on functional bowel disorders in general, and on IBS specifically.^{18, 5} Some mind-body therapies, such as gut-focused hypnotherapy, have already gained approval as an effective treatment in reducing symptoms of IBS.¹⁹ Similarly to already established mind-body therapies, Tai Chi may positively impact symptoms of IBS-C by changing sensory perception or even calming colonic motility. Tai Chi practice could lead to reduced abdominal distention and improved anxiety and depression scores.

II. Specific Aims

This is a single center pilot study. The purpose of the study is to evaluate the efficacy of Tai Chi practice in reducing symptoms of IBS. Patients who meet the Rome IV criteria for IBS-C and who meet the inclusion criteria will be offered participation in the study. We hypothesize that patients practicing Tai Chi will have reduced symptoms of IBS-C as measured through the Global Assessment of Relief, Irritable Bowel Syndrome Severity Scoring System (IBS-SSS), Irritable Bowel Syndrome Quality of Life (IBS-QOL), Visual Analogue Pain Scale, and abdominal distention. We also hypothesize that daily entries made through the GeoPain app will show a trend toward reduced pain intensity.

III. Subject Selection

This study aims to recruit 24 total subjects to be enrolled at one site, Massachusetts General Hospital. The 24 subjects that this study aims to recruit factors in a dropout rate of 15%, with a final sample size of 20 subjects.

INCLUSION/EXCLUSION CRITERIA:

Inclusion

1. Age 18 – 70 years
2. BMI \leq 35
3. Rome IV criteria for IBS-C
4. Continued IBS-C throughout run-in period
5. Compliant with reporting during run-in
6. Ability to follow verbal and written instructions
7. Ability to record daily patient reported outcomes via RedCap survey
8. Ability to use the GeoPain app on a smart phone
9. Ability to use Zoom as a platform for conducting study visits virtually
10. Ability to respond to 80% of the daily diaries
11. Ability to attend at least 7 out of 8 Tai Chi classes
12. Informed consent form signed by the subjects

Exclusion

1. Unwilling to abstain from participation in Tai Chi (other than that provided for the study) or other mind-body practices (i.e. yoga that is new to regimen) until completion of the study
2. Non-English speaking
3. Participation in any other clinical trial with active intervention within the last 30 days
4. Non-compliance with reporting during run-in period (less than 80% completed REDCap and GeoPain entries)
5. Inability to stand without assistance for 20 minutes
6. Patients reporting any usage of a prohibited medication during the run-in period
7. History of regular opiate or narcotic pain-reliever use
8. Current use of prescribed or illicit opioids
9. Change in current medication regimen related to GI motility, laxatives, or antidepressants
10. Abdominal pain severity of 4 on a 0-4 visual analogue scale, where 4 is the worst possible pain, during pre-screen or run-in
11. Severe osteoarthritis
12. Severe rheumatoid arthritis
13. Severe constipation defined as <1 bowel movement per week without use of laxatives
14. History of GI lumen surgery (including gastric bypass) at any time or other GI or abdominal operations within 60 days prior to entry into the study
15. History of small bowel resection (except if related to appendectomy)
16. Subjects anticipating surgical intervention during the study
17. Angina, coronary bypass, or myocardial infarction within 6 months prior to Screening Visit
18. Crohn's disease or ulcerative colitis
19. History of intestinal stricture (e.g., Crohn's disease)
20. BMI >35
21. Pregnancy (or positive urine pregnancy test(s) in females of childbearing potential)
22. Known history of diabetes (type 1 or 2)
23. History of gastroparesis
24. History of abdominal radiation treatment
25. History of pancreatitis
26. History of malabsorption or celiac disease
27. History of intestinal obstruction or subjects at high risk of intestinal obstruction including

