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Defining Optimal Care for Functional Gut Disorders - Multi-Disciplinary Versus Standard Care: A Randomized Controlled Trial Protocol

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A B S T R A C T

Background: Functional gastrointestinal disorders (FGIDs) are the commonest reason for gastroenterological consultation, with patients usually seen by a specialist working in isolation. There is a wealth of evidence testifying to the benefit provided by dieticians, behavioral therapists, hypnotherapists and psychotherapists in treating these conditions, yet they rarely form a part of the therapeutic team, and these treatment modalities are rarely offered as part of the therapeutic management. There has been little examination of different models of care for FGIDs. We hypothesize that multi-disciplinary integrated care is superior to standard specialist-based care in the treatment of functional gut disorders.

Methods: The "MANTRA" (Multidisciplinary Treatment for Functional Gut Disorders) study compares comprehensive multi-disciplinary outpatient care with standard hospital outpatient care. Consecutive new referrals to the gastroenterology and colorectal outpatient clinics of a single secondary and tertiary care hospital of patients with an FGID, defined by the Rome IV criteria, will be included. Patients will be prospectively randomized 2:1 to multi-disciplinary (gastroenterologist, gut-hypnotherapist, psychiatrist, behavioral therapist ('biofeedback') and dietician) or standard care (gastroenterologist or colorectal surgeon). Patients are assessed up to 12 months after completing treatment. The primary outcome is an improvement on a global assessment scale at the end of treatment. Symptoms, quality of life, psychological well-being, and healthcare costs are secondary outcome measures.

Discussion: There have been few studies examining how best to deliver care for functional gut disorders. The MANTRA study will define the clinical and cost benefits of two different models of care for these highly prevalent disorders.

TRIAL REGISTRATION Number: Clinicaltrials.gov NCT03078634

Registered on Clinicaltrials.gov, completed recruitment, registered on March 13th 2017.

Ethics and Dissemination:

Ethical approval has been received by the St Vincent's Hospital Melbourne human research ethics committee (HREC-A 138/16). The results will be disseminated in peer-reviewed journals and presented at international conferences.

Protocol version 1.2

Abbreviations: FGID, Functional gastrointestinal disorder; MANTRA study, Multi-disciplinary treatment of functional gut disorders study; GISSI, Gastrointestinal symptom severity index; IBS-SSS, Irritable bowel syndrome – Symptom severity score; MDT, Multi-disciplinary team; HADS, Hospital anxiety and depression scale

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1. Background

Functional gastrointestinal disorders (FGIDs) are the commonest reason for consultation in gastroenterological practice [1]. These disorders encompass a range of syndromes [2], but most commonly include chronic constipation, irritable bowel syndrome and functional dyspepsia [2].

Typically, gastroenterologists or colorectal surgeons manage these patients without employing ancillary forms of care. Patient satisfaction, degree of symptom resolution, and long-term outcomes of the standard medical, stand-alone specialist model of care has received little or no evaluation [95, 96]. Some specialists use ancillary therapists outside of their hospital clinic or practice, referring patients on an as-needed basis. These ancillary therapists include dieticians, bowel-focused behavioral therapists and providers of psychotherapy (clinical psychologists, psychiatrists, and counsellors). The proportion of clinics which utilize and integrate these therapists has not been characterized but is thought to be very small.

The lack of evaluation of the efficacy of "standard care" stands in contrast to the many studies showing efficacy of various ancillary treatments for various FGIDs. This evidence base extends from single drug treatments [3–6] and dietary treatments [7] to various forms of psychological intervention [8,9], including gut-focused hypnotherapy [10], and behavioral interventions [11–13]. These studies have usually examined specific, single treatments for specific homogenous diagnostic populations [7,14,15] such as irritable bowel syndrome [3] or idiopathic constipation [4,5]. Commonly, however, patients have gut symptoms that overlap these conditions [16]. Further, some distinct functional syndromes are likely manifestations of the same disorder, such as constipation predominant irritable bowel syndrome and functional constipation [17,18].

