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Study Protocol

Naturopathic approaches to irritable bowel syndrome: protocol for a prospective observational study in academic teaching clinics

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ABSTRACT

Background: Irritable bowel syndrome (IBS) is a common functional bowel disorder with a worldwide prevalence estimated between 10% and 20%. It has a significant impact on quality of life and societal expense. While there are pharmaceutical options available, few can be reliably recommended. Many IBS sufferers turn to complementary and alternative medicine including naturopathy. Naturopathic approaches to IBS are poorly studied to date.
Methods: We aim to describe naturopathic approaches to IBS as well as establish pilot data on before and after changes in validated IBS instruments. The study will employ a multi-centered, international, prospective, observational, naturalistic design. The uncontrolled before-and-after study will examine the outcomes associated with individualized, whole system naturopathic care as determined by each provider. We will recruit adult patients diagnosed with IBS and presenting to a participating naturopathic academic teaching clinic. Participants' IBS symptoms will be measured using validated instruments (IBS-SSS and IBS-AR). Quality of life will be measured by using the PROMIS-29 profile. Adverse events will be tracked, as followed for treatment descriptions. Our primary outcomes will be before-and-after differences using week twelve as the primary endpoint. A p values will be set at 0.05, and descriptive and summary data will be presented.

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Discussion: This study is designed to plug significant evidence gaps and to gather preliminary evidence to guide the design of a follow-up randomized active controlled trial.
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1. Background

Irritable bowel syndrome (IBS) is a common functional bowel disorder with an estimated international incidence of 11%.[1] It presents a significant economic burden to the health system with IBS patients incurring approximately 50% more health care costs than matched cohorts without IBS. Annual direct and indirect expenditures are estimated at $20 billion in the United States alone.[2] Individuals with IBS report restricted activity for over 70 days per year and experience a poor health-related quality of life.[3] In addition, current medical approaches to IBS are limited. A 2014 review of conventional IBS management found that only two pharmaceuticals could be strongly recommended.[4]

Complementary and alternative medicine (CAM) – a cluster of treatments and therapies not traditionally taught or practiced within conventional medicine[5] – is often chosen by individuals with chronic disease to manage the symptoms and progression of their health condition. Considering the significant financial and medical burden associated with IBS, juxtaposed with limited pharmaceutical options, it is not too surprising that IBS patients turn toward alternatives with approximately 50% of them reporting the use of CAM therapies for their IBS.[6]

Naturopathic medicine is a distinct CAM system of healthcare that uses a whole systems-based approach individualized to the patient and their presentation of symptoms. Naturopathy is a "system of healthcare with a deep history of traditional philosophies and practice"[7] through which practitioners integrate medical knowledge with natural treatment options.[7] While naturopathy originated in Germany, the profession is now practiced in every region of the world.[8] As a profession, naturopathy is defined by core philosophies, theories and principles.[7] These elements manifest in a clinical practice approach to treatment that is holistic and naturopathy is best characterized by this holistic clinical approach more so than specific treatments prescribed.[9]

Naturopathy is a commonly used CAM. In one large survey, approximately 10% of individuals who used CAM for a gastrointestinal complaint reported using naturopathy.[10] According to the unpublished results from an ongoing Delphi study of naturopathic IBS experts, it appears naturopathic approaches to IBS are distinct from that of conventional medicine[11] and preliminary case reports suggest that that can be a useful component of a multi-disciplinary approach in the effective management of IBS symptoms.[12] However, aside from the aforementioned preliminary work, to date, there is little published research on naturopathic approaches for IBS.

In order to fill this evidence gap, we aim to conduct an international prospective observational before-and-after study on naturopathic approaches to IBS. This study will allow us to better describe naturopathic approaches to this disorder, establish the feasibility of not only building an international consortium of academic naturopathic clinics but also recruiting participants. Our ultimate goal is to follow this observational study with a randomized active controlled trial using the same consortium and benefiting from lessons learned during this study.

2. Methods

2.1. Study Aim/s

We aim to describe naturopathic approaches to IBS as well as establish pilot data on before-and-after changes in validated IBS instruments. Secondary aims include assessment of the feasibility of recruitment and operations of a multi-center clinical trial across more than nine sites in four countries as a part of the establishment of an international research network of naturopathic teaching clinics; exploration of the experience of patients seeking naturopathic care for IBS; and comparing the consensus results of our Delphi panel of naturopathic IBS experts to the care received at the teaching clinics.