- suspected small bowel adhesions
28. History of human immunodeficiency virus
 29. History of cancer within the past 5 years (except adequately-treated localized basal cell skin cancer or *in situ* uterine cervical cancer)
 30. Neurological disorders, metabolic disorders, or other significant disease that would impair their ability to participate in the study
 31. Any other clinically significant disease interfering with the assessments according to the Investigator (e.g., disease requiring corrective treatment, potentially leading to study discontinuation)
 32. Any relevant biochemical abnormality interfering with the assessments according to the Investigator
 33. Inability to attend at least 7 out of the 8 Tai Chi classes
 34. Inability to respond to 80% of the daily diaries

a.) Source of subjects and recruitment process

Subjects will be recruited from the MGH Gastroenterology Unit based on the enrollment criteria. GI physicians at MGH will be informed of the study and can refer patients if they are deemed appropriate for the study. Study staff will review subject's electronic medical records to confirm inclusion and exclusion criteria. Additionally, electronic medical records of potential subjects coming into the GI clinic for an appointment will be screened in order to identify eligible patients with IBS. When an eligible patient is identified, their provider will be contacted in order to confirm the patient's eligibility as well as to gain permission to contact the patient. The treating physician/investigator will first present the study to the subject during a clinic visit. If the subject is interested in the study, the subject will be approached by one of the licensed physician investigators listed on the protocol or the study coordinator to obtain consent. If treating physicians are approaching their own patients, consent will be obtained by a study coordinator to avoid any coercion. All patients will be explicitly told that their decision to enroll in the study will have no bearing on their current or future treatment and this statement will be mandated as part of the protocol.

Subjects may also be identified using the Research Patient Data Registry (RPDR) system. Electronic medical records of potential subjects will be reviewed to confirm inclusion and exclusion criteria. The patient's provider will be contacted to confirm the patient's eligibility as well as to gain permission to contact the patient. The recruitment letter by the PI and the patient's provider will be sent. Patients who agreed to direct contact (RODY YES) will receive a recruitment letter from the PI. If the patient does not contact the study coordinator within 1 week, they will be contacted by phone and/or email by the study coordinator. All subjects will undergo telephone prescreening by the study staff.

In addition to patients of MGH, subjects from the general greater Boston population will also be recruited. Subjects from the general population will be recruited through the Partners Clinical Trials system. Through this service, interested respondents may provide their contact information to be contacted by research study staff. Due to COVID-19 restrictions, social distancing, and the conduct of the study entirely remotely, subjects who reside outside the state of Massachusetts who reach out to the study staff may also be recruited for the study and screened for eligibility.

Subjects from the larger population of Facebook and/or Instagram will be also be recruited. A Facebook page, that is specific to this research study will be published and will provide links to

both the Partners Rally website and a REDCap pre-screening survey, both of which will be used by study staff to contact patients by phone or email (Send Secure) for administration of the phone screening. A Facebook ad will be created and published onto the MGH Tai Chi Study Facebook page for potential participants to view and access Rally or the REDCap survey. Security settings will be put into place to ensure that no posts will be allowed on this page or the ads, it will only be used to provide the links to interested participants who will then agree to be contacted by study staff.

IV. Subject Enrollment

a.) Methods of enrollment

1. Patients may be approached by a licensed physician investigator listed on the protocol or a research coordinator in the GI clinics if they have a history of IBS and agree to hear more about the trial.
2. After receiving approval from a patient's physician, patients may be contacted by the research coordinator prior to their appointment and asked if they would like to hear more about the trial.
3. Any patients agreeing to hear more about the trial will learn more before beginning the informed consent process should they agree to participate as well as determining whether they meet all of the inclusion criteria.
4. Patients may be contacted about the research study by their MGH physician on behalf of the research team. Afterward, patients may then be contacted by the research team directly.
5. Subjects who have provided their contact information through the Partners Clinical Trials system may be contacted by the research team directly.

b.) Procedures for obtaining informed consent

1. Patients agreeing to participate will sign an informed consent with the study physician or research coordinator at the time of enrollment, after proper informed consent has been provided by the site. Due to COVID-19 restrictions and social distancing, REDCap eConsent will take the place of written documentation of informed consent.