Studies of various treatments have typically focused on a single intervention, rather than a 'package' of care suitable for all patients attending with a functional gut disorder. This is driven by the need to simplify clinical trial design but fails to address the diverse needs of this patient population. Furthermore, to address the diverse requirements of this patient population there have been repeated recommendations for a multi-disciplinary model among key opinion leaders in the field of functional gut disorders [2,19–21].

We hypothesize that a multi-disciplinary clinic employing ancillary therapists alongside gastroenterologists will provide better outcomes for patients. A key feature of this model of care is that it will provide individualized multidisciplinary management rather than a 'one-size-fits-all' approach. This model of care would also address the problem of patients having more than one symptom or problem (multi-morbidity) that might respond to specific treatments.

The MANTRA study is the first randomized, controlled, prospective, parallel arm, trial comparing an integrated (in-house) multi-disciplinary model of outpatient care for gut disorders with the current standard outpatient model based on medical specialist care (gastroenterologists and colorectal surgeons). This paper describes the design of the MANTRA study.

2. Methods and design

This study protocol adheres to the requirements set by the 2013 SPIRIT statement, defining standard protocol items in clinical trials [22].

2.1. Study objective

The primary objective of the MANTRA study is to evaluate the effectiveness of a multi-disciplinary outpatient model of care for the treatment of FGIDs compared with a standard gastrointestinal clinic model staffed only by medical personnel.

The effectiveness of the two models of care will be assessed on the basis of participants i) symptoms, ii) cost to the healthcare system, iii) quality of life, and iv) psychological well-being.

2.2. Study design

This is a prospective, parallel arm, un-blinded, single-center, randomized controlled trial, comparing two outpatient models of care: multi-disciplinary care versus standard care for patients with functional gut disorders as defined by the Rome IV criteria [2].

2.3. Clinic models

The MANTRA study will compare a novel multidisciplinary model of care with standard outpatient care for patients referred with a functional gastrointestinal disorder.

The models of care have been defined as follows:

Intervention: Multi-disciplinary outpatient care for functional gastrointestinal disorders

Outpatient clinic where care for patients with FGIDs is provided by gastroenterologists working in the same clinic as gut disorder-focused psychiatrists, psychologists, hypnotherapists, behavioral therapists (physiotherapists specializing in gut and pelvic floor problems) and dieticians. Gastroenterologists will provide the first consultation and then either continue to provide care themselves or, at their discretion, refer to one or many of the therapists working within the clinic. Patients attending the clinic will be discussed in a case-conference at the end of each clinic to coordinate care.

Comparator: Standard outpatient care for functional gastrointestinal disorders

Outpatient clinic in the same hospital staffed by gastroenterologists and colorectal surgeons, but no other professions allied to medicine. Specialists will be allowed to refer patients to therapists outside the clinic, at their discretion, but such a service will not be routinely provided, and will not work within the same clinic.

2.4. Participating center and center characteristics

St Vincent's Hospital is a public, secondary and tertiary referral, university-associated teaching general hospital in Melbourne, Australia. It provides gastrointestinal and colorectal care. General practitioners and specialists refer to the gastroenterology or colorectal surgery clinics for evaluation and treatment of functional gastrointestinal symptoms. The clinics also manage the full spectrum of gastrointestinal and colorectal conditions. Care is provided free of charge to patients, as part of Australia's publicly-funded universal healthcare system.

Patients with functional GI symptoms are referred to either the gastroenterology or colorectal surgery clinics at the discretion of the referring doctor. The proportion of different functional gut disorders differs between the two clinics. There are disproportionally more patients with functional constipation and fecal incontinence in the colorectal surgery clinic and more patients with functional dyspepsia and irritable bowel syndrome in the gastroenterology clinic. Patients will be recruited from both clinics for the MANTRA study.

2.5. Study population and recruitment

Consecutive new referrals to the gastroenterology and colorectal clinics will be assessed for inclusion into the trial. Referral letters describing gastrointestinal symptoms suggestive of a functional gut disorder will be contacted by phone for further screening. Patients whose referral letters describe symptoms that may be associated with organic gut disease, such as weight loss, raised inflammatory markers or other abnormal investigations will be excluded from the trial. Referral letters which reference any other exclusion criteria will also be excluded from the study.

Patients whose letters have not led to exclusion at this stage will be

called by study coordinators for consideration of inclusion in the study. The phone call will be used to characterize Rome IV diagnoses, to ensure no exclusion criteria apply, and to seek consent for study inclusion. The phone call and review of letters will be conducted by a clinician knowledgeable of the Rome IV criteria.

2.6. Inclusion criteria

- Patients with a Rome IV functional gastrointestinal disorder
- Age greater than 18 years and less than 80 years

2.7. Rationale for inclusion criteria

The Rome IV criteria for FGIDs represent an internationally accepted nosology for these disorders, allowing for comparability of research studies of causation and treatment in diverse settings [2].

Functional gastrointestinal disorders embrace a wide range of symptom syndromes [16,17] which frequently overlap. This study aims to include nearly all of the Rome IV conditions, in order to reflect real-life practice.

2.8. Exclusion criteria

See Table 1

2.9. Rationale for specific exclusion criteria

2.9.1. Opioid dependence

Patients dependent on narcotic analgesics are excluded as the standard and multi-disciplinary clinics do not incorporate addiction medicine specialists [23].

2.9.2. Active eating disorder

Patients presenting to gastrointestinal units with gastrointestinal symptoms may have an underlying eating disorder [24,25]. These 'atypical anorexia nervosa' patients have been found to better respond to treatment in specialized eating disorder units [24]. Due to the inability of either clinic to provide this subspecialty care, patients with active eating disorders have been excluded from the study. Patients with typical eating disorders, such as Anorexia nervosa or Bulimia Nervosa will also be excluded from the study.

2.10. Randomization

After screening referral letters for patients with a likely diagnosis of a FGID, this is further confirmed during the screening phone call. Verbal consent is then obtained during that phone call. Patients will then be randomized in a ratio of 2:1 to the multi-disciplinary care clinic or standard care clinic at the time of the phone call.

Randomization on a 2:1 basis is designed to garner as much detail about the active arm as possible.

Stratification is intended to ensure that subgroups are equally represented in both arms of a study [26]. These are 1) The patient's main functional gut syndrome, then classified according to Rome IV criteria, and 2) the clinic the patient is referred to (Gastroenterology vs Colorectal).

The reason for stratification on the basis of the patient's functional disorder is based on the varied nature of symptoms [2], response to treatment and natural history of each FGID [27].

The Gastroenterology and Colorectal surgery clinics differ in relation to the functional disorders that are seen. For example, idiopathic constipation is more common in the Colorectal clinic, where irritable bowel syndrome is more common in the Gastroenterology clinic. This is a relevant covariate due to the proportions of different syndromes and probable different consultation practices [28]..

Randomization will be in blocks of 3. The allocation table has been constructed independent of study investigators by the data capture and management tool REDCap [29], a web based centralized platform.

2.11. Rationale for randomization before first visit

Both clinics see patients at the same time point in their medical-consultation journey, that is immediately after referral, and randomization prior to their first visit. Continuity of care is with the same clinician is maintained in both study arms, while maintaining a trial design which compares two different clinic models from study start to finish.

2.12. Blinding and bias

The intervention of a clinic where additional clinicians provide care, cannot be blinded. It is recognized that the greater number of encounters with clinicians in a multi-disciplinary clinic may influence the outcome [30]. This extra 'clinician-exposure' will be measured to evaluate its possible contribution to the clinical outcome; the number of visits to either clinic will be assessed for its contribution to the primary outcome in a multi-variable analysis.

Placebo response rates have been shown to reduce significantly for studies with longer follow up periods [31]. There is no real 'placebo' in this study – every interaction with a health care professional constitutes some type of active treatment. The contribution of differences in the number or duration of consultations between arms may influence the study outcomes; to some extent this may be mitigated by the long term follow up which is part of this trial. Performance bias is also partially mitigated by patients completing self-administered assessments separate from their consultations.

2.13. Consent

Verbal consent will be obtained at the initial phone call, prior to the first visit. Written consent will be obtained at the initial consultation.

2.14. Treatments employed in the intervention clinic

Due to the pragmatic nature of the trial, clinicians in both clinics will be allowed to investigate and administer therapies at their own discretion. Patients within the intervention arm may be referred to one or more therapists working within the clinic, i.e. dietician, behavioral therapist, hypnotherapist, psychologist or psychiatrist.

In the intervention arm, an individualized care plan for each patient may be influenced by discussion with the multidisciplinary team.

Table 1
Exclusion criteria.

- Non-English speaking or illiterate
- Incapable of completing surveys
- Patients incapable of providing informed consent
- Patients who live in rural areas, incapable of attending clinics on a regular basis
- Organic gastrointestinal disorders
- Previous gastrointestinal surgery which may explain a patient's symptom:
  - o Will be considered on a case-by case basis
- Medications which may explain a patient's symptoms
- Severe organ dysfunction not related to the gastrointestinal tract
- Opioid dependence or misuse
- Active eating disorder
- Pregnancy, undergoing assisted reproductive treatment, or planning pregnancy during trial
- Major active psychiatric disorder
  - o Active suicidality, psychosis, catatonic depression
  - o Active psychiatric disorder that the clinician feels would preclude a patient from safely participating in the study or preventing them from accurately completing questionnaires.
- Patients who have been seen in St Vincent's Hospital Gastroenterology or Colorectal surgery clinics within the last 24 months.

Table 2
The modalities and therapies available as part of the multi-disciplinary model of care include.

Therapist	Treatment offered
Behavioral therapist	1 to 5 sessions with a behavioral therapist which involves education and biofeedback
Psychologist or Psychiatrist	Short course: 1 to 12 sessions of cognitive behavioral therapy or psychodynamic psychotherapy. Long course: Greater than 12 sessions of cognitive behavioral, psychodynamic or interpersonal psychotherapy.
Hypnotherapist	2–10 sessions of gut-focused hypnotherapy delivered by a psychologist
Dietician	Any dietary advice as requested by treating specialist or the patient A maximum of 2 visits, over 6–8 weeks, when a low FODMAP trial is instituted and food is re-introduced
Medications	There will be no restrictions on the medications that can be prescribed in either clinic.

The number of clinic visits, the types of clinicians involved, and the types and doses of medications employed will be recorded for each subject. The same record will be kept for patients in the standard arm (Table 2).

2.15. Time points

2.15.1. Definitions of time points

Patients are evaluated at baseline, discharge and long term follow up.

The baseline visit is the first visit to a clinic after being referred.

The discharge time point is the clinic visit when patients are discharged from the clinic's care. If a patient is seen and discharged at their baseline visit, an evaluation will be performed 1 month afterwards. If a patient has not been discharged from clinical care 9 months after their baseline visit, this will be deemed their discharge time point.

The long-term follow-up time point is 12 months after the patient's discharge time point.

2.15.2. Rationale for time points

Patients with FGIDs vary in their bio-psycho-social needs. Patients will therefore achieve therapeutic benefit after varying durations of time. For this reason it was felt inappropriate to use a fixed time point for outcome evaluation. The time of discharge, or a reasonable duration of treatment (9 months), were felt to be the best time points for outcome evaluation.

For patients who are seen and discharged at their baseline visit, end-of-treatment care will be evaluated one month later. This was deemed more likely to provide a measured response from the patient about the outcome of care than administering the survey at the same visit (Fig. 1).

2.16. Endpoints

Outpatient clinical care for patients with functional gastrointestinal symptoms should address a wide range of concerns including symptoms, quality of life and psychological health while providing a cost-effective service for the healthcare system. We hypothesize that a multi-disciplinary model will provide superior symptom outcomes, improved quality of life, similar-or-better psychological health while remaining a cost-effective service to the healthcare system.

2.17. Primary endpoint

The primary endpoint is the proportion of patients in each arm who are classed as responders at the discharge visit. Response will be defined by a modified global assessment on a 5-point Likert scale.

Patients will be asked the following question at their discharge visit and at long term follow up:

Compared with before I was first seen in clinic, I feel my gut condition is now:

1) *Much worse*
2) *Slightly worse*
3) *Same*
4) *Slightly better*
5) *Much better*

Patients who select slightly better (4) or much better (5) will be classed as responders.

This question is a modified global assessment, similar to those found in the subjective global assessment of relief (SGA) [32] and global improvement scale (GIS) [33]. The question is reworded to compare change in the patient's condition from before attending the clinic to the time the question is completed.

Endpoints which assess global relief have been shown to meet acceptable performance measures (validity and reliability) [34]. They have been shown to be responsive to treatments [34], and validated for clinical satisfaction and productivity significance [33]. A global relief score is also applicable among the various functional conditions being examined in this trial. Global assessment endpoints also allow patients to integrate the contribution of their disparate group of symptoms, and their relative importance to them, into a single global clinical rating [35,36].

The United States Federal Drug Administration (FDA) no longer recommends the use of binary or global endpoints in the design of trials for irritable bowel syndrome [37]. The current recommendation is to evaluate efficacy using a scale for abdominal pain, stool frequency and stool consistency. This recommendation has been incorporated in many

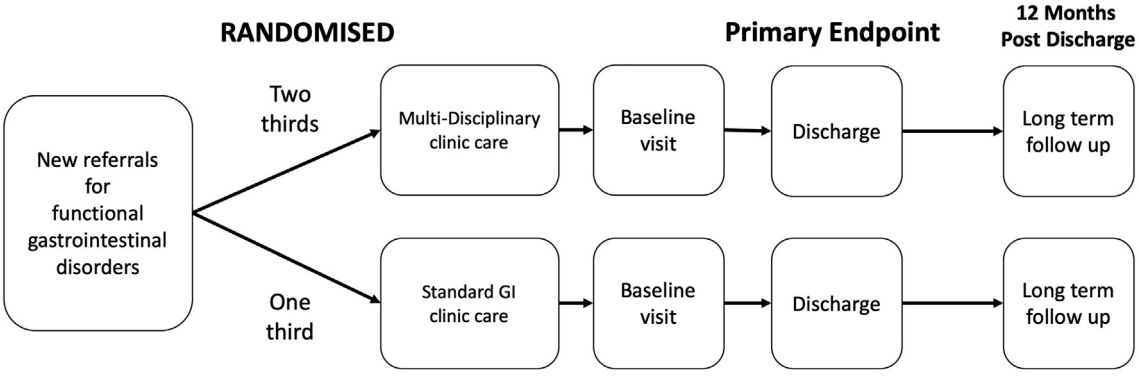

Fig. 1. Flow chart of study design.

of the latest trials for irritable bowel syndrome [3,38]. The MANTRA study is not designing a new drug, biologic or procedure which is regulated by the FDA [39], but is comparing two modes of delivering clinical care for functional gut disorders; hence the use of a global scale.

2.18. Secondary endpoints

2.18.1. Gastrointestinal symptoms

Secondary endpoints will include overall symptom relief, IBS symptoms, central abdominal pain, dyspepsia, constipation, and fecal incontinence using validated scoring systems.

The Gastrointestinal Symptom Severity Index (GISSI score) will be used in all patients for an overall assessment of functional gut symptoms [40]. It comprises six gastrointestinal symptom clusters using 39 items including: constipation and difficult defecation, abdominal pain and discomfort, dyspepsia, diarrhea, fecal incontinence, gastro-esophageal reflux and chest symptoms, nausea and vomiting [40].

In addition to the GISSI score the most common conditions will be evaluated with condition-specific scales.

The irritable bowel syndrome symptom severity scale (IBS-SSS) [41] will be used to evaluate patients with irritable bowel syndrome and centrally mediated abdominal pain syndrome. It has been shown to be a valid [42], responsive [43] and clinically meaningful [44] measure. The Nepean dyspepsia index is a validated, responsive [45] scoring system which will be used for patients with functional dyspepsia. The Cleveland clinic constipation scale has been validated in patients with constipation [46]. The St Mark's fecal incontinence score has been shown to sensitive to treatment-related change of symptoms [47]. Patients with other functional conditions will have their symptoms measured by the respective symptom clusters measured in the GISSI. Symptom responders are defined, a priori, as having a 50% reduction in their original symptom scores [48,49].

2.18.2. Quality of life

Due to the varied conditions being evaluated, generic quality of life measures will be employed, these being the Euro-QoL EQ-5D-5L [50] and the medical outcomes study RAND Short Form 36 [51]. Both have been evaluated in functional gastrointestinal disorders including Irritable bowel syndrome [52,53], functional dyspepsia [54,55] and constipation [56]..

2.18.3. Costs

The financial cost of these two forms of care delivery will be compared, including the cost of providing the service, investigations, and visits to GPs and other specialists.

Health economic modeling to estimate the potential cost-effectiveness of a multi-disciplinary clinic model: Decision analysis [57] will be used to compare the downstream consequences of a multi-disciplinary model versus a standard clinic model. The incorporation of Markov [58] and life-tabling [59] techniques will allow for the modeling of outcomes beyond 12 months post discharge. The main output of interest in health economic modeling is incremental cost-effectiveness ratios in terms of net costs per unit of health gain. Net costs will comprise the differential costs of the multi-disciplinary clinic model and standard clinic model minus costs saved from the reduction in downstream health services utilization. Health gains can be measured in a variety of ways. In this project, other than clinical outcomes, we will be also estimating quality-adjusted life years (QALYs) gained. Both are enabled by the collection of time-to-outcome data and the latter also by collection of quality of life data. All health economic analyses will be undertaken in accordance with recommended approaches, such as 5% discounting of estimated future costs and health gains. To account for any uncertainty in the data inputs for health economic modeling, sensitivity and uncertainty analyses will be undertaken via Monte Carlo simulation [60].

The time horizon of the modelled economic evaluation will be five years, which is a long enough to be of 'real-world' significance, but short enough that inaccuracy is limited. A Markov model will define specific health outcomes of interest in simulations of the progress of patients over time, and life-table methods will allow for the value of data inputs (eg, disease risks and costs) to evolve over time. The accuracy of the modelled outputs will be validated against observed longitudinal data.

2.18.4. Psychological wellbeing

Psychological state (somatisation [61–63], depression [63,64] and anxiety [64]) are related to symptoms, quality of life [65,66] and healthcare utilisation [67] in patients with functional gut disorders. Somatization will be assessed using the Somatic Symptom Scale-8 [68], and depression and anxiety using the Hospital Anxiety and Depression Scale (HADS) [69].

2.19. Sample size calculation

Sample size calculation is based on an alpha value of 0.05 (one-sided), power of 80%, an expected rate of the primary outcome of 60% in the intervention arm and 35% in the comparator arm. Allowing for a dropout rate of 33%, a total of 188 patients will be required, 125 in the multi-disciplinary and 63 in the standard care clinic.

These expected response rates are based on the average weighted means of the most common FGIDs to be seen in the clinic. The known proportions of FGIDs in the clinics are approximately 33% irritable bowel syndrome, 33% functional dyspepsia, 20% constipation, 5% fecal incontinence, 6% centrally mediated abdominal pain syndrome and 3% other functional gut conditions.

The average weighted mean is calculated using the proportions of the disorders within the clinic and the expected outcome rates based on the following trials: irritable bowel syndrome and chronic abdominal pain syndrome [14,9], functional dyspepsia [70,71], constipation [15,72,73] and fecal incontinence [11,74,75]. We estimated outcome for 'other functional gastrointestinal conditions' as 60% intervention clinic versus 50% standard care. The study is not powered to determine differences in secondary outcomes, or between different functional gut disorders.

The dropout rates are high in trials of functional gastrointestinal disorders and is expected to be higher in trials of a longer duration [76]. We conservatively estimated the dropout rate to be 33% to ensure study power is maintained.

2.20. Rationale for one-sided test

A multi-disciplinary clinic is unlikely to result in harm or inferiority. Hypnotherapy [77], dietary therapies [78] and psychological therapies [8], which are more readily available in the MDT clinic, have been repeatedly shown to have a superior response compared to standard care [79].

2.21. Patient and public involvement

Patients and the public were not involved in the development of the research question or the design of the study. The primary outcome and many of the secondary outcomes (quality of life, psychological wellbeing and symptom sub-scores) are assessed by the patients themselves. The study results will be disseminated to the patients, after the study has been completed in a published form.

3. Definition of protocol non-adherence

3.1. Medications

If a patient does not adhere to a medication prescribed by a clinician, they will not be characterized as a protocol violator.

3.2. Clinic visits

In both arms of the study (where relevant) non-adherence to the study protocol will be defined as non-attendance at two consecutive clinic appointments.

3.3. Planned data analysis

The primary analysis will be based on an intention to treat (ITT) principle. A per-protocol analysis will also be undertaken, in relation to patients who adhered to the protocol of their randomized group. The per-protocol analysis will include patients who attended all of their prescribed appointments, irrespective of adherence to treatments. Comparison of categorical variables will be undertaken using chi-squared tests (or Fisher's Exact tests for small samples), while continuous variables will be compared using (parametric) *t*-tests and (non-parametric) Mann-Whitney tests for symmetrically and asymmetrically distributed data, respectively. STATA version 13.0 will be used to conduct the statistical analysis. The analysis of the primary outcome will be unadjusted however, if significant differences on key baseline characteristics are found we will explore the impact of this on the intervention by into account co variables. Regression analyses will be performed to determine factors which may be associated with outcomes.

Patients who are lost to follow up, in whom no primary outcome can be ascertained, will not be included in the primary analysis. Where the primary outcome has been ascertained at the discharge visit, but not at 12 months, the missing data will have the last observation carried forward. Sensitivity analyses will be undertaken to explore the impact of missing data on treatment effect.

To minimize loss to follow up patients are contacted on three separate occasions at least two weeks apart by email or phone to re-establish contact.

4. Ethics and dissemination

4.1. Institutional board ethics

The MANTRA study has been approved by the St Vincent's Hospital Melbourne Human Research and Ethics Committee (HREC-A 138/16). The committee is nationally recognized to meet the standards set by the Australian National Health and Medical Research Council (NHMRC). The MANTRA study commenced recruitment in March 2017.

4.2. Publication

The results of this study will be published in peer-reviewed journals and presented at national and international conferences.

4.3. Data safety and de-identification of data

Patient data will be kept in secured servers with password protection. Login and password information will only be available to study investigators. All clinical care provided at the hospital will be accessible through the hospital's secure electronic medical record.

5. Discussion

Despite patients with FGIDs being treated mainly as outpatients, there are virtually no data on the outcome of such care [95, 96]. Despite the strong evidence about the value of a range of psychologically and behaviorally based treatments, there are few data on their application in the real-world clinical setting. There are few studies comparing different forms of delivering outpatient care for functional gut disorders. The MANTRA study aims to address these deficiencies.

In a 2006 review of gastrointestinal services in the United Kingdom, the British Society of Gastroenterology recommended that more research was needed into the integration of a multi-disciplinary approach for FGIDs within secondary services [19]. There have been other repeated recommendations for a multi-disciplinary approach for severe functional gastrointestinal disorders [21,80,81], including in the most recent release of the Rome IV classification of functional gut disoders [2,82]. The multi-disciplinary healthcare model of treating functional gastrointestinal disorders needs to be prospectively evaluated and compared with the current standard of care. Current attempts to evaluate the benefit of this approach have primarily been uncontrolled or retrospective.

Kinsinger et al. [83], retrospectively reviewed referrals made by gastroenterologists to psychologically based therapists within their service. They found that patients mostly accepted and attended these therapists, and that there was reduced healthcare utilization by patients who attended on follow up.

Delivery of care in which gastroenterologists and psychologically-trained therapists provide a simultaneous, joint consultation for patients with functional gut disorders has received some attention [84–86]. Kruimel et al. [85] prospectively examined the effect of a joint medical and psychiatric consultation model for the management of patients with complex functional gut disorders referred to their center. Patients showed significant improvement in psychological and quality of life indices, but not in gastrointestinal symptom scores, at 12 months. In a pilot, prospective randomized controlled trial, Gerson et al. [84] showed that patients attending a joint, gastroenterologist-psychologist consultation, significantly improved symptom scores and global assessment scales when compared with gastroenterologist-only treatment. These two joint-consultation studies provide encouraging evidence for the use of an integrated service for patients with functional gut disorders. Patient satisfaction in particular appeared to be particularly improved by this type of care [86]. However, this one-size-fits-all approach has limitations. Many patients attending gastroenterology clinics are unwilling to accept a psychological contribution to their symptoms, or are not motivated to engage in psychologically based care [87]. These patients may require a carefully timed referral to ancillary therapists, or no such referral at all. Many patients will accept benefit from less “confrontational” behavioral therapy or gut-focused hypnotherapy [88].

A prospective controlled evaluation of multi-disciplinary education-based models for patients with functional gut disorders has been examined previously [89,90]. The use of multiple therapists in these education-based models is welcomed and proven to be useful. However, these studies have not examined the use of these therapists as ongoing treatment for patients in conjunction with their gastroenterologist.

Multidisciplinary pain services have been shown to be beneficial for patients with chronic abdominal pain [91] and chronic pelvic pain [92] syndromes. However, neither of these studies employed a randomized controlled evaluation of this form of specialist care, leading to questions of selection bias and generalizability of the results.

Many studies which have aimed to evaluate multi-disciplinary care have been restricted to the integration of psychological services with gastroenterology. However, there is good evidence supporting the treatment by dieticians [7], behavioral therapists [11,12,73] and hypnotherapists [93] in the care of these patients. We are aware of only one study, published in abstract form, which prospectively evaluated a multi-disciplinary service for patients with FGIDs [94] with dieticians, psychologists and behavioral therapists. This uncontrolled study found 35% of patients achieved adequate symptom relief and a significant reduction in pain scores at the end of follow up.

The MANTRA study will compare two clinics in a hospital. This has the advantage that patients seen in the two comparative clinics are drawn from the same patient population. We believe the gastroenterologist –only standard care clinic is representative of other centers' practice, although this has not been tested.

In addition to evaluating effectiveness for this type of care, the

MANTRA study will evaluate costs. In most countries, the 'gastroenterologist' model is funded but the multi-disciplinary model is not, forcing patients down a pathway that we hypothesize has limited effectiveness and is financially wasteful. Furthermore, a pathway that does not include psychologically-trained therapists may delay the diagnosis and treatment of psychological illness, which is highly prevalent in this population.

We believe that the traditional outpatient model for treating patients with FGIDs, involving almost exclusively gastroenterologists, is outdated. Further, we expect that the proposed multidisciplinary model will have several advantages. First, referral to ancillary therapists is likely to be more acceptable to and convenient for patients. Patients will engage with a clinic where multidisciplinary care is considered routine and where the gastroenterologist lends 'legitimacy' to the ancillary therapists, including psychiatrists and psychologists. In such a milieu, we predict that referral to these ancillary therapists within the team will be acceptable to patients. Secondly, the co-location of the various disciplines, and the end-of-clinic case discussions, will allow effective and efficient communication and continuity of care. Thirdly this study will address the 'norm' in which effective forms of evidence-based care are not provided.

Ethics approval and consent to participate

Ethical approval has been received by the St Vincent's Hospital Melbourne human research ethics committee (HREC-A 138/16). The St Vincent's Hospital Human research ethics committee is a body approved by the national health and medical research council of Australia. Patients are required to sign consent forms to participate within the study.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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Authors contributions

Chamara Basnayake (CB) is the guarantor of the article. CB, MAK, MS and AJT devised the concept. CB acquired the data, reviewed the papers and constructed the protocol under the supervision of MAK, MS, and AJT. DL contributed to the statistical analysis plan and construction of the protocol. CB, AK, AWOB, KB and AS developed the protocol in form submitted for ethical review. NJT consulted on the trial design. CB wrote the manuscript. All authors provided critical revision of the manuscript for important intellectual content.

Declaration of Competing interest

The authors declare they have no competing interests.

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