2.2. Study design

This project employs a novel whole practice observational model that better reflects the clinical realities of practice in real world settings.[13] The study will be a naturalistic observational exploration of naturopathic consultations using individualized treatment for the management of IBS. Treatment by naturopathic practitioners will not be influenced by participation in the study; rather, each naturopath will practice and prescribe treatments as they would normally.

2.3. Study sites

The participating naturopathic academic teaching clinics will be selected from a recently established International Research Consortium of Naturopathic Academic Clinics.[14] Clinic name, location, size, and parent academic institution of participating sites are listed in Table 1. The treating clinicians will be naturopathic students providing care to ambulatory patients within a clinical setting associated with an academic institution and supervised by a qualified naturopath.

Table 1 – Trial Sites for the Observational Study of Naturopathic Approaches to Irritable Bowel Syndrome in Academic Teaching Clinics

Clinic	Location	Annual visits	Parent Academic Institution
The Boucher Naturopathic Medical Clinic	New Westminster, British Columbia, Canada	11,000	Boucher Institute of Naturopathic Medicine
Robert Schad Naturopathic Clinic	Toronto, Ontario, Canada	35,000	The Canadian College of Naturopathic Medicine
The Bastyr Center for Natural Health	Seattle, WA, USA	35,000	Bastyr University
	San Diego, CA USA	8000	
National University Whole Health Center	Lombard, IL, USA	unknown	National University of Health Sciences
SCNM Medical Center	Phoenix, AZ, USA	16,000	Southwestern College of Naturopathic Medicine and Health Sciences
Wellnation Clinics	Melbourne, Victoria, Australia	1500	Endeavour College of Natural Health
	Brisbane, Queensland, Australia	2000	
Paua Clinic	Ellerslie, Auckland, New Zealand	600	South Pacific College of Natural Medicine
Rema Clinic	Grey Lynn, Auckland, New Zealand	300	Wellpark College of Natural Therapies

2.4. *Participants*

2.4.1. *Inclusion criteria*

Eligible participants are adults (≥18 years of age) who present to one of the participating naturopathic academic teaching clinics with a diagnosis of IBS (either preexisting or diagnosed by the naturopathic physician). IBS must also be a primary cause of the visit (listed within the top 3 diagnoses for the visit and addressed in the individualized treatment plan).

2.4.2. *Exclusion criteria*

Due to the naturalistic observational design, the only exclusion criterion will be that participants must have competent English skills to be able to understand and fill out the assessment forms.

2.4.3. *Sample size*

Two hundred participants will be recruited across nine academic teaching clinics in four countries.

2.4.4. *Recruitment*

The institutions will select at least one clinic lead who will serve to coordinate the dissemination of project information within each clinic. Site leads will be selected to maximize the degree of interaction between the research team and the providers and students at the teaching clinics. Site leads will train clinical supervisors and student clinicians in the study design, eligibility criteria, and ethically appropriate recruitment procedures.

The recruitment phase will be in practice for 12 months. Participants will be recruited directly through the academic teaching clinics. Collateral will be placed both in patient waiting areas as well as clinician meeting rooms. Each student naturopath will screen new patients for their potential eligibility to participate in the study based on the inclusion and exclusion criteria. The student naturopath will invite them to complete an online consent document. This document will detail the study and serve as a Participant Information Sheet. Through this document the research team will obtain informed consent. Once consent is given, the participant is asked to provide their email address; through which, automated questionnaires will be sent to the participant at week zero, four, and twelve (see Fig. 1).

2.4.5. *Randomization and allocation concealment*

As this is an observation study no randomization will occur. However, all participants will receive treatment based upon the clinical assessment of the clinical team (student and clinical supervisor).

2.4.6. *Blinding*

No blinding will occur.

2.4.7. *Ethical considerations*

The study will comply with the international standards for ethical research involving humans. Participants will be informed of the study, but participation will be voluntary. Participants will be able to withdraw at any time without repercussions. Personal information and health history will not be collected from patients without explicit approval. Data will be aggregated for storage and reporting. Ethical clearance will be sought from all relevant bodies for each study site. A full IRB review was sought at the parent sites (Bastyr University and Endeavour College of Natural Health) and approval was granted (IRB 17-1597 Bastyr University and #20171101 Endeavour College of Natural Health). Documentation submitted for ethical review was then shared with the sister sites for their own ethical review process. Each site will be responsible for receiving their own IRB review and approval as per the policy and regulations of their institutions.

2.4.8. *Interventions*

The intervention for this study will be naturopathic care as it occurs in a proxy real-world setting. All treating clinicians in each setting will have completed all theoretical content required to underpin clinical practice as a primary

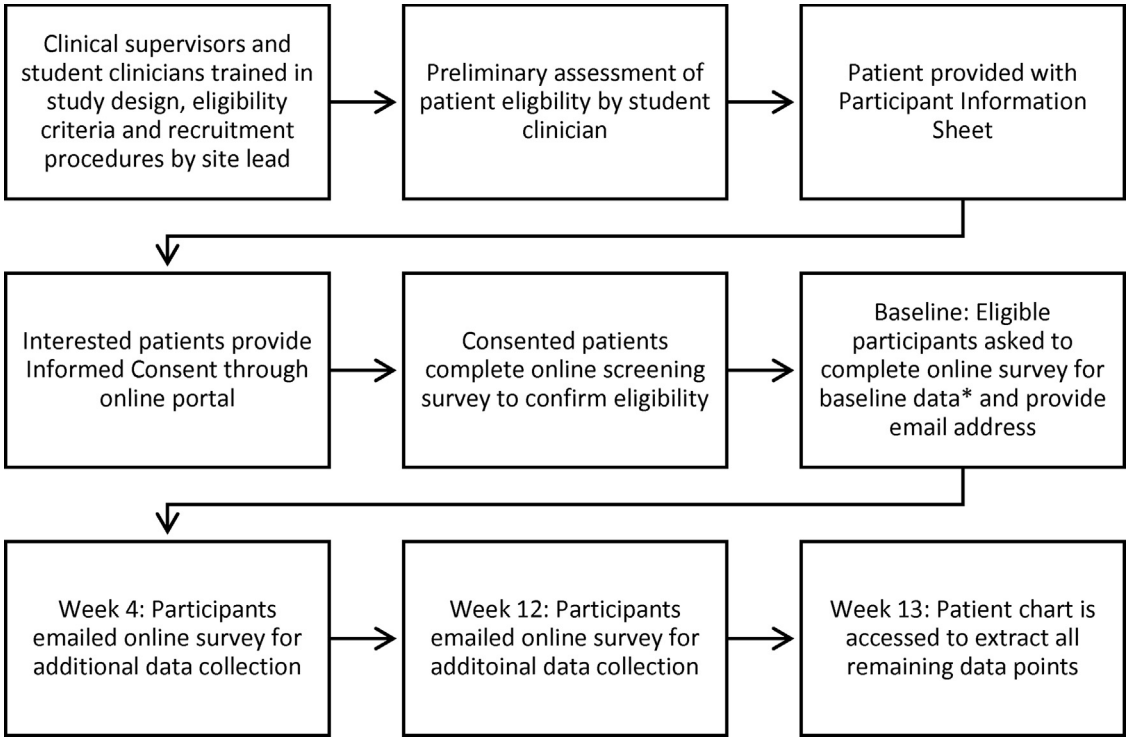

Fig. 1 – Participant recruitment and data collection procedure.

care naturopathic practitioner in their region. In each location, the student clinician will be responsible for collecting and documenting the patient's case-history and information from other relevant examinations during a face-to-face individual consultation with the participant. Student clinicians will collaborate with the qualified naturopath responsible for supervising the academic clinic to finalize the treatment prescription and overall treatment plan. Due to the multimodal and individualized approach characteristic of naturopathy, it is expected that the details of the intervention will vary among participants but will be employed through the lens of naturopathic treatment principles. There will be no restrictions or requirements placed on students with regards to the treatment plan for any participants. Each student naturopath will conduct their consultation in accordance with the legislation, policies, systems and processes appropriate to their country, region and institution. Decisions to discontinue or modify interventions will be made on a case-by-case basis in collaboration between the student naturopath and clinical supervisor. There will be no strategies to improve adherence to treatment protocols predetermined by the research team. Any commitment care and interventions deemed appropriate by the individual participant or their treating naturopathic student and supervisor will be permitted. As such, this study will document treatment as it occurs in natural practice, at the discretion of the practitioner.

2.4.9. *Outcome measures*

IBS research has been plagued with a myriad of outcomes at different levels of validation.[15] For ease of comparability to other works, we will be inclusive of more than one common outcome measure (see Table 2). Each of the six measures is to be completed by each participant at visit zero, week four, and week twelve. In week 13, treatment details will be documented through standardized patient chart extraction for each participant. *Note*: As this is an observational, hypothesis generating study, rather than an interventional study, we are monitoring treatment for twelve weeks. The follow-up session time-points remain at the discretion of the student naturopath, as we are observing naturalistic practice.

2.4.10. *Primary outcome: IBS-Severity Scoring System (IBS-SSS)*

The IBS-SSS is a validated instrument developed in 1997 which measures patient-reported IBS symptoms including pain, distension, bowel dysfunction and quality of life/global well-being. The maximum achievable IBS-SSS score is 500 with respondents' scores able to be categorized into mild (75-175), moderate (175–300) and severe (>300) cases.[16] Our *a priori* primary outcome is the proportion of IBS-SSS responders at week twelve which we define as the proportion of complete cases who achieve a 50 or greater point improvement in their baseline to week twelve IBS-SSS score.[16]

2.4.11. *PROMIS-29*

The Patient Reported Outcomes Measurement Information System (PROMIS) provides a standardized, reliable, and valid measure of health status.[17] The profile is a collection of self-report short forms containing items from seven PROMIS domains (Physical Function, Anxiety, Depression, Fatigue, Sleep Disturbance, Ability to Participate in Social Roles and Activities, Pain Interference, and Pain Intensity). The PROMIS-29 profile offers various advantages over legacy instruments including its reduced survey burden, ability to standardize to

Table 2 – Instruments Used at Each Data Collection Point

Interventions	Baseline	Week 4	Week 12	Week 13
Informed consent	√			
Inclusion/Exclusion	√			
Participant history	√			
Clinical assessment	√	√	√	
IBS-SSS	√	√	√	
PROMIS-29	√	√	√	
Adequate relief from symptoms	√	√	√	
CARE measure		√	√	
Empowerment scale		√	√	
Adverse event assessment				√
Standardized chart extraction				√

the general US population, usefulness in program and health service valuation, and the potential application of computer-adaptive testing.[17–19] The PROMIS-29 Profile consists of four questions per domain rated on a 5-point rating scale along with a 1 question Pain Intensity section rated on an 11-point scale. The assessments of each domain are anchored to the past 7 days, except for the Physical Function domain, which is not anchored to a specific time frame. PROMIS-29 provides a continuous severity score for each domain. A raw scores range from 29 to 150, and can be converted into T-scores which are referenced to mean score levels in the general U.S. population. Lower PROMIS scores have been shown to predict reduced health related quality of life for multiple chronic conditions.[18,20–26] We will measure average change in each participant's PROMIS-29 score from week zero to week twelve.

2.4.12. Secondary outcome: IBS-Adequate Relief (IBS-AR) from symptoms

The IBS-AR is a binary (yes/no) global assessment of IBS symptoms which simply assesses whether or not the patient has experienced adequate relief of their IBS symptoms in the last 7 days.[27] The FDA, Rome committee and other investigators have encouraged the use of IBS-AR in IBS clinical trials as an important, valid patient-oriented assessment tool.[27–29] In this study IBS-AR will be defined as the proportion of complete cases who report "adequate relief" at week twelve.

2.4.12.1. Secondary outcome: adverse events. Total number of adverse events and serious adverse events (using NIH's Common Terminology Criteria for Adverse Events version 4.0). This will be measured by practitioner report using chart abstraction.

2.4.12.2. Secondary outcome: treatment description. We will collect data which permits the description of treatment characteristics both in terms of the interpersonal dynamics of the consultation and the frequency and nature of the recommended treatment and prescriptions across the study period. Through chart extraction, the average number of visits within the study period will be documented, as will the average length of initial and follow-up visits. The clinician's interpersonal practice will be described through the CARE measure, a 10-item validated instrument designed to evaluate patient experiences of practitioner empathy.[30] CARE will be slightly modified, changing "doctor" to "practitioner", in order to suit the common nomenclature used in all study sites. The CARE measure has demonstrated validity across a variety of health-care settings[30–32] and its preliminary application in CAM settings suggests reliability in this setting.[33,34] In addition, the 5-item Empowerment scale will be employed[34,35] to evaluate the patient experiences of the clinical consultation with regards to the degree to which the practitioner encourages patient empowerment.

The naturopathic diagnosis and treatment characteristics for each participant will also be extracted from patient charts. In particular, the naturopathic and differential diagnosis, and details of all prescribed treatments (e.g. diets, supplements, medications, lifestyle changes) including doses and frequencies will be documented.

2.4.12.3. Secondary outcome: Lived experience. We will conduct a nested qualitative study within this study. At the conclusion of week twelve a limited number of participants will be interviewed using semi-structured questionnaires asking about the lived experience of patients as they received naturopathic care. The protocol for this nested study will be described in detail elsewhere.

2.5. Data collection

Patient reported outcomes will be collected via REDCap after the first visit before beginning any treatment prescriptions or recommendations (visit zero) and again four and twelve weeks from visit zero. REDCap is an encrypted online application used for managing surveys and questionnaires in a research environment.[36] The questionnaires have been designed to be thorough but also to minimize participant time commitment. Based on internal pilot testing for face validity and appropriateness, the questionnaires are expected to take participants 10-15 minutes to complete at each data collection point.

After the final questionnaires have been completed, a study personnel will use a piloted template to extract information related to the student clinician's diagnosis and treatment recommendations and prescriptions as well as treatment adherence. All extractors will be trained in data extraction methods. A second extractor will extract a portion of each chart at random to serve as an accuracy check. The extracted items will be entered into a piloted, encrypted online platform using Redcap.

Standardized questionnaires have been chosen to maximize generalizability of the results. All source data will be anonymized, with access to, and handling of, data restricted to

delegated study staff who must comply with the requirements of the Data Protection Act 1998. Disclosure of confidential information can only be made during routine procedures such as monitoring and auditing by the study sponsor or in emergency situations such as when a compelling medical need arises.

2.6. Data management

All data collected through REDCAP will be managed by the lead investigator (JG). Each site lead will be provided with identifying information for each participant at the end point of their involvement in the study to permit chart extraction. Data extracted from each participant's chart will be input into a spreadsheet with the participants' identification code and shared electronically with the lead investigator to collate for analysis. Participants' charts will remain at the local clinical site at all times. Electronic files will be retained on a password protected drive accessible only by the research team at each site for seven years.

2.7. Data analysis

In this uncontrolled study, before-and-after differences between baseline and endpoint values will be calculated. Analysis of data will be conducted with blinding to site allocations. The twelve week endpoint will be the primary endpoint of the study. The p values will be set at 0.05. As a pilot observational study target sample size will be 200 participants.

Data will be presented in descriptive and summary form. Our primary analysis will describe outcomes as a complete case analysis that is only including those participants for whom we have no missing outcome data. We will also conduct a sensitivity analysis for our primary outcome using the last observation carried forward for missing values. A matched t-test will be used to measure the change in symptom scores across participants over the course of the study. Secondary analyses will be conducted by country of care, IBS diagnosis status, naturopathic diagnosis, naturopathic medicine as adjunctive versus sole care, adherence (as determined by patient reported compliance), resistance to treatment (previous unsuccessful use of other treatment modalities/providers), and severity of baseline condition (as determined by the baseline IBS-SSS score).

2.8. Declaration of interests

The research team have no conflicts of interest to declare.

2.9. Access to data

The lead investigator will be the custodian of the trial data; however, the aggregated de-identified data will be accessible by all members of the research team after data collection has completed and without limitation. A data management agreement is in place between all investigators.

3. Discussion

Recent research suggests that while cautiously embracing standard research methods, the naturopathic community remains somewhat hesitant regarding the limitations of standard randomized controlled trials when applied to complex systems such as naturopathy.[37] As naturalistic and observational, this study may alleviate some of these concerns while serving to fill the substantial evidence gaps in naturopathic approaches to IBS that current exists. This is an essential first step in building an evidence base to inform future RCTs and guideline generation.

However, it is important to note that this study design cannot speak to efficacy as there is no control group. Also this study will recruit participants who have already chosen to seek out naturopathic care and as such their result may not be applicable to patients randomly allocated to naturopathic care. Additionally, in order to be descriptive of care as it is currently provided, there will be no standardized protocol for treatment. Each provider will treat as they see fit and so we therefore expect high clinical heterogeneity. We hope to address all of these concerns in a follow-up randomized active controlled trial using a standardized protocol informed by the results of our ongoing Delphi consensus work and the findings from this study.

Trial status

Recruitment will commence in December 2017 and finish in December 2018 with data collection finalized in March 2019.

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Conflict of interest

The authors declare no conflict of interest.

Ethics approval

IRB 17-1597 Bastyr University; #20171101 Endeavour College of Natural Health

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