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Persistence of gastrointestinal symptoms in irritable bowel syndrome and ulcerative colitis: study protocol for a 3-arm randomised controlled trial (SOMA.GUT-RCT)

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ABSTRACT:

Introduction: Ulcerative colitis (UC) and irritable bowel syndrome (IBS) are distressing chronic diseases associated with abdominal pain and altered bowel habits of unknown aetiology. Results from previous studies indicate that, across both diseases, increased levels of illness-related anxiety and dysfunctional symptom expectations contribute to symptom persistence. Thus, comparing both disorders with regard to common and disease-specific factors in the persistence and modification of gastrointestinal symptoms seems justified. Our primary hypothesis is that persistent gastrointestinal symptoms in UC and IBS can be improved by modifying dysfunctional symptom expectations and illness-related anxiety using expectation management strategies.

Methods and analysis: To assess the extent to which persistent somatic symptoms are modifiable in adult patients with UC and IBS, we will conduct an observer-blinded, 3-arm randomised controlled trial. A total of 117 patients with UC and 117 patients with IBS will be randomised into three groups of equal size: targeted expectation management aiming to reduce illness-related anxiety and dysfunctional symptom expectations in addition to standard care (intervention 1), non-specific supportive treatment in addition to standard care (intervention 2), or standard care only (control). Both active intervention groups will comprise 3 individual online consultation sessions and a booster session after 3 months. The primary outcome is baseline to post-interventional change in gastrointestinal symptom severity.

Ethics and dissemination: The study was approved by the Ethics Committee of the Hamburg Medical Association (2020-10198-BO-ff). The study will shed light onto the efficacy and mechanisms of action of a targeted expectation management intervention for persistent gastrointestinal symptoms in patients with UC and IBS. Further, the detailed analysis of the complex biopsychosocial mechanisms will allow the further advancement of aetiological models and according evidence-based intervention strategies.

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KEY WORDS:

Persistent Somatic Symptoms; Irritable Bowel Syndrome; Ulcerative Colitis; Mechanisms; Expectations; Anxiety; Online Intervention; Randomised Controlled Trial

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study specifically investigates the modification of two hypothesised risk factors for persistent gastrointestinal symptoms: dysfunctional symptom expectations and illness-related anxiety.
- The parallel investigation of these risk factors in ulcerative colitis and irritable bowel syndrome enables the determination of whether they are effective across both diseases or in a disease-specific manner.
- The 3-arm study design enables the differentiation of specific and non-specific treatment effects.
- A systematic search in PubMed and the International Clinical Trials Registry Platform (ICTRP) indicated no studies, which aim at alleviating persistent gastrointestinal symptoms in patients with UC and IBS by targeting illness-specific expectations or anxiety.
- This trial is powered with regard to the difference between the expectation management intervention versus the control condition; if it should turn out that the power is not sufficient to show a meaningful difference between the two active interventions, mediation analyses will be consulted to investigate the mechanisms of action.

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INTRODUCTION

Background

Ulcerative colitis (UC) and irritable bowel syndrome (IBS) are two distressing chronic diseases with considerable overlap concerning their gastrointestinal symptoms, in particular abdominal pain and altered bowel habits. There is good evidence to assume that, across both diseases, increased levels of illness-related anxiety and dysfunctional symptom expectations contribute to the persistence of gastrointestinal symptoms. Since both factors can potentially be modified by targeted interventions, this study will investigate defined mechanisms of action; namely, whether persistent gastrointestinal symptoms in UC and IBS can be influenced by modifying dysfunctional symptom expectations and illness-related anxiety. Studying a primarily inflammatory and a primarily functional bowel disease in parallel allows for the investigation of whether the same mechanisms of symptom persistence are involved for these two different, yet related diseases.

Ulcerative Colitis (UC)

Clinical presentation, aetiology and risk factors: UC is a chronic and potentially disabling inflammatory bowel disease that causes gastrointestinal symptoms such as abdominal pain, rectal bleeding, and diarrhoea. UC affects 0.04% to 0.4% of the general population in Western Europe.[1] The exact aetiology of UC is unknown. Dysregulation of the innate and the adaptive immune systems in complex interactions with intestinal microbes under homeostatic conditions has been proposed as a possible mechanism.[2] About 25% of UC patients develop persistent IBS-like symptoms even in endoscopic remission.[3] Notably, experimental placebo and nocebo studies indicate an important role of expectations and conditioning processes in the development and persistence of chronic gastrointestinal symptoms.[4]

Psychological factors: Numerous studies found substantially increased rates of depression and anxiety in patients with UC compared to the general population and in patients with

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active compared to inactive UC, respectively.[5] Recent longitudinal studies indicate a bidirectional relationship between psychological symptoms and gastrointestinal disease activity,[2] which may be explained by neural, hormonal, and immune communication links.[6] Psychotherapy can improve depression, anxiety, perceived stress, and quality of life of UC patients.[7 8] However, the few studies that have investigated the effects of psychotherapy on gastrointestinal symptoms, disease activity, and relapse rates in UC produced inconsistent results.[6-9] Of note, an online survey in 631 patients with inflammatory bowel disease indicated a large demand for psychotherapy.[10]

Research needs: Given the well-documented bidirectionality of the gut-brain axis, illness-specific expectations and anxiety, stress, depression, and other psychological factors may contribute to the persistence of gastrointestinal symptoms in UC. However, currently there are no studies examining this potential link. For other conditions, it was shown that targeted expectation management can improve treatment outcomes.[11 12] After systematically searching PubMed and the International Clinical Trials Registry Platform (ICTRP), we found no studies which aimed at alleviating persistent gastrointestinal symptoms in patients with UC by targeting illness-specific expectations or anxiety. Thus, an attempt to investigate a targeted modification of expectations and psychological symptoms on persistent somatic symptoms in UC is warranted.

Irritable Bowel Syndrome (IBS)

Clinical presentation, aetiology and risk factors: IBS is conceptualised as a disorder of gut-brain functions with complex and multi-factorial aetiology[13] that has a worldwide prevalence of 4.1% (Rome IV criteria).[14] According to the Rome IV criteria, the main symptom of IBS is recurring abdominal pain associated with defecation, and/or change in frequency of bowel movements and/or consistency of stool.[15] Patients experience substantial functional impairment and impaired quality of life.[16] Established risk factors in the pathogenesis of IBS include stress, coping, prior abuse experience, comorbid depression, anxiety, and

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somatisation. Moreover, studies have found that IBS patients are affected by alterations in gut motility, visceral hypersensitivity, differential central nervous system processing of afferent gut signals, differences in colonic microbiota, and immune responses after gastrointestinal infections.[13 16-18]

Psychological factors: A recent systematic review detected a 2.5-fold increased odds in patients with IBS with regard to suffering from either anxiety (23%) or depressive disorders (23%) compared to healthy subjects.[19] In a prior study of our group, IBS patients reported significantly higher levels of depression, anxiety, somatic symptom burden, neuroticism, illness-related anxiety, and perceived stress compared to those without IBS.[20] Recent systematic reviews have found that both psychotherapy and antidepressants are effective in sustainably improving IBS symptoms and daily functioning.[21 22] Expectations regarding the severity of the symptoms seem to play an important role, and reduction of illness-related anxiety and cognitions were proposed to be promising starting points for treatment.[23 24]

Research needs: In IBS, the contribution of psychological factors, in particular illness-related anxiety and expectations, to gastrointestinal symptoms is well established. Thus, modifying expectations and illness-related anxiety in IBS patients may be promising in improving gastrointestinal symptoms. This assumption is further supported by a study, which suggests that illness-related cognitions are mediators of change for gastrointestinal symptom severity in IBS patients.[25] A systematic search in PubMed and the ICTRP indicated that so far no study has investigated the efficacy of expectation-focused interventions for IBS symptoms. Therefore, investigation of a targeted modification of expectations and anxiety on persistent somatic symptoms in patients with IBS appears important.

Joint characteristics of UC and IBS

UC and IBS are predominantly considered distinct diagnostic entities characterised by different levels of inflammation that require different therapies.[26] Nevertheless, substantial

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overlap between both disorders exist (**Figure 1**): Both are chronic and potentially disabling conditions that share some symptoms and typically start in early adulthood. Further commonalities include the potential effect of expectations on symptoms, high rates of mental health comorbidity, dysregulation of the enteric nervous system, an altered microbiome, at least some degree of mucosal inflammation, and increased activation of the gut-brain axis.[18] [27] Subjects with UC also have a higher likelihood of meeting IBS criteria than subjects without UC.[27] [28] Given the similarities and differences between UC and IBS, we believe that comparing both disorders with regard to common and disease-specific factors in the persistence and modification of gastrointestinal symptoms will be highly informative.

*Please insert **Figure 1** approximately here*

Objectives and hypotheses

Objectives:

1. Modification of known risk factors: To investigate whether brief targeted expectation management strategies can improve patients' gastrointestinal symptom severity via the modification of dysfunctional symptom expectations and illness-related anxiety in UC and IBS.
2 Investigation of further risk factors: To prospectively identify further risk factors involved in the aggravation/maintenance of persistent gastrointestinal symptoms in UC and IBS and to deduct conceptual models of gastrointestinal symptom persistence, deterioration, and improvement in both diseases.
3. Comparison between diseases: To compare risk factors, aggravating and maintaining factors across UC and IBS, and to identify disease-specific and generic factors for gastrointestinal symptom persistence.

Two hypotheses are assigned to the first two objectives:

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Hypothesis 1: Persistent gastrointestinal symptoms in UC and IBS can be improved by modifying dysfunctional symptom expectations and illness-related anxiety using expectation management strategies. The hypothesised mechanisms of action are illustrated in **Figure 2**.

Hypothesis 2: In addition, further biological, psychological, and social factors contributing to the persistence of gastrointestinal symptoms in both UC and IBS can be identified.