c.) Treatment Assignment

1. All patients will participate in 8 weeks of one-hour Tai Chi sessions once per week.

V. Study Procedures

a) Remote conduct of study visits and procedures

Due to COVID-19 and its restrictions, all eligibility screening and study visits listed below will be performed remotely until restrictions are lifted at the study site. All remote visits will be conducted over Zoom and the visit schedule will not change. All research staff will follow the MGH requirements for using Zoom (Enterprise Zoom as well as Healthcare Zoom- for any study visits involving patient care.) All questionnaires will be administered remotely via REDCap or over the phone. All Zoom link invites will be password protected and emailed by research staff to study participants using Send Secure or unencrypted email, depending on the subject's preference.

b.) Study visits and parameters to be measured

1. Eligibility Screen (to be conducted via Healthcare Zoom)

- a. Obtain informed consent (performed by research staff)
- b. Collect demographic data (performed by research staff)
- c. Assessment of sufficient space to perform Tai Chi in-home (performed by research staff)
- d. Assess inclusion/exclusion criteria (performed by research staff)
- e. Rome IV questionnaire to screen for IBS-C (performed by research staff)
- f. Collect medical and surgical history (performed by research staff)
- g. Collect concomitant medications (performed by research staff)
- h. Self report of height, weight, and waist measurement (if restrictions are lifted and study visits are being performed on site, vital signs will be recorded) (performed by research staff)
- i. Perform brief physical examination by study physician
- j. Visual Analogue Pain Scale (performed by research staff)
- k. Questionnaires including Global Assessment of Relief, Hospital Anxiety and Depression Scale (HADS), Gastrointestinal Symptom Rating Scale-IBS version (GSRS-IBS), Irritable Bowel Syndrome-Behavioral Responses Questionnaire (IBS-BRQ), Fear of Food Questionnaire (FFQ), Visceral Sensitivity Index (VSI), IBS-SSS, and IBS-QOL(performed by research staff)
- l. Record whether study participant verbally states they are pregnant or not for women of child-bearing potential (If restrictions are lifted and study visits are being performed on site, perform urine pregnancy test on women of child-bearing potential) (performed by research staff)
- m. Self-reported leg strength assessment

2. Run-In Period

After a screening visit in which patient eligibility will be determined through use of the Rome IV IBS-C criteria along with other inclusion and exclusion criteria as above, there will be a 2-week run-in period. The 2-week run-in period may occur up to 3 months before the trial start date to facilitate accumulation of enough patients for a 10-person class.

Prohibited Medications

During this time no use of contraindicated medication per exclusion criteria will be allowed.

- a. Opiate and narcotic pain-relievers

Permitted Medications at Stable Doses

The following medications are permitted as long as the medication dose has been stable for 3 months prior to the run-in period:

- a. Laxatives (e.g. linaclotide, lubiprostone, bisacodyl, senna, MiraLAX)
- b. Prokinetic medications (e.g. domperidone, metoclopramide, erythromycin, prucalopride)
- c. Antidepressant medications (e.g. SSRIs, SNRIs, TCAs, trazodone, bupropion)
- d. Neuromodulators (e.g. gabapentin, pregabalin, buspirone)

- e. Aluminum/Magnesium
- f. Calcium-channel blockers (e.g. amlodipine, diltiazem, nifedipine, nicardipine)

During the run-in period, subjects will be asked to complete a daily REDCap diary entry, a daily GeoPain entry, as well as complete the Visual Analogue Pain Scale, and turn in a stool sample within 2 weeks before the start of the treatment period. A stool kit may be mailed to subjects' homes, which subjects will then mail completed back to the research site.

Rescue Medications

If a subject does not have any documented bowel movement for 5 consecutive days and is in need of a rescue treatment, they will be asked to please contact the study doctor or study coordinator immediately. The study doctor will recommend the following rescue treatments, as applicable, in the following order:

- a. Laxatives: either MiraLAX or Dulcolax
- b. Glycerin suppository
- c. Enema

Administration of the rescue treatment will be at the discretion of the investigator based on their assessment of the subject's symptoms; administration of rescue treatment will be monitored and recorded.

3. Treatment Period (Day 0 to 49)

One day prior to the treatment period, subjects will again complete the Rome IV questionnaire confirming that inclusion and exclusion criteria continue to be satisfied.

Subjects will be asked to refrain from making any major lifestyle changes (e.g. starting a new diet or changing their exercise pattern outside of Tai Chi practice) during the study.

During the treatment period, subjects will meet via Zoom once per week for one-hour Tai Chi lessons with an experienced instructor. A member of the research staff will send the password-protected Zoom invitation link to the subject's preferred email address via Send Secure or regular email, depending on the subject's preference. Subjects will also be instructed to practice Tai Chi at home outside of the lessons using the instructions, handouts, and guidance from the instructor.

Subjects will be instructed to complete a daily REDCap diary entry and a daily GeoPain entry to record information about stool frequency and consistency, abdominal bloating, abdominal discomfort, and abdominal pain. Subjects will also use the REDCap diary to report rescue medication use and daily Tai Chi practice.

The lessons will occur on Days 0, 7, 14, 21, 28, 35, 42, and 49. The Tai Chi lessons will take place remotely via Zoom. Should restrictions be lifted and study visits be performed on site, lessons will take place in the Simches Research Center at 185 Cambridge Street.

On Days 0, 21, and 49 subjects will be phoned by a member of the research staff for

assessments prior to their regularly scheduled Tai Chi lesson. Assessments will include vitals (if the study is operating on site only), weight, height, waist circumference, leg strength, and questionnaires. Assessments will be completed with research staff over the phone or, if restrictions are lifted and study visits are conducted on site, at the Center for Neurointestinal Healthcare at 165 Cambridge Street, after which subjects will go to their regularly scheduled Tai Chi lesson at Simches. Participants will also complete a qualitative survey over the phone with a member of the study staff that will be audio recorded and later transcribed in order to gain a full, complete, qualitative understanding of the patient’s perspective of the investigational treatment that was used.

4. Post-Treatment Period (Day 77)

Subjects will complete a REDCap diary entry regarding symptoms 28 days post-treatment, 4 weeks after the final study visit.

5. Schedule of Events

Study Procedures	Screening	Run-In (Up to 3 months prior to Treatment)	Treatment								Post-Treatment
	Visit 1 (Up to 3 months prior to treatment)		Visit 2 (Day 0)	Visit 3 (Day 7)	Visit 4 (Day 14)	Visit 5 (Day 21)	Visit 6 (Day 28)	Visit 7 (Day 35)	Visit 8 (Day 42)	Visit 9 (Day 49)	4 Weeks Post-Treatment (Day 77)
Informed Consent	X										
Inclusion/exclusion criteria	X										
Demographics, medical history, and medication history	X										
Concurrent medical conditions and concomitant medications	X		X			X				X	X
Physical examination	X										
Vital signs	X		X			X				X	X
Weight, height, waist circumference (a)	X		X			X				X	X
Pregnancy test	X										
Tai Chi Lessons			X	X	X	X	X	X	X	X	
Stool Sample	X									X	X
Daily Diary		X	X	X	X	X	X	X	X	X	X
GeoPain Reporting		X	X	X	X	X	X	X	X	X	X
Global Assessment of Relief	X		X	X	X	X	X	X	X	X	X
HADS	X		X			X				X	X
VSI	X		X			X				X	X
Visual Analogue Pain Scale	X		X	X	X	X	X	X	X	X	X

Rome IV Questionnaire	X									
IBS-SSS	X		X			X			X	X
IBS-QOL	X		X			X			X	X
GSRS-IBS	X		X						X	X
IBS-BRQ	X		X						X	X
Fear of Food Questionnaire	X		X						X	X
Leg strength Assessment	X		X			X			X	X
Treatment Satisfaction									X	X
Pre-treatment AE Assessment	X	X								
AE Assessment	X		X			X			X	X
Qualitative Post-Tx Survey									X	
CSQ									X	
Instructor Assessment									X	X

(a) Weight, height, and waist circumference are measured and BMI is calculated at initial screening visit only. Weight and waist circumference only is measured at subsequent visits.

6. Investigational Treatment to be Used

Subjects will practice Tai Chi via Zoom (if on site, at the Simches Research Center.) We will use a standardized Tai Chi protocol derived from previously tested trials^{10,11,12,13}. The Tai Chi program will be based upon the classical Yang Tai Chi philosophy which includes 108 postures show to be a moderate intensity exercise.

In the first session, the Tai Chi instructor will explain the program, exercise theory, and procedures of Tai Chi. The patients will be provided with printed materials on the Tai Chi Mind-Body program including Tai Chi principles, practicing techniques, and safety precautions. Subjects will then begin Tai Chi practice under the instruction of the Tai Chi instructor. The Tai Chi instructor will have extensive experience (>20 years) conducting Tai Chi mind-body programs and will be following a Tai Chi protocol specifically designed for individuals with IBS-C.

Every session will include the following components: (1) Tai Chi warm ups with a strong emphasis on balance between strength and flexibility while reviewing Tai Chi principles; (2) Tai Chi breathing with self-massage (3) Tai Chi relaxation with meditation and visualizations (4) Tai Chi form which includes 10 moves from the Yang style Tai Chi (5) Tai Chi drills which are the Tai Chi individual postures practice (6) Tai Chi combination of movements and principles which are part of the Tai Chi philosophy. We will instruct patients to practice at least 30 minutes a day at home throughout the intervention period.

7. Data to be Collected and Timeline for Collection

a. Primary endpoints

1. IBS-SSS (pre-treatment, halfway point, and at conclusion of study)

- b. Secondary endpoints
 1. Likelihood of continuing treatment (5-point scale, end of study)
 2. Treatment satisfaction (5-point scale, end of study)
 3. Global Assessment of Relief and Visual Analogue Pain Scale (pre-treatment and each study visit)
 4. Change of IBS-QOL, VSI, and HADS (pre-treatment, halfway point, and at conclusion of study)
 5. For each BM: Bristol stool scale, stool frequency (CSBMs and SBMs; for each BM, during run-in and during study)
 6. Waist circumference measurements (pre-treatment, halfway point, and at conclusion of study)
 7. Daily: Bloating Scale, Abdominal Discomfort Scale, Constipation Severity Scale
 8. Gastrointestinal Symptom Rating Scale-IBS version (GSRS-IBS), Irritable Bowel Syndrome-Behavioral Responses Questionnaire (IBS-BRQ), Fear of Food Questionnaire (FFQ) (pre treatment, study visit 2, and at conclusion of study)
 9. Leg strength assessment patient (pre-treatment, halfway point, and at conclusion of study)
 10. Instructor assessment as to confidence that patient has mastered technique (x1 at end of study, 5-point scale)
 11. Client satisfaction questionnaire and qualitative survey (at conclusion of study)
 12. Stool for metabolomics; and microbiome (pre-treatment and at conclusion of study)

8. Compliance

- a. Study coordinator will remind subjects of Tai Chi sessions and monitor completion of daily diaries, reports of home practice, and rescue medication use. Subject attendance will be monitored during each Zoom/in-person session by staff-completed attendance forms as well as class sign-in sheets. Number of missed sessions for each subject will be tracked.
- b. During Run-in Period, subjects must complete 80% of REDCap and GeoPain entries to be considered compliant with reporting and to remain eligible to participate in the study.

b.) Adverse Events

1. Definition of adverse events
 - a. An adverse event (AE) is any untoward medical occurrence (sign, symptom, illness, abnormal laboratory value, or other medical event) in a subject, whether or not related to the investigational medical device. This includes events related to the procedures involved (any procedure in the Clinical Investigation Plan).
2. A serious adverse event (SAE) is any AE that:
 - a. Led to death
 - b. Resulted in a life-threatening condition
 - c. Resulted in a permanent impairment of a body structure or a body function
 - d. Required inpatient hospitalization or prolongation of existing hospitalization for \geq

- 24 h (elective hospitalizations and/or hospitalizations for treatment of pre-existing conditions that did not worsen from baseline are not considered AEs and should not be reported as SAEs)
- e. Resulted in a medical or surgical intervention to prevent permanent impairment to a body structure or a body function
 - f. Led to fetal distress, fetal death or a congenital abnormality, or birth defect
3. Adverse event recording, assessment, and reporting procedure
- a. All AEs regardless of seriousness or relationship to treatment including those occurring during the screening period (after the signature of the Informed Consent Form) are to be recorded in the appropriate electronic CRF.
 - b. AEs reported by subject will be discussed in detail and recorded by the Investigator at each visit. AEs will be collected until 28 days after the last administration of the investigational treatment (i.e., until subject terminates his/her participation in the study).
 - c. The Investigator should specify the date of onset, severity, action taken with respect to the investigational treatment, corrective treatment, outcome, and whether or not there is a reasonable possibility that the AE may have been caused by the investigational treatment.
 - d. Should an AE be reported by a study participant that resides/is located outside the state of Massachusetts and that is determined to have been caused by the investigational treatment, the Investigator will contact the participant's local providers to assess the need for follow-up.
 - e. AEs are graded as follows:
 - 1. Mild: sign or symptom, usually transient, requiring no special treatment and generally not interfering with usual activities.
 - 2. Moderate: sign or symptom, which may be ameliorated by simple therapeutic measures, may interfere with usual activity.
 - 3. Severe: sign or symptom intense or debilitating and interfering with usual activities without being immediately life-threatening. Recovery is usually aided by therapeutic measures.
 - 4. Very Severe: sign or symptom life-threatening. Urgent intervention indicated.
 - f. The assessment of the relationship of an AE to the investigational treatment is a clinical decision based on all available information at the time of the completion of the electronic CRF:
 - 1. Most probably related: follows a reasonable temporal sequence from treatment use and cannot be reasonably explained by known characteristics of the subject's clinical data.
 - 2. Possibly related: follows a reasonable temporal sequence from treatment use but could have been produced by the subject's clinical state regardless of the medical device.
 - 3. Probably not related: temporal association is such that the treatment use is not likely to have had any reasonable association with the observed event.
 - 4. Not related: no relationship to the use of the treatment is perceived.
 - g. Abnormalities of vital signs and laboratory results are to be recorded as AEs only if they are considered by the Investigator as clinically significant (symptomatic, requiring corrective treatment, leading to discontinuation, or fulfilling a seriousness

- criteria).
- h. Any pre-existing conditions or signs and/or symptoms present in a subject prior to the Screening Visit should be recorded as medical/surgical history.
 - i. In this study, the following events will be reported to the authorities on expedited basis:
 - 1. All SAEs will be expeditiously reported to the relevant Regulatory Authorities and the Ethics Committees.
- 4. Anticipated adverse treatment effects
 - a. No adverse treatment effects are anticipated.
 - 5. Pregnancy
 - a. In case of pregnancy, the investigational treatment will be discontinued.

VI. Sample Processing

a.) Stool

Upon receiving the samples, stool will be centrifuged and separated from the fixative. Samples will then be aliquoted and stored at -80°C before microbiome analysis. The sample in the ethanol solution will be stored in -80°C without removing the solution.

- 1. Metabolomics
Stool will be stored to check for metabolomics that may profile changes between the pre-treatment and treatment sample.
- 2. Microbiome Analysis
Standard 16s rRNA sequencing for taxonomic identification and metagenomic profiling of the gut microbiome will be performed on stool samples to profile microbiome diversity and changes in microbiome between the pre-treatment and treatment sample.

VII. Biostatistical Analysis

a.) Endpoint analyses

- 1. Primary endpoint: IBS-SSS will be compared in a paired fashion for individual patients before and after the intervention using repeated measures t-test.
- 2. Secondary endpoints: The secondary endpoints (as outlined in section V.a.6.b.) will be compared in a similar fashion.

b.) Power analysis

This is a single-center clinical exploratory pilot investigating the treatment of IBS-C using Tai Chi. As a pilot study, we hope to enroll 24 subjects with a final sample size of 20 subjects. The study will be conducted in two cycles of at least 10 subjects each to facilitate a full classroom size. Based on a previous pilot study involving Tai Chi as treatment for rheumatoid arthritis¹², 20 subjects appears to be a feasible number for detecting a trend toward outcomes that can be investigated in a future larger clinical trial.

VIII. Risks and Discomforts

a.) Tai Chi

Tai Chi is a relatively safe practice that is unlikely to cause injury if done with proper instruction. Caution should be exercised with conditions such as pregnancy, hernia, joint problems, and severe osteoporosis.

b.) Other Possible Risks

Other possible risks and side effects include skin irritation from inadvertently coming in contact with preservatives in the specimen collection materials, breach of confidentiality involving protected health information, and that information about taking part in a metabolic/microbiome study could influence insurance companies or employers regarding the patient's health. Study IDs will be utilized to minimize breaches of confidentiality. Filling out questionnaires could cause patients to feel uncomfortable.

IX. Potential Benefits

a.) It is hypothesized that Tai Chi may be of benefit in patients with IBS-C. Potential benefits may include a decrease in self-reported abdominal pain/discomfort, straining, bloating, and constipation severity, as well as improved quality of life and symptoms severity.

b.) All subjects will be provided with free parking stickers for each visit and \$50 upon completion of Days 0, 21, and 49 (Visit 2, 5, and 9).

X. Monitoring and Quality Assurance

a.) Good clinical practice

The investigator will ensure that this study is conducted in accordance with the principles of "Good Clinical Practice", as outlined in Title 21 of Code of Federal Regulations (CFR), Part 312, subpart D, "Responsibilities of Sponsors and Investigators"; 21 CFR, part 50, "Protection of Human Subjects"; 21 CFR, part 54, "Financial Disclosure by Clinical Investigators"; 21 CFR, part 56, "Institutional Review Boards"; and 21 CFR, Part 11, "Electronic Records, Electronic Signature", are adhered to.

b.) Institutional review board (IRB) approval

The protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to the MGH IRB. Approval from the IRB must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted approval. Any modifications made to the protocol after receipt of IRB approval must also be submitted to the IRB for approval before implementation.

c.) Informed consent

Due to COVID-19 restrictions and social distancing, consent will be obtained remotely using REDCap eConsent/Paperless consent in place of written informed consent, in accordance with 21 CFR Part 11. The eConsent is equivalent to written consent. The Partners approved

REDCap eConsent template will be used to deliver the approved consent form and obtain an electronic signature from study participants and the principal investigator. All electronic consent documents will be stored in the subject's research record in a password protected, Partners encrypted/secured device.

Written informed consent, in accordance with 21 CFR Part 50, must be obtained prior to participation in the study when social distancing restrictions are lifted and the study is operating on site. Within the context of the inclusion criteria, a proportion of eligible patients may be exhibiting significant cognitive impairment and the lack of capacity to provide consent. As such, all patients will require surrogate consent by a legally authorized representative. The investigator or staff will determine the appropriate family member-person to contact regarding the study, based on the standard operating procedures of MGH and local and state laws. The signed consent form must remain in the patient's medical chart and must be available for verification at any time.

d.) Liability and insurance

The civil liability of the investigator, the persons instructed by the investigator and the hospital, practice, or institute in which they are employed, and the liability of the financial loss due to personal injury and other damage which may arise as a result of the carrying out of this study are governed by the terms and conditions set forth in the Clinical Trial Agreement and applicable law.

e.) Documentation of study findings

Required information will be entered into the appropriate CRFs. All CRFs are to be completed accurately and promptly and should be updated as needed so they reflect the latest information on the patient's file. All records are to be kept in conformance with applicable guidelines and SOPs. When the study is completed, the investigator must retain the essential documents for as long as needed to comply with regulatory authority, local regulations and sponsor requirements further detailed in Section 10.2.5. The investigator shall notify the sponsor prior to moving or destroying any of the study documents.

f.) Study monitoring

1. For Investigator-Initiated Research Studies, Investigators are responsible for ensuring proper monitoring of the investigation. The Investigator's assigned clinical monitors are responsible for inspecting the CRFs throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of data; and adherence to GCPs. The monitors should have access to patient medical records and other study-related records needed to verify entries on the CRFs. In accordance to ICH Good Clinical Practice (ICH/GCP) guidelines, the Investigator's assigned clinical monitors must have direct access to the investigator's source documentation in order to verify the data recorded in the CRFs for consistency.
2. The monitor is responsible for routine review of the eCRFs at regular interval throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

g.) Access to Information for Auditing or Inspections

Representatives of regulatory authorities, IRB, or of the Sponsor may conduct inspections or audits of this clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Sponsor immediately. The investigator agrees to provide to representatives of a regulatory agency, IRB or IEC, or Sponsor access to source documents/records, facilities, and personnel for the effective conduct of any inspection or audit.

h.) Data quality assurance

Data will be entered into a secure and validated database using eCRFs. Data entered may be checked at the point of entry and through external validation checks for accuracy. After resolution of any discrepancies and automated data-review procedures, the final data sets will be subject to a quality assurance audit. When the database is declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made by written notice. The investigator will be responsible for ensuring the accuracy, completeness, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRFs, which are derived from source documents, should be consistent with source documents or the discrepancies should be explained. To ensure the quality of the clinical data across all participants and sites, a clinical data management review will be performed on all patient data. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to protocol and GCPs. To resolve any questions arising from the clinical data-review process, data queries will be sent for the site to complete. The principal investigator will electronically sign and date the indicated places on the CRF. This signature will indicate that the principal investigator inspected or reviewed the data on the CRF and the data queries, and that the investigator agreed with the content.

i.) Study Files and Retention of Records

1. The investigator must maintain adequate and accurate records to fully document the conduct of the study and to ensure that study data is subsequently verified. These documents should be classified into two separate categories: (1) investigator's study file, and (2) patient clinical source documents. The investigator's study file will contain the protocol/amendments, printed (or electronically archived) copies of the patient CRFs, IRB, and governmental approval with correspondence, informed consent, drug accountability (receipt/dispensing) records, staff curriculum vitae and authorization forms, information regarding monitoring activities, investigator correspondence, and other appropriate documents and correspondence.
2. Patient clinical source documents for this study would include, but are not limited to, the following:
 - a. Patient identification (name, date of birth, gender)
 - b. Documentation that patient meets eligibility criteria, i.e., relevant medical history, physical examination, and confirmation of diagnosis
 - c. Dated notes of the day of entry into the study including study number, patient identification number, verification that the trial was discussed and written informed consent was obtained
 - d. Dated notes for each protocol assessment and documentation that protocol specific procedures were performed
 - e. Documentation of all adverse events, including any action taken with regard to study intervention and outcome

- f. Concomitant medications (including start and end date, dose if relevant)
- g. Date of trial completion and reason for early discontinuation, if applicable

j). Confidentiality

The investigator must ensure that all participants' confidentiality will be strictly maintained and that their identities are protected from unauthorized parties. Only patient initials, date of birth, and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names and addresses for all patients screened and for all patients enrolled in the trial. On CRFs or other documents that are submitted to the sponsor, participants should be identified by an identification code and not by their names.

k.) Protocol and Protocol Amendments

1. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. No amendments will be permitted to this protocol or to the conduct of the study without approval from the IRB. These communications will be documented in writing.
2. All protocol amendments must be submitted to the IRB in accordance with local requirements. Approval must be obtained before changes are implemented.

XI. References

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