*Please insert **Figure 2** approximately here*

METHODS AND ANALYSIS

Study design

Study design and rationale: In order to identify the effect of a targeted modification of illness-related symptom expectations and anxiety on persistent gastrointestinal symptoms and to differentiate this effect from general modes of action, a randomised comparison between a specifically treated group, a group treated non-specifically in the same dose and a control group without additional treatment must be conducted. A control group is necessary to test whether the experimental interventions have a positive effect compared to no intervention and to investigate objectives 2 and 3. Thus, we will use the design of a 3-arm randomised controlled trial (RCT), in which 33% of each disease group will undergo targeted expectation management in addition to standard care (SC), 33% will undergo non-specific supportive treatment in addition to SC, while 33% will receive SC only (**Figure 3**). In the control group, we will additionally investigate the contribution of predefined risk factors to gastrointestinal symptom persistence. The study will be monocentric and entail nationwide recruitment. This study is part of the SOMACROSS research unit (FOR 5211), funded by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) which investigates mechanisms of somatic symptom persistence across different medical conditions. The overarching protocol of the SOMACROSS research unit is published elsewhere.[29]

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*Please insert **Figure 3** approximately here*

Setting: For recruitment, we will use our outpatient clinics as well as our established network of cooperating gastroenterologists.[17 20 30] We will also recruit via social media campaigns with support of cooperating patient organisations (Deutsche Morbus Crohn / Colitis ulcerosa Vereinigung, DCCV e.V. and Deutsche Reizdarmselbsthilfe e.V.). In addition, the "Informationsforum für Magen-Darm-Erkrankungen der Deutschen Gesellschaft für Neurogastroenterologie und Motilität (MAGDA)" will support recruitment. The experimental interventions will be carried out as online consultations, which corresponds to the preferences expressed by patients in our mixed-methods pilot study (available on request), and also allows for a nationwide outreach.

Patient and public involvement: The design of the experimental interventions is based on the preferences expressed by the patients in our pilot study. The two cooperating patient organisations were involved from the beginning of the development of the study protocol and will continue to be so during the course of the study.

Inclusion criteria: Age ≥ 18 years; diagnosis of UC or IBS (Rome IV); at least moderate gastrointestinal symptoms according to the Irritable Bowel Syndrome - Severity Scoring System (IBS-SSS ≥ 175),[31] UC/IBS treatment according to the current German AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften) guidelines, and informed consent. Exclusion criteria: necessity of acute emergency treatment, acute suicidality, psychotherapeutic treatment in the past 3 months, and insufficient German language skills.

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Experimental interventions and control intervention

Experimental intervention 1 (GUT.EXPECT + SC): This experimental intervention consists of an expectation management intervention (GUT.EXPECT) in addition to standard care (SC). The manualised intervention primarily aims at optimising expectations about symptoms, treatment outcome, and coping strategies and at reducing illness-related anxiety.[17 24] The design of the intervention is based on the demonstrated effectiveness of the expectation management interventions from the PSY-HEART and the PSY-BREAST trials,[12 32] and other previous studies.[11 33-35] The theoretical basis of the intervention are the Response Expectancy Theory,[36] the Social Cognitive Theory,[37] the Common Sense Model of Self-Regulation of Health and Illness,[38] as well as the Integrative Model of Patients' Expectations Undergoing Medical Treatment.[39] The intervention consists of three individual online video consultation sessions in intervals of 2 weeks each and a booster session after three months, with each session lasting 45 minutes. The cognitive-behavioural techniques from the PSY-HEART and PSY-BREAST expectation modification interventions[12 32] will be adapted for patients with UC or IBS. In the first session, the patient's illness-related anxiety and expectations regarding symptoms and treatment will be assessed through a semi-structured interview so that the intervention can be adapted accordingly within the framework of the treatment manual. The intervention components include psychoeducation aimed at developing functional expectations regarding symptoms and treatment outcome, techniques to foster expectations of personal control, and developing a written list of personal goals. In a “tool box”, illness-specific dysfunctional expectations and anxiety are assigned to specific therapeutic interventions. Homework will be given after each session to deepen the acquired skills. The intervention thus addresses the topics "dealing with anxiety", "improving expectations" as well as patients’ need for information about their disease.

Experimental intervention 2 (GUT.SUPPORT + SC): This experimental intervention consists of a non-specific supportive intervention (GUT.SUPPORT) in addition to SC. GUT.SUPPORT is identical to GUT.EXPECT in terms of common and non-specific treatment elements, i.e.

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time, personal attention and emotional support, but does not use specific interventions aimed at modifying expectations and illness-related anxiety. In contrast to GUT.EXPECT, which focuses primarily on changing dysfunctional symptom expectations for the future, GUT.SUPPORT focuses exclusively on coping with stressful situations in the present. GUT.SUPPORT is manualised and adapted from the supportive therapy we use in the PSY-HEART-II trial (German Clinical Trials Register: DRKS00016793).

Control intervention (standard care): The control intervention consists of SC only. In all study groups, SC entails the patient's usual medical treatment without any interference by the study and all treatments received will be documented. The SC group is also needed for the comparison of predictors of persistent somatic symptoms across diseases in the SOMACROSS research unit.[29]

Assessment and study outcomes

Measurement points: Assessments will be carried out at baseline, after 3 months (post intervention), 6 and 12 months. An intermediate assessment after 6 weeks will be conducted for the mediator analyses, which investigate whether a change in gastrointestinal symptom severity is mediated via changes in dysfunctional symptom expectations and illness-related anxiety. All outcomes will be collected through electronic data entry by patients at home; if this should not be feasible in individual cases, data collection will alternatively be done by paper questionnaires sent by post or telephone interviews conducted by trained and blinded raters. A blood sample will be taken by the patient's primary care physician or in secondary care and the stool samples will be collected by the patients at home and sent by post to the study management.

Primary outcome: To test the effect of the expectation management intervention on persistent gastrointestinal symptoms in UC or IBS, the primary outcome for this study is the baseline to post-interventional change in gastrointestinal symptom severity (3-months follow-

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up). Gastrointestinal symptom severity will be assessed using the Irritable Bowel Syndrome - Severity Scoring System (IBS-SSS), which is applicable in both IBS and UC and validated in English and German in various forms of intestinal diseases.[40 41,31] On a scale of 0 to 500, the IBS-SSS measures gastrointestinal pain, the degree of distension, satisfaction with bowel movement, and the perceived impairment of quality of life during the past 10 days.

Secondary outcomes include changes between baseline and follow-up measurements in total somatic symptom severity (PHQ-15),[42] disease activity, time to next treatment and utilisation of medical treatment, adverse effects, and satisfaction with the intervention. C-reactive protein (CRP), interleukin 6 (IL-6), tumour necrosis factor (TNF-α), and faecal calprotectin will be assessed at baseline and the 3-months post-intervention assessment. Illness-related worries (WI-7),[43] psychological burden related to somatic symptoms or associated health concerns (SSD-12),[44] expectations of symptom severity, treatment outcome and coping with symptoms (TEX-Q; NRS),[45 46] will be investigated as pre-specified mediator variables. Additionally, we will apply joint SOMACROSS core instruments[29] to identify risk factors and mechanisms for the persistence of somatic symptoms across diseases. Supplements from the core set include adverse childhood experiences, neuroticism, negative affectivity, stigmatization, health care use, and diagnosis of somatic symptom disorder according to DSM-5. All these additional data will be collected at baseline and at the follow-up assessments.

Sample size: This trial is powered with regard to the difference between intervention 1 (GUT.EXPECT + SC) versus the control condition (SC). Based on the literature reviewed, we assume a within-group standard deviation (SD) of 75 points on the IBS-SSS.[41] Given this SD, a difference of 40 points on the IBS-SSS can be detected with a power of 80%, using a two-sided alpha of 5%, by including 29 patients per group, yielding a total sample size of n=87 for UC and IBS, respectively. Based on the results of our prospective cohort study,[17] we assume a loss to follow-up between baseline and the primary outcome measurement (i.e., 3-months

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follow-up) of 25%, resulting in a total of n=117 randomised patients for UC and IBS, respectively. Assuming that 50% of patients with UC or IBS will meet the inclusion criteria, N=234 patients per diagnostic group will be assessed for eligibility. **Figure 4** shows the anticipated flow of participants throughout the trial. If it should turn out that the power in our study is not sufficient to show a meaningful difference between the two active interventions, the mediation analyses will be consulted to investigate the mechanisms of action.

*Please insert **Figure 4** approximately here*

Statistical methods: The primary analysis and all pre-specified secondary analyses will be conducted in the intention-to-treat sample consisting of all randomised patients. In consideration of the assumed loss-to-follow-up, missing data will be imputed if more than 5% of the data are missing. The number of imputations will be chosen depending on the proportion of missing data.[47] Objective 1: An analysis of covariance will be used to investigate the group differences in the IBS-SSS, adjusted for baseline IBS-SSS. The underlying disease (UC vs. IBS) and sex will be added as additional factors. Assuming no interaction effect, this is more effective than analysing both disease conditions independently. If the overall comparison yields a significant difference, pairwise comparisons can be performed without adjustment of the type 1 error because of the closure testing principle. In order to analyse whether effects on persistent gastrointestinal symptoms resulted through changes in expectations or illness-related anxiety, we will conduct mediation analyses. Objective 2: To identify risk factors involved in the persistence of gastrointestinal symptoms and deduct conceptual models of gastrointestinal symptom persistence, we will use longitudinal data from the control group (UC and IBS) and conduct multivariate regression analyses adjusted for the diagnostic group, while taking into account the number of predictors and sample size. To avoid bias, patients from the intervention groups will not be included in these analyses. Objective 3: To compare risk factors across UC and IBS and to identify disease-specific and generic factors for gastrointestinal symptom persistence over

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time, we will conduct exploratory multivariate regression analyses including all patients from the control group with disease as a factor. We will also compare the results of the disease-specific regression analysis for symptom persistence in UC versus IBS and conduct further exploratory analyses.

Methods against bias: Randomisation will be carried out electronically, stratified by diagnostic group and sex. Patient drop-out will be minimized by contacting patients according to a schedule of repeated contact attempts and by allowing written or telephone data collection if electronically not feasible. Telephone interviews will be performed by trained interviewers who are not involved in the treatment and are observer-blinded with respect to all treatment conditions. The attending clinicians will not be informed about group allocation. Patients in the GUT.EXPECT and GUT.SUPPORT groups will be blinded with regard to their group assignment. Full patient and therapist blinding is not feasible as their active involvement in the intervention is necessary. Both interventions will be manualised. Therapists and interviewers will be trained and supervised regularly. As a manipulation check regarding potentially overlapping content, contamination, and carry-over effects between the two interventions, patients will complete a rating scale on treatment content and on subjective treatment mechanisms after the post-intervention outcome assessment. Any questions regarding patient exclusions, serious adverse events, and potential study termination will be reviewed by the study's Data Safety and Monitoring Board (DSMB). The DSMB will audit the study annually and assess, independently of the investigators and the sponsor, the accuracy of the study conduct and compliance with ethical conditions. The study was prospectively registered at the ISRTCN registry (ISRCTN30800023).

Feasibility of recruitment: In our previous studies, we were able to successfully recruit patients within our network of cooperating gastroenterologists and clinics.[17 20 30] In addition, social media and three large organisations (Deutsche Reizdarmselbsthilfe, DCCV, MAGDA) will support recruitment. In a pilot study for this trial, we enrolled N=35 patients within one

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month, and many patients displayed high interest in the planned intervention study. This again corresponds to the well-documented need of patients with UC and IBS for support and information.[10 48] The format as an online video consultation and the brevity of the intervention will also facilitate patient enrolment.

ETHICS AND DISSEMINATION

Ethical approval: The study protocol was approved by the Ethics Committee of the Hamburg Medical Association on 25 January 2021 (reference number: 2020-10198-BO-ff). The trial will be conducted in accordance with the Declaration of Helsinki, guidelines for Good Clinical Practice, national and local laws. Before inclusion, eligible participants will be informed about the course of the study verbally and in written form and they will provide written informed consent. The data will be stored in pseudonymised form. Any changes to the study protocol will be listed in the study registry and publications.

Adverse events: To the best of our knowledge, there is no risk for serious adverse events caused by the application of expectation management interventions.[12 32] Nevertheless, patients may develop severe somatic complications of UC or other medical conditions. In such cases, the patient will be informed and advised to initiate appropriate treatment with his or her attending gastroenterologist. In case of an emergency, medical treatment will be offered at the University Medical Centre Hamburg-Eppendorf.

Suicide risk: Patients at risk to commit suicide may be detected; either by the PHQ-9 questionnaire or during the intervention. If patients endorse suicidal ideation in the interview, additional questions will be presented to judge severity and clinical relevance of the suicidal thoughts. A proven algorithm on how to process cases of suicidal ideation (e.g., to contact the physician, to provide suicide prevention hotline numbers or to consider psychiatric treatment in case of severe and acute suicidality) is already available as it was used in our

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prior studies (e.g., GETFEEDBACK.GP trial[49]). Before the conduct of the trial, the staff will be carefully advised to follow these guidelines.

Documentation and stopping rules: Adverse events will be monitored and reported to the DSMB. Serious adverse events which need to be monitored comprise acute suicidality, suicidal acts, and life threatening deterioration of health status. For the individual patient, the trial procedure will stop, if serious adverse events or withdrawal of informed consent occur. The whole trial will be discontinued, if the team of investigators or the DSMB detect significant associations between study participation and serious adverse events or a differential association between the experimental conditions and adverse events. The trial will also be terminated if procedures to handle adverse events are noncompliant with ethical standards.

Data Safety and Monitoring Board (DSMB): Any questions regarding patient exclusions, serious adverse events and potential study termination will be reported to and reviewed by the DSMB. In addition, the DSMB will annually monitor the study. Where appropriate, recommendations will be made to continue, modify or terminate the study or to unmask participants in case of serious adverse events.

Possible disadvantages of participating in the study: Since all three groups of the proposed RCT continue to receive their regular medical treatment, there are most probably no disadvantages for participants compared to non-participants. The experimental groups have the advantage that the interventions tested could have a positive effect on their persistent gastrointestinal symptoms.

Data sharing: In accordance with the ethics committee approval and the German Research Foundation (DFG) guidelines for the handling of research data adopted in 2015, de-identified individual patient data will be made publicly available. Data sharing will follow the *FAIR* Data

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Principles (Findable, Accessible, Interoperable and Reusable) and international naming conventions (e.g., Systematized Nomenclature of Medicine) to maximise transparency and scientific reproducibility. According to the WHO Statement on Public Disclosure of Clinical Trials (www.who.int/ictrp/results/reporting/en/), the main findings will be submitted for publication in a peer-reviewed journal within 12 months of study completion.

Conclusion

To the best of our knowledge, this is the first study to test the mechanisms of symptom persistence in two gastrointestinal diseases in parallel. The results of our analyses for hypothesis 1 will allow us to draw conclusions regarding the efficacy and mechanisms of a targeted expectation management intervention. If the effectiveness of the intervention via the proposed modes of action can be proven, it will serve as a model for the development of personalised interventions in UC and IBS and for cross-validation studies in other conditions. If the results either do not confirm our hypotheses or show unclear differences between the two active interventions, the results of the mediation analyses and the exploratory analyses will provide valuable insights into risk factors for persistent gastrointestinal symptoms. The confirmation or falsification of hypothesis 2 will significantly contribute to a better understanding of the development of persistent somatic symptoms in UC and IBS and will clarify which risk factors and mechanisms are disease-specific and which are valid across diseases. Data regarding mechanisms of symptom persistence from the control group will be pooled and compared across all RU SOMACROSS projects (objective 3). We expect that the study will promote the development of more effective interventions for patients with persistent somatic symptoms and will thus have a clinical and potentially socio-economic impact in the long term.

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Author contributions

Bernd Löwe and Ansgar W. Lohse are principal investigators on the study, Yvonne Nestoriuc and Viola Andresen contribute as co-applicants to the study. Antonia Zapf and Eik Vettorazzi provide statistical expertise in clinical trial design. Bernd Löwe drafted the first version of the study protocol. All authors, i.e., Viola Andresen, Sina Hübener, Bernd Löwe, Ansgar W. Lohse, Kerstin Maehder, Yvonne Nestoriuc, Luisa Peters, Eik Vettorazzi, and Antonia Zapf, contributed to the refinement of the study protocol, read and approved the final version.

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Competing interests

None

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REFERENCES

1. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018;390:2769-78.
2. Gracie DJ, Guthrie EA, Hamlin PJ, et al. Bi-directionality of Brain-Gut Interactions in Patients With Inflammatory Bowel Disease. *Gastroenterology* 2018;154:1635-46.e3.
3. Henriksen M, Høivik ML, Jelsness-Jørgensen LP, et al. Irritable Bowel-like Symptoms in Ulcerative Colitis are as Common in Patients in Deep Remission as in Inflammation: Results From a Population-based Study [the IBSEN Study]. *Journal of Crohn's & colitis* 2018;12:389-93.
4. Elsenbruch S, Enck P. Placebo effects and their determinants in gastrointestinal disorders. *Nature reviews Gastroenterology & hepatology* 2015;12:472-85.
5. Mikocka-Walus A, Knowles SR, Keefer L, et al. Controversies Revisited: A Systematic Review of the Comorbidity of Depression and Anxiety with Inflammatory Bowel Diseases. *Inflammatory bowel diseases* 2016;22:752-62.
6. Abautret-Daly Á, Dempsey E, Parra-Blanco A, et al. Gut-brain actions underlying comorbid anxiety and depression associated with inflammatory bowel disease. *Acta neuropsychiatrica* 2018;30:275-96.
7. Tarricone I, Regazzi MG, Bonucci G, et al. Prevalence and effectiveness of psychiatric treatments for patients with IBD: A systematic literature review. *J Psychosom Res* 2017;101:68-95.
8. Gracie DJ, Irvine AJ, Sood R, et al. Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: a systematic review and meta-analysis. *The lancet Gastroenterology & hepatology* 2017;2:189-99.
9. Wynne B, McHugh L, Gao W, et al. Acceptance and Commitment Therapy Reduces Psychological Stress in Patients With Inflammatory Bowel Diseases. *Gastroenterology* 2019;156:935-45.e1.

For peer review only

10. Klag T, Mazurak N, Fantasia L, et al. High Demand for Psychotherapy in Patients with Inflammatory Bowel Disease. *Inflammatory bowel diseases* 2017;23:1796-802.
11. Kube T, Glombiewski JA, Rief W. Using different expectation mechanisms to optimize treatment of patients with medical conditions: A systematic review. *Psychosom Med* 2018;80:535-43.
12. Rief W, Shedden-Mora MC, Laferton JA, et al. Preoperative optimization of patient expectations improves long-term outcome in heart surgery patients: results of the randomized controlled PSY-HEART trial. *BMC medicine* 2017;15:4.
13. Halland M, Saito YA. Irritable bowel syndrome: new and emerging treatments. *Bmj* 2015;350:h1622.
14. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. *Gastroenterology* 2020
15. Lacy BE, Patel NK. Rome Criteria and a Diagnostic Approach to Irritable Bowel Syndrome. *Journal of clinical medicine* 2017;6
16. Enck P, Aziz Q, Barbara G, et al. Irritable bowel syndrome. *Nature reviews Disease primers* 2016;2:16014.
17. Löwe B, Lohse A, Andresen V, et al. The Development of Irritable Bowel Syndrome: A Prospective Community-Based Cohort Study. *Am J Gastroenterol* 2016;111:1320-9.
18. Schmid J, Langhorst J, Gaß F, et al. Placebo analgesia in patients with functional and organic abdominal pain: a fMRI study in IBS, UC and healthy volunteers. *Gut* 2015;64:418-27.
19. Zamani M, Alizadeh-Tabari S, Zamani V. Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 2019;50:132-43.
20. Althaus A, Broicher W, Wittkamp P, et al. Determinants and frequency of irritable bowel syndrome in a German sample. *Z Gastroenterol* 2016;54:217-25.

For peer review only

21. Ford AC, Lacy BE, Harris LA, et al. Effect of Antidepressants and Psychological Therapies in Irritable Bowel Syndrome: An Updated Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2019;114:21-39.

22. Laird KT, Tanner-Smith EE, Russell AC, et al. Short-term and Long-term Efficacy of Psychological Therapies for Irritable Bowel Syndrome: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2016;14:937-47.e4.

23. Flik CE, Bakker L, Laan W, et al. Systematic review: The placebo effect of psychological interventions in the treatment of irritable bowel syndrome. *World J Gastroenterol* 2017;23:2223-33.

24. Windgassen S, Moss-Morris R, Chilcot J, et al. The journey between brain and gut: A systematic review of psychological mechanisms of treatment effect in irritable bowel syndrome. *British journal of health psychology* 2017;22:701-36.

25. Reme SE, Stahl D, Kennedy T, et al. Mediators of change in cognitive behaviour therapy and mebeverine for irritable bowel syndrome. *Psychol Med* 2011;41:2669-79.

26. Spiller R, Major G. IBS and IBD - separate entities or on a spectrum? *Nature reviews Gastroenterology & hepatology* 2016;13:613-21.

27. Gracie DJ, Ford AC. IBS-like symptoms in patients with ulcerative colitis. *Clinical and experimental gastroenterology* 2015;8:101-9.

28. Halpin SJ, Ford AC. Prevalence of Symptoms Meeting Criteria for Irritable Bowel Syndrome in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis. *The American Journal Of Gastroenterology* 2012;107:1474.

29. Löwe B, Andresen V, Van den Bergh O, et al. Persistent SOMAtic Symptoms ACROSS Diseases - From Risk Factors to Modification: Scientific Framework and Overarching Protocol of the Interdisciplinary SOMACROSS Research Unit (RU 5211). *BMJ open* 2021; provisionally accepted for publication

30. Löwe B, Andresen V, Fraedrich K, et al. Psychological outcome, fatigue, and quality of life after infection with shiga toxin-producing Escherichia coli O104. *Clin Gastroenterol Hepatol* 2014;12:1848-55.

For peer review only

31. Betz C, Mannsdörfer K, Bischoff SC. [Validation of the IBS-SSS]. *Z Gastroenterol* 2013;51:1171-6.

32. Shedden-Mora MC, Pan Y, Heisig SR, et al. Optimizing expectations about cancer treatment: Results of the randomized controlled PSY-BREAST trial. *Clinical Psychology in Europe* 2020;2:e2695.

33. Pan Y, Meister R, Löwe B, et al. Non-concealed placebo treatment for menopausal hot flushes: Study protocol of a randomized-controlled trial. *Trials* 2019;20:508.

34. Pan Y, Heisig SR, von Blanckenburg P, et al. Facilitating adherence to endocrine therapy in breast cancer: stability and predictive power of treatment expectations in a 2-year prospective study. *Breast cancer research and treatment* 2018;168:667-77.

35. Nestoriuc Y, von Blanckenburg P, Schuricht F, et al. Is it best to expect the worst? Influence of patients' side-effect expectations on endocrine treatment outcome in a 2-year prospective clinical cohort study. *Ann Oncol* 2016;27:1909-15.

36. Kirsch I. Response expectancy theory and application: A decennial review. . *Appl Prev Psychol* 1997;6:69-79.

37. Schwarzer R. Optimism, Vulnerability, and self-beliefs as health-related cognitions: A systematic overview. *Psychol Health Med* 1994;9:161–80.

38. Cameron LDL, H. The self-regulation of health and illness behavior: New York: Routledge 2003.

39. Laferton JA, Kube T, Salzmann S, et al. Patients' Expectations Regarding Medical Treatment: A Critical Review of Concepts and Their Assessment. *Front Psychol* 2017;8:233.

40. Volz MS, Farmer A, Siegmund B. Reduction of chronic abdominal pain in patients with inflammatory bowel disease through transcranial direct current stimulation: a randomized controlled trial. *Pain* 2016;157:429-37.

41. Ishaque SM, Khosruzzaman SM, Ahmed DS, et al. A randomized placebo-controlled clinical trial of a multi-strain probiotic formulation (Bio-Kult(R)) in the management of diarrhea-predominant irritable bowel syndrome. *BMC gastroenterology* 2018;18:71.

For peer review only

42. Kroenke K, Spitzer RL, Williams JB, et al. The Patient Health Questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. *Gen Hosp Psychiatry* 2010;32:345-59.

43. Hiller W, Rief W. Internationale Skalen für Hypochondrie: Deutschsprachige Adaptation des Whiteley-Index (WI) und der Illness Attitude Scales (IAS). Göttingen: Hogrefe 2004.

44. Toussaint A, Hüsing P, Kohlmann S, et al. Detecting DSM-5 somatic symptom disorder: criterion validity of the Patient Health Questionnaire-15 (PHQ-15) and the Somatic Symptom Scale-8 (SSS-8) in combination with the Somatic Symptom Disorder - B Criteria Scale (SSD-12). *Psychol Med* 2019:1-10.

45. Rief W, Burton C, Frostholm L, et al. Core Outcome Domains for Clinical Trials on Somatic Symptom Disorder, Bodily Distress Disorder, and Functional Somatic Syndromes: European Network on Somatic Symptom Disorders Recommendations. *Psychosom Med* 2017;79:1008-15.

46. Alberts J, Löwe B, Glahn MA, et al. Development of the generic, multidimensional Treatment Expectation Questionnaire (TEX-Q) through systematic literature review, expert surveys and qualitative interviews. *BMJ Open* 2020;10:e036169.

47. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in medicine* 2011;30:377-99.

48. Flik CE, van Rood YR, de Wit NJ. Systematic review: knowledge and educational needs of patients with irritable bowel syndrome. *Eur J Gastroenterol Hepatol* 2015;27:367-71.

49. Kohlmann S, Lehmann M, Eisele M, et al. Depression screening using patient-targeted feedback in general practices: study protocol of the German multicentre GET.FEEDBACK.GP randomised controlled trial. *BMJ Open* 2020;10:e035973.

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FIGURE LEGENDS

Figure 1. Commonalities and differences between ulcerative colitis and irritable bowel syndrome

Figure 2. Hypothetical cross-disease model of pathomechanisms for persistent gastrointestinal symptoms in IBS and UC. Illness anxiety and dysfunctional expectations as hypothesised mechanisms of action for persistent gastrointestinal symptoms are marked in red.

Figure 3. Study design and outcome assessment. GUT.EXPECT = expectation management intervention; GUT.SUPPORT = supportive intervention

Figure 4. Anticipated flow of participants through the course of the study. *Outcomes after 6 and 12 months are secondary and were not included in the sample size estimation. GUT.EXPECT = expectation management intervention; GUT.SUPPORT = supportive intervention

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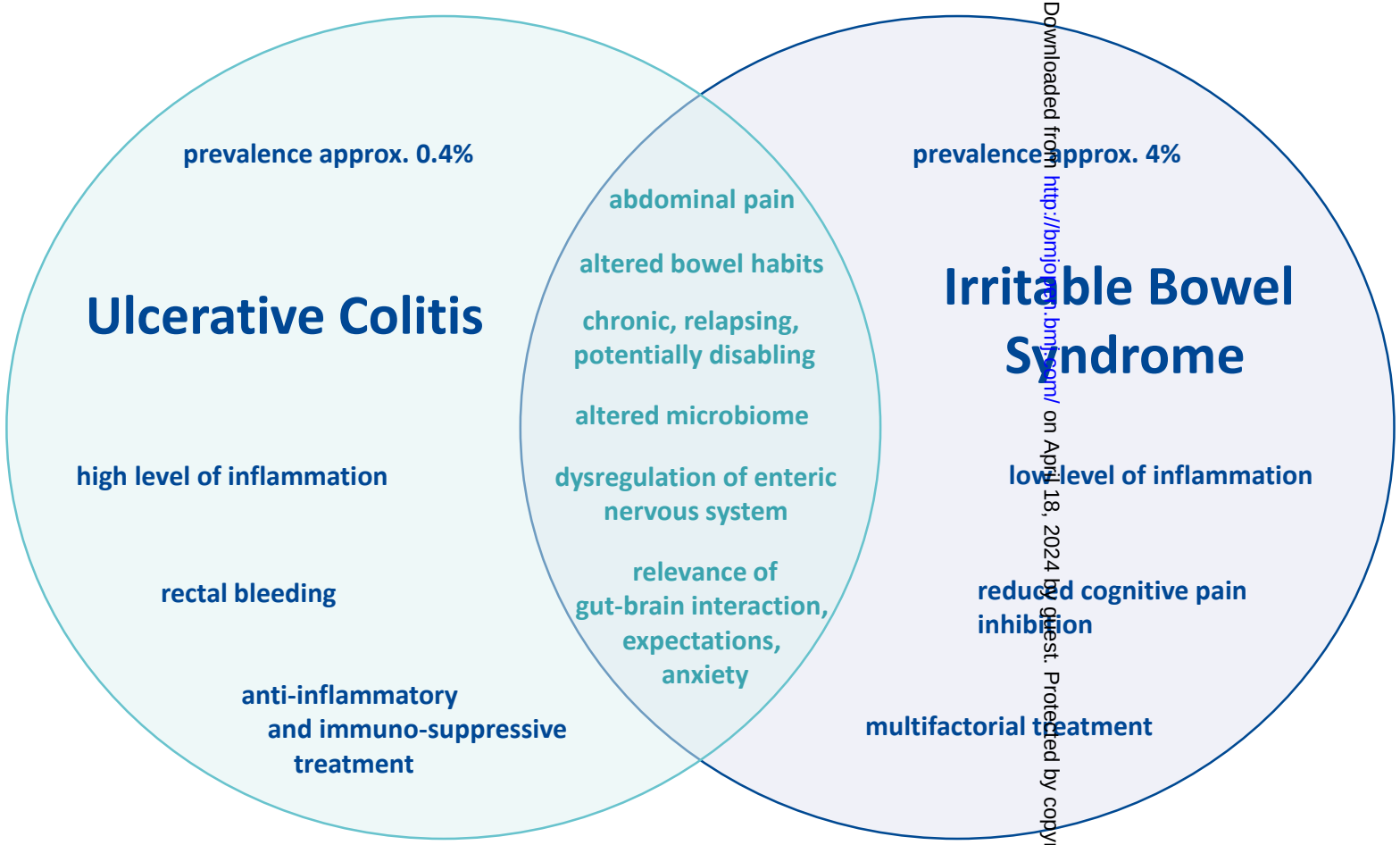

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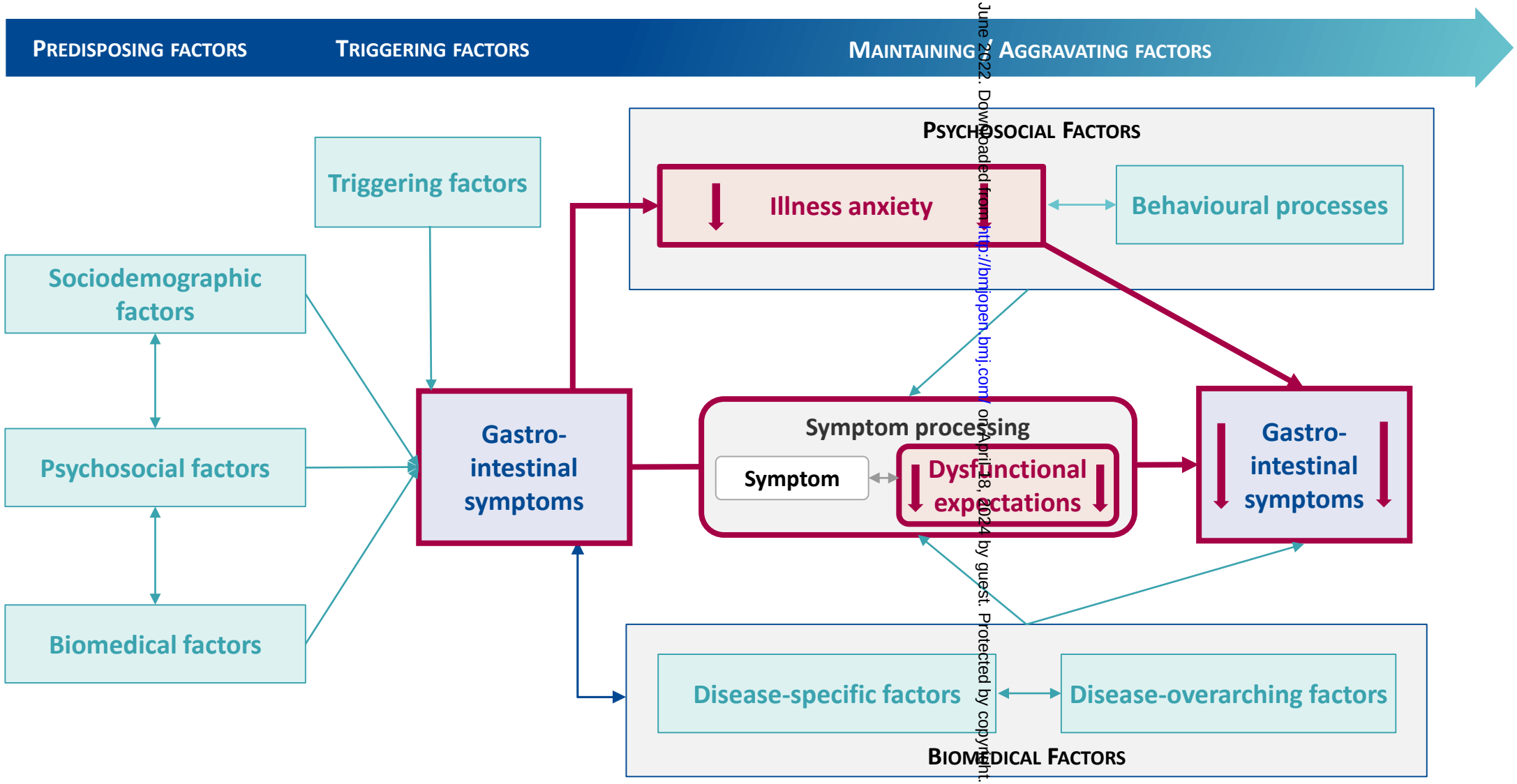

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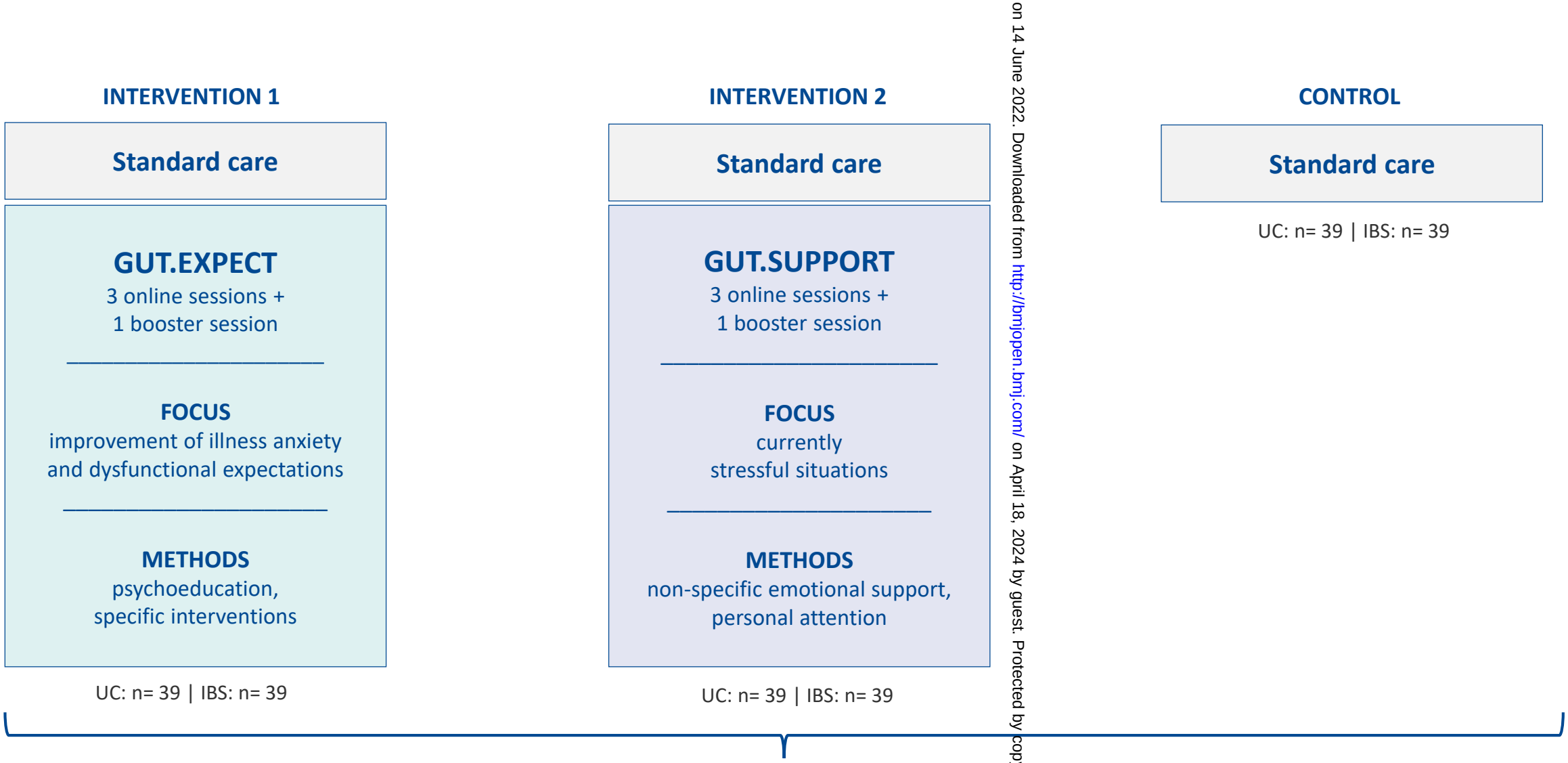

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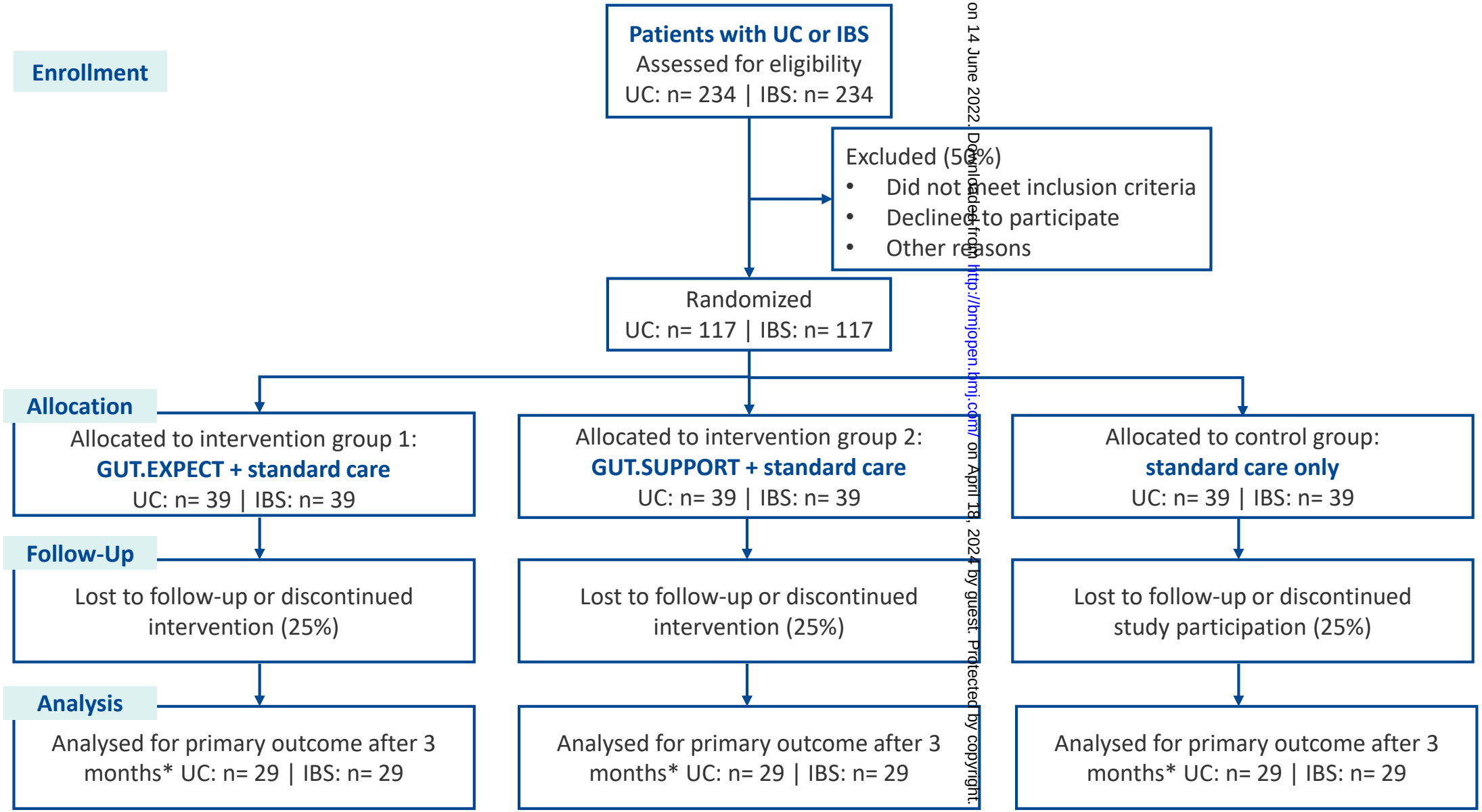

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 20
	5b	Name and contact information for the trial sponsor	20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16, 18, 20

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-9
	6b	Explanation for choice of comparators	11-13
Objectives	7	Specific objectives or hypotheses	9, 10
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13, 14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-14, Fig, 3, Fig 4

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14, 16
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10, 15
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	16
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13, 14_
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16, 20
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17,18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	available from authors
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Persistence of gastrointestinal symptoms in irritable bowel syndrome and ulcerative colitis: study protocol for a 3-arm randomised controlled trial (SOMA.GUT-RCT)

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Secondary Subject Heading:	General practice / Family practice, Mental health
Keywords:	Functional bowel disorders < GASTROENTEROLOGY, Inflammatory bowel disease < GASTROENTEROLOGY, Gastroenterology < INTERNAL MEDICINE, MENTAL HEALTH

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Persistence of gastrointestinal symptoms in irritable bowel syndrome and ulcerative colitis: study protocol for a 3-arm randomised controlled trial (SOMA.GUT-RCT)

Hamburg, Germany, March 28, 2022, Version 3.1.

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Note: This study protocol has undergone independent peer review to gain funding from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG). The project is funded by the German Research Foundation (https://gepris.dfg.de/gepris/projekt/460370451) from October 2021 to September 2025. The study protocol received formal ethical approval by the Ethics Committee of the Hamburg Medical Association, Hamburg, Germany, on January 25, 2021 (Reference number: 2020-10198-BO-ff).

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ABSTRACT:

Introduction: Ulcerative colitis (UC) and irritable bowel syndrome (IBS) are distressing chronic diseases associated with abdominal pain and altered bowel habits of unknown aetiology. Results from previous studies indicate that, across both diseases, increased levels of illness-related anxiety and dysfunctional symptom expectations contribute to symptom persistence. Thus, comparing both disorders with regard to common and disease-specific factors in the persistence and modification of gastrointestinal symptoms seems justified. Our primary hypothesis is that persistent gastrointestinal symptoms in UC and IBS can be improved by modifying dysfunctional symptom expectations and illness-related anxiety using expectation management strategies.

Methods and analysis: To assess the extent to which persistent somatic symptoms are modifiable in adult patients with UC and IBS, we will conduct an observer-blinded, 3-arm randomised controlled trial. A total of 117 patients with UC and 117 patients with IBS will be randomised into three groups of equal size: targeted expectation management aiming to reduce illness-related anxiety and dysfunctional symptom expectations in addition to standard care (intervention 1), non-specific supportive treatment in addition to standard care (intervention 2), or standard care only (control). Both active intervention groups will comprise 3 individual online consultation sessions and a booster session after 3 months. The primary outcome is baseline to post-interventional change in gastrointestinal symptom severity.

Ethics and dissemination: The study was approved by the Ethics Committee of the Hamburg Medical Association (2020-10198-BO-ff). The study will shed light onto the efficacy and mechanisms of action of a targeted expectation management intervention for persistent gastrointestinal symptoms in patients with UC and IBS. Further, the detailed analysis of the complex biopsychosocial mechanisms will allow the further advancement of aetiological models and according evidence-based intervention strategies.

Trial registration number: ISRCTN30800023

For peer review only

KEY WORDS:

Persistent Somatic Symptoms; Irritable Bowel Syndrome; Ulcerative Colitis; Mechanisms; Expectations; Anxiety; Online Intervention; Randomised Controlled Trial

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study specifically investigates the modification of two hypothesised risk factors for persistent gastrointestinal symptoms: dysfunctional symptom expectations and illness-related anxiety.
- The parallel investigation of these risk factors in ulcerative colitis and irritable bowel syndrome enables the determination of whether they are effective across both diseases or in a disease-specific manner.
- The 3-arm study design enables the differentiation of specific and non-specific treatment effects.
- A systematic search in PubMed and the International Clinical Trials Registry Platform (ICTRP) indicated no studies, which aim at alleviating persistent gastrointestinal symptoms in patients with UC and IBS by targeting illness-specific expectations or anxiety.
- This trial is powered with regard to the difference between the expectation management intervention versus the control condition; if it should turn out that the power is not sufficient to show a meaningful difference between the two active interventions, mediation analyses will be consulted to investigate the mechanisms of action.

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INTRODUCTION

Background

Ulcerative colitis (UC) and irritable bowel syndrome (IBS) are two distressing chronic diseases with considerable overlap concerning their gastrointestinal symptoms, in particular abdominal pain and altered bowel habits. There is good evidence to assume that, across both diseases, increased levels of illness-related anxiety and dysfunctional symptom expectations contribute to the persistence of gastrointestinal symptoms. Since both factors can potentially be modified by targeted interventions, this study will investigate defined mechanisms of action; namely, whether persistent gastrointestinal symptoms in UC and IBS can be influenced by modifying dysfunctional symptom expectations and illness-related anxiety. Studying a primarily inflammatory and a primarily functional bowel disease in parallel allows for the investigation of whether the same mechanisms of symptom persistence are involved for these two different, yet related diseases.

Ulcerative Colitis (UC)

Clinical presentation, aetiology and risk factors: UC is a chronic and potentially disabling inflammatory bowel disease that causes gastrointestinal symptoms such as abdominal pain, rectal bleeding, and diarrhoea. UC affects 0.04% to 0.4% of the general population in Western Europe.[1] The exact aetiology of UC is unknown. Dysregulation of the innate and the adaptive immune systems in complex interactions with intestinal microbes under homeostatic conditions has been proposed as a possible mechanism.[2] About 25% of UC patients develop persistent IBS-like symptoms even in endoscopic remission.[3] Notably, experimental placebo and nocebo studies indicate an important role of expectations and conditioning processes in the development and persistence of chronic gastrointestinal symptoms.[4]

Psychological factors: Numerous studies found substantially increased rates of depression and anxiety in patients with UC compared to the general population and in patients with

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active compared to inactive UC, respectively.[5] Recent longitudinal studies indicate a bidirectional relationship between psychological symptoms and gastrointestinal disease activity,[2] which may be explained by neural, hormonal, and immune communication links.[6] Psychotherapy can improve depression, anxiety, perceived stress, and quality of life of UC patients.[7 8] However, the few studies that have investigated the effects of psychotherapy on gastrointestinal symptoms, disease activity, and relapse rates in UC produced inconsistent results.[6-9] Of note, an online survey in 631 patients with inflammatory bowel disease indicated a large demand for psychotherapy.[10]

Research needs: Given the well-documented bidirectionality of the gut-brain axis, illness-specific expectations and anxiety, stress, depression, and other psychological factors may contribute to the persistence of gastrointestinal symptoms in UC. However, currently there are no studies examining this potential link. For other conditions, it was shown that targeted expectation management can improve treatment outcomes.[11-14] Recently, a review paper has nicely summarised the 'power' of expectations and conditioning processes in shaping gastrointestinal symptoms in gastrointestinal diseases.[4] After systematically searching PubMed and the International Clinical Trials Registry Platform (ICTRP), we found no studies which aimed at alleviating persistent gastrointestinal symptoms in patients with UC by targeting illness-specific expectations or anxiety. Thus, an attempt to investigate a targeted modification of expectations and psychological symptoms on persistent somatic symptoms in UC is warranted.

Irritable Bowel Syndrome (IBS)

Clinical presentation, aetiology and risk factors: IBS is conceptualised as a disorder of gut-brain functions with complex and multi-factorial aetiology[15] that has a worldwide prevalence of 4.1% (Rome IV criteria).[16] According to the Rome IV criteria, the main symptom of IBS is recurring abdominal pain associated with defecation, and/or change in frequency of bowel movements and/or consistency of stool.[17] Patients experience substantial functional

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impairment and impaired quality of life.[18] Established risk factors in the pathogenesis of IBS include stress, coping, prior abuse experience, comorbid depression, anxiety, and somatisation. Moreover, studies have found that IBS patients are affected by alterations in gut motility, visceral hypersensitivity, differential central nervous system processing of afferent gut signals, differences in colonic microbiota, and immune responses after gastrointestinal infections.[15 18-20]

Psychological factors: A recent systematic review detected a 2.5-fold increased odds in patients with IBS with regard to suffering from either anxiety (23%) or depressive disorders (23%) compared to healthy subjects.[21] In a prior study of our group, IBS patients reported significantly higher levels of depression, anxiety, somatic symptom burden, neuroticism, illness-related anxiety, and perceived stress compared to those without IBS.[22] Recent systematic reviews have found that both psychotherapy and antidepressants are effective in sustainably improving IBS symptoms and daily functioning.[23 24] Current research on the mechanisms of change in psychotherapy indicate that directly targeting gastrointestinal symptom specific anxiety in particular seems promising.[25 26] In addition, expectations regarding the severity of the symptoms seem to play an important role, and reduction of illness-related anxiety and cognitions were proposed to be promising starting points for treatment.[27 28] For a detailed description of Cognitive Behavioural Therapy (CBT) for IBS, we refer to a recent review.[29]

Research needs: In IBS, the contribution of psychological factors, in particular illness-related anxiety and expectations, to gastrointestinal symptoms is well established. Thus, modifying expectations and illness-related anxiety in IBS patients may be promising in improving gastrointestinal symptoms. This assumption is further supported by a study, which suggests that illness-related cognitions are mediators of change for gastrointestinal symptom severity in IBS patients.[30] A systematic search in PubMed and the ICTRP indicated that so far no study has investigated the efficacy of expectation-focused interventions for IBS symptoms.

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Therefore, investigation of a targeted modification of expectations and anxiety on persistent somatic symptoms in patients with IBS appears important.

Joint characteristics of UC and IBS

UC and IBS are predominantly considered distinct diagnostic entities characterised by different levels of inflammation that require different therapies.[31] Nevertheless, substantial overlap between both disorders exist (**Figure 1**): Both are chronic and potentially disabling conditions that share some symptoms and typically start in early adulthood. Further commonalities include the potential effect of expectations on symptoms, high rates of mental health comorbidity, dysregulation of the enteric nervous system, an altered microbiome, at least some degree of mucosal inflammation, and increased activation of the gut-brain axis.[20 32] Subjects with UC also have a higher likelihood of meeting IBS criteria than subjects without UC.[32 33] Given the similarities and differences between UC and IBS, we believe that comparing both disorders with regard to common and disease-specific factors in the persistence and modification of gastrointestinal symptoms will be highly informative.

*Please insert **Figure 1** approximately here*

Objectives and hypotheses

Objectives:

1. Modification of known risk factors: To investigate whether brief targeted expectation management strategies can improve patients' gastrointestinal symptom severity via the modification of dysfunctional symptom expectations and illness-related anxiety in UC and IBS.
2 Investigation of further risk factors: To prospectively identify further risk factors involved in the aggravation/maintenance of persistent gastrointestinal symptoms in UC and IBS and to deduct conceptual models of gastrointestinal symptom persistence, deterioration, and improvement in both diseases.

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3. Comparison between diseases: To compare risk factors, aggravating and maintaining factors across UC and IBS, and to identify disease-specific and generic factors for gastrointestinal symptom persistence.

Two hypotheses are assigned to the first two objectives:

Hypothesis 1: Persistent gastrointestinal symptoms in UC and IBS can be improved by modifying dysfunctional symptom expectations and illness-related anxiety using expectation management strategies. The hypothesised mechanisms of action are illustrated in **Figure 2**.

Hypothesis 2: In addition to illness-related anxiety and dysfunctional symptom expectations, further biological, psychological, and social factors contributing to the persistence of gastrointestinal symptoms in both UC and IBS can be identified.

*Please insert **Figure 2** approximately here*

METHODS AND ANALYSIS

Study design

Study design and rationale: In order to identify the effect of a targeted modification of illness-related symptom expectations and anxiety on persistent gastrointestinal symptoms and to differentiate this effect from general modes of action, a randomised comparison between a specifically treated group, a group treated non-specifically in the same dose and a control group without additional treatment must be conducted. A control group is necessary to test whether the experimental interventions have a positive effect compared to no intervention and to investigate objectives 2 and 3. Thus, we will use the design of a 3-arm randomised controlled trial (RCT), in which 33% of each disease group will undergo targeted expectation management in addition to standard care (SC), 33% will undergo non-specific supportive treatment in addition to SC, while 33% will receive SC only (**Figure 3**). In the control group,

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we will additionally investigate the contribution of predefined risk factors to gastrointestinal symptom persistence. The study will be monocentric and entail nationwide recruitment. This study is part of the SOMACROSS research unit (FOR 5211), funded by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) which investigates mechanisms of somatic symptom persistence across different medical conditions. The overarching protocol of the SOMACROSS research unit is published elsewhere.[34]

*Please insert **Figure 3** approximately here*

Setting: For recruitment, we will use our outpatient clinics as well as our established network of cooperating gastroenterologists.[19 22 35] We will also recruit via social media campaigns with support of cooperating patient organisations (Deutsche Morbus Crohn / Colitis ulcerosa Vereinigung, DCCV e.V. and Deutsche Reizdarmselbsthilfe e.V.). In addition, the "Informationsforum für Magen-Darm-Erkrankungen der Deutschen Gesellschaft für Neurogastroenterologie und Motilität (MAGDA)" will support recruitment. The experimental interventions will be carried out as online consultations, which corresponds to the preferences expressed by patients in our mixed-methods feasibility study,[36] and also allows for a nationwide outreach.

Patient and public involvement: The design of the experimental interventions is based on the preferences expressed by the patients in our feasibility study.[36] The two cooperating patient organisations were involved from the beginning of the development of the study protocol and will continue to be so during the course of the study.

Inclusion criteria: Age ≥ 18 years; diagnosis of UC or IBS (Rome IV); at least moderate gastrointestinal symptoms according to the Irritable Bowel Syndrome - Severity Scoring System (IBS-SSS ≥ 175),[37] UC/IBS treatment according to the current German AWMF (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften) guidelines,

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and informed consent. Exclusion criteria: necessity of acute emergency treatment, acute suicidality, psychotherapeutic treatment in the past 3 months, and insufficient German language skills.

Experimental interventions and control intervention

Experimental intervention 1 (GUT.EXPECT + SC): This experimental intervention consists of an expectation management intervention (GUT.EXPECT) in addition to standard care (SC). The manualised intervention primarily aims at optimising expectations about symptoms and treatment outcome and at reducing illness-related anxiety.[19 28] The design of the CBT-based intervention is based on the demonstrated effectiveness of the expectation management interventions from the PSY-HEART and the PSY-BREAST trials,[12 38] and other previous studies.[11 39-41] The theoretical basis of the intervention are the Response Expectancy Theory,[42] the Social Cognitive Theory,[43] the Common Sense Model of Self-Regulation of Health and Illness,[44] as well as the Integrative Model of Patients' Expectations Undergoing Medical Treatment.[45] The structure of the intervention in terms of length and online format is based on preferences expressed by patients in our feasibility study.[36] The intervention consists of three individual online video consultation sessions in intervals of 2 weeks each and a booster session after three months, with each session lasting 45 minutes. The cognitive-behavioural techniques from the PSY-HEART and PSY-BREAST expectation modification interventions[12 38] have been adapted for patients with UC or IBS. In the first session, the patient's illness-related anxiety and expectations regarding symptoms and treatment will be assessed through a semi-structured interview so that the intervention can be adapted accordingly within the framework of the treatment manual. The intervention components include psychoeducation aimed at developing functional expectations regarding symptoms and treatment outcome, techniques to foster expectations of personal control, and developing a written list of personal goals. In a “tool box”, illness-specific dysfunctional expectations and anxiety are assigned to specific therapeutic interventions. The contents of the 3 intervention sessions and the booster session are shown in **Table 1**. Homework will be

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given after each session to deepen the acquired skills, and the experiences gained will be discussed with the patients at each subsequent treatment session. The intervention thus addresses the topics "dealing with anxiety", "improving expectations" as well as patients' need for information about their disease.

*Please insert **Table 1** approximately here*

Experimental intervention 2 (GUT.SUPPORT + SC): This experimental intervention consists of a non-specific supportive intervention (GUT.SUPPORT) in addition to SC. GUT.SUPPORT is identical to GUT.EXPECT in terms of common and non-specific treatment elements, i.e. time, personal attention and emotional support, but does not use specific interventions aimed at modifying expectations and illness-related anxiety. In contrast to GUT.EXPECT, which focuses primarily on changing dysfunctional symptom expectations for the future, GUT.SUPPORT focuses exclusively on coping with stressful situations in the present. GUT.SUPPORT is manualised and adapted from the supportive therapy we use in the PSY-HEART-II trial (German Clinical Trials Register: DRKS00016793).

Control intervention (standard care): The control intervention consists of SC only. In all study groups, SC entails the patient's usual medical treatment without any interference by the study and all treatments received will be documented. The SC group is also needed for the comparison of predictors of persistent somatic symptoms across diseases in the SOMACROSS research unit.[34]

Assessment and study outcomes

Measurement points: Assessments will be carried out at baseline, after 3 months (post intervention), 6 and 12 months. An intermediate assessment after 6 weeks will be conducted for the mediator analyses, which investigate whether a change in gastrointestinal symptom severity is mediated via changes in dysfunctional symptom expectations and illness-related

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anxiety. All outcomes will be collected through electronic data entry by patients at home; if this should not be feasible in individual cases, data collection will alternatively be done by paper questionnaires sent by post or telephone interviews conducted by trained and blinded raters. A blood sample will be taken by the patient's primary care physician or in secondary care and the stool samples will be collected by the patients at home and sent by post to the study management.

Primary outcome: To test the effect of the expectation management intervention on persistent gastrointestinal symptoms in UC or IBS, the primary outcome for this study is the baseline to post-interventional change in gastrointestinal symptom severity (3-months follow-up). Gastrointestinal symptom severity will be assessed using the Irritable Bowel Syndrome - Severity Scoring System (IBS-SSS), which is applicable in both IBS and UC and validated in English and German in various forms of intestinal diseases.[46 47,37] On a scale of 0 to 500, the IBS-SSS measures gastrointestinal pain, the degree of distension, satisfaction with bowel movement, and the perceived impairment of quality of life during the past 10 days. For the German version of the IBS-SSS, a high sensitivity to assess changes in gastrointestinal symptom severity has been described[37]

Secondary outcomes include changes between baseline and follow-up measurements in total somatic symptom severity (PHQ-15),[48] disease activity (Simple Clinical Colitis Activity Index, SCCAI),[49 50] time since last treatment and utilisation of medical treatment, adverse effects, and satisfaction with the intervention. C-reactive protein (CRP), interleukin 6 (IL-6), tumour necrosis factor (TNF-α), and faecal calprotectin will be assessed at baseline and the 3-months post-intervention assessment. Illness-related worries (WI-7),[51] psychological burden related to somatic symptoms or associated health concerns (SSD-12),[52] expectations of symptom severity, treatment outcome and coping with symptoms (TEX-Q; NRS),[53 54] will be investigated as pre-specified mediator variables. Additionally, we will apply joint SOMACROSS core instruments [34] to identify risk factors and mechanisms for the persistence

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of somatic symptoms across diseases. Supplements from the core set include adverse childhood experiences, neuroticism, negative affectivity, stigmatization, health care use, and diagnosis of somatic symptom disorder according to DSM-5. All these additional data will be collected at baseline and at the follow-up assessments.

Sample size: This trial is powered with regard to the difference between intervention 1 (GUT.EXPECT + SC) versus the control condition (SC). Based on the literature reviewed, we assume a within-group standard deviation (SD) of 75 points on the IBS-SSS.[47] Given this SD, a difference of 40 points on the IBS-SSS can be detected with a power of 80%, using a two-sided alpha of 5%, by including 29 patients per group, yielding a total sample size of n=87 for UC and IBS, respectively. Based on the results of our prospective cohort study,[19] we assume a loss to follow-up between baseline and the primary outcome measurement (i.e., 3-months follow-up) of 25%, resulting in a total of n=117 randomised patients for UC and IBS, respectively. Assuming that 50% of patients with UC or IBS will meet the inclusion criteria, N=234 patients per diagnostic group will be assessed for eligibility. **Figure 4** shows the anticipated flow of participants throughout the trial. If it should turn out that the power in our study is not sufficient to show a meaningful difference between the two active interventions, the mediation analyses will be consulted to investigate the mechanisms of action.

*Please insert **Figure 4** approximately here*

Statistical methods: The primary analysis and all pre-specified secondary analyses will be conducted in the intention-to-treat sample consisting of all randomised patients. In consideration of the assumed loss-to-follow-up, missing data will be imputed if more than 5% of the data are missing. The number of imputations will be chosen depending on the proportion of missing data.[55] Objective 1: An analysis of covariance will be used to investigate the group differences in the IBS-SSS, adjusted for baseline IBS-SSS. The underlying disease (UC vs. IBS) and sex will be added as additional factors. Assuming no

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interaction effect, this is more effective than analysing both disease conditions independently. If the overall comparison yields a significant difference, pairwise comparisons can be performed without adjustment of the type 1 error because of the closure testing principle. In order to analyse whether effects on persistent gastrointestinal symptoms resulted through changes in expectations or illness-related anxiety, we will conduct mediation analyses. Objective 2: To identify risk factors involved in the persistence of gastrointestinal symptoms and deduct conceptual models of gastrointestinal symptom persistence, we will use longitudinal data from the control group (UC and IBS) and conduct multivariate regression analyses adjusted for the diagnostic group, while taking into account the number of predictors and sample size. To avoid bias, patients from the intervention groups will not be included in these analyses. Objective 3: To compare risk factors across UC and IBS and to identify disease-specific and generic factors for gastrointestinal symptom persistence over time, we will conduct exploratory multivariate regression analyses including all patients from the control group with disease as a factor. We will also compare the results of the disease-specific regression analysis for symptom persistence in UC versus IBS and conduct further exploratory analyses.

Methods against bias: Randomisation will be carried out electronically, stratified by diagnostic group and sex. Patient drop-out will be minimized by contacting patients according to a schedule of repeated contact attempts and by allowing written or telephone data collection if electronically not feasible. Telephone interviews will be performed by trained interviewers who are not involved in the treatment and are observer-blinded with respect to all treatment conditions. The attending clinicians will not be informed about group allocation. Patients in the GUT.EXPECT and GUT.SUPPORT groups will be blinded with regard to their group assignment. Full patient and therapist blinding is not feasible as their active involvement in the intervention is necessary. Both interventions will be manualised. Therapists and interviewers will be trained and supervised regularly. The treatment sessions will be recorded to ensure treatment fidelity. As a manipulation check regarding potentially

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overlapping content, contamination, and carry-over effects between the two interventions, patients will complete a rating scale on treatment content and on subjective treatment mechanisms after the intervention at the end of the primary outcome assessment. Any questions regarding patient exclusions, serious adverse events, and potential study termination will be reviewed by the study's Data Safety and Monitoring Board (DSMB). The DSMB will audit the study annually and assess, independently of the investigators and the sponsor, the accuracy of the study conduct and compliance with ethical conditions. The study was prospectively registered at the ISRTCN registry (ISRCTN30800023).

Feasibility of recruitment: In our previous studies, we were able to successfully recruit patients within our network of cooperating gastroenterologists and clinics.[19 22 35] In addition, social media and three large organisations (Deutsche Reizdarmselbsthilfe e.V., DCCV e.V., MAGDA) will support recruitment. In a feasibility study for this trial,[36] we enrolled N=35 patients within one month, and many patients displayed high interest in the planned intervention study. This again corresponds to the well-documented need of patients with UC and IBS for support and information.[10 56] The format as an online video consultation and the brevity of the intervention will also facilitate patient enrolment.

ETHICS AND DISSEMINATION

Ethical approval: The study protocol was approved by the Ethics Committee of the Hamburg Medical Association on 25 January 2021 (reference number: 2020-10198-BO-ff). The trial will be conducted in accordance with the Declaration of Helsinki, guidelines for Good Clinical Practice, national and local laws. Before inclusion, eligible participants will be informed about the course of the study verbally and in written form and they will provide written informed consent. The data will be stored in pseudonymised form. Any changes to the study protocol will be listed in the study registry and publications.

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Adverse events: To the best of our knowledge, there is no risk for serious adverse events caused by the application of expectation management interventions.[12 38] Nevertheless, patients may develop severe somatic complications of UC or other medical conditions. In such cases, the patient will be informed and advised to initiate appropriate treatment with his or her attending gastroenterologist. In case of an emergency, medical treatment will be offered at the University Medical Centre Hamburg-Eppendorf.

Suicide risk: Patients at risk to commit suicide may be detected; either by the PHQ-9 questionnaire or during the intervention. If patients endorse suicidal ideation in the interview, additional questions will be presented to judge severity and clinical relevance of the suicidal thoughts. A proven algorithm on how to process cases of suicidal ideation (e.g., to contact the physician, to provide suicide prevention hotline numbers or to consider psychiatric treatment in case of severe and acute suicidality) is already available as it was used in our prior studies (e.g., GETFEEDBACK.GP trial[57]). Before the conduct of the trial, the staff will be carefully advised to follow these guidelines.

Documentation and stopping rules: Adverse events will be monitored and reported to the DSMB. Serious adverse events which need to be monitored comprise acute suicidality, suicidal acts, and life threatening deterioration of health status. For the individual patient, the trial procedure will stop, if serious adverse events or withdrawal of informed consent occur. The whole trial will be discontinued, if the team of investigators or the DSMB detect significant associations between study participation and serious adverse events or a differential association between the experimental conditions and adverse events. The trial will also be terminated if procedures to handle adverse events are noncompliant with ethical standards.

Data Safety and Monitoring Board (DSMB): Any questions regarding patient exclusions, serious adverse events and potential study termination will be reported to and reviewed by

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the DSMB. In addition, the DSMB will annually monitor the study. Where appropriate, recommendations will be made to continue, modify or terminate the study or to unmask participants in case of serious adverse events.

Possible disadvantages of participating in the study: Since all three groups of the proposed RCT continue to receive their regular medical treatment, there are most probably no disadvantages for participants compared to non-participants. The experimental groups have the advantage that the interventions tested could have a positive effect on their persistent gastrointestinal symptoms.

Data sharing: In accordance with the ethics committee approval and the German Research Foundation (DFG) guidelines for the handling of research data adopted in 2015, de-identified individual patient data will be made publicly available. Data sharing will follow the *FAIR* Data Principles (Findable, Accessible, Interoperable and Reusable) and international naming conventions (e.g., Systematized Nomenclature of Medicine) to maximise transparency and scientific reproducibility. According to the WHO Statement on Public Disclosure of Clinical Trials (www.who.int/ictrp/results/reporting/en/), the main findings will be submitted for publication in a peer-reviewed journal within 12 months of study completion.

Conclusion

To the best of our knowledge, this is the first study to test the mechanisms of symptom persistence in two gastrointestinal diseases in parallel. The results of our analyses for hypothesis 1 will allow us to draw conclusions regarding the efficacy and mechanisms of a targeted expectation management intervention. If the effectiveness of the intervention via the proposed modes of action can be proven, it will serve as a model for the development of personalised interventions in UC and IBS and for cross-validation studies in other conditions. If the results either do not confirm our hypotheses or show unclear differences between the two active interventions, the results of the mediation analyses and the exploratory analyses

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will provide valuable insights into risk factors for persistent gastrointestinal symptoms. The confirmation or falsification of hypothesis 2 will significantly contribute to a better understanding of the development of persistent somatic symptoms in UC and IBS and will clarify which risk factors and mechanisms are disease-specific and which are valid across diseases. Data regarding mechanisms of symptom persistence from the control group will be pooled and compared across all RU SOMACROSS projects (objective 3). We expect that the study will promote the development of more effective interventions for patients with persistent somatic symptoms and will thus have a clinical and potentially socio-economic impact in the long term.

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Author contributions

Bernd Löwe and Ansgar W. Lohse are principal investigators on the study, Yvonne Nestoriuc and Viola Andresen contribute as co-applicants to the study. Antonia Zapf and Eik Vettorazzi provide statistical expertise in clinical trial design. Bernd Löwe drafted the first version of the study protocol. All authors, i.e., Viola Andresen, Sina Hübener, Bernd Löwe, Ansgar W. Lohse, Kerstin Maehder, Yvonne Nestoriuc, Luisa Peters, Eik Vettorazzi, and Antonia Zapf, contributed to the refinement of the study protocol, read and approved the final version.

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Competing interests

None

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REFERENCES

1. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018;390:2769-78.
2. Gracie DJ, Guthrie EA, Hamlin PJ, et al. Bi-directionality of brain-gut interactions in patients with inflammatory bowel disease. *Gastroenterology* 2018;154:1635-46.e3.
3. Henriksen M, Høivik ML, Jelsness-Jørgensen LP, et al. Irritable bowel-like symptoms in ulcerative colitis are as common in patients in deep remission as in inflammation: Results from a population-based study [the IBSEN study]. *Journal of Crohn's & colitis* 2018;12:389-93.
4. Elsenbruch S, Enck P. Placebo effects and their determinants in gastrointestinal disorders. *Nature Reviews Gastroenterology & Hepatology* 2015;12:472-85.
5. Mikocka-Walus A, Knowles SR, Keefer L, et al. Controversiesrevisited: A systematic review of the comorbidity of depression and anxiety with inflammatory bowel diseases. *Inflammatory bowel diseases* 2016;22:752-62.
6. Abautret-Daly Á, Dempsey E, Parra-Blanco A, et al. Gut-brain actions underlying comorbid anxiety and depression associated with inflammatory bowel disease. *Acta Neuropsychiatrica* 2018;30:275-96.
7. Tarricone I, Regazzi MG, Bonucci G, et al. Prevalence and effectiveness of psychiatric treatments for patients with IBD: A systematic literature review. *J Psychosom Res* 2017;101:68-95.
8. Gracie DJ, Irvine AJ, Sood R, et al. Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: a systematic review and meta-analysis. *The Lancet Gastroenterology & Hepatology* 2017;2:189-99.
9. Wynne B, McHugh L, Gao W, et al. Acceptance and commitment therapy reduces psychological stress in patients with inflammatory bowel diseases. *Gastroenterology* 2019;156:935-45.e1.
10. Klag T, Mazurak N, Fantasia L, et al. High demand for psychotherapy in patients with inflammatory bowel disease. *Inflammatory bowel diseases* 2017;23:1796-802.
11. Kube T, Glombiewski JA, Rief W. Using different expectation mechanisms to optimize treatment of patients with medical conditions: A systematic review. *Psychosom Med* 2018;80:535-43.
12. Rief W, Shedden-Mora MC, Laferton JA, et al. Preoperative optimization of patient expectations improves long-term outcome in heart surgery patients: results of the randomized controlled PSY-HEART trial. *BMC Medicine* 2017;15:4.

For peer review only

13. Pan Y, Meister R, Löwe B, et al. Open-label placebos for menopausal hot flushes: a randomized controlled trial. *Sci Rep* 2020;10:20090.

14. Roscoe JA, O'Neill M, Jean-Pierre P, et al. An exploratory study on the effects of an expectancy manipulation on chemotherapy-related nausea. *J Pain Symptom Manage* 2010;40:379-90.

15. Halland M, Saito YA. Irritable bowel syndrome: new and emerging treatments. *BMJ* 2015;350:h1622.

16. Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide prevalence and burden of functional gastrointestinal disorders, results of Rome Foundation Global Study. *Gastroenterology* 2020

17. Lacy BE, Patel NK. Rome Criteria and a Diagnostic Approach to Irritable Bowel Syndrome. *Journal of Clinical Medicine* 2017;6

18. Enck P, Aziz Q, Barbara G, et al. Irritable bowel syndrome. *Nature reviews Disease primers* 2016;2:16014.

19. Löwe B, Lohse A, Andresen V, et al. The development of irritable bowel syndrome: a prospective community-based cohort study. *Am J Gastroenterol* 2016;111:1320-9.

20. Schmid J, Langhorst J, Gaß F, et al. Placebo analgesia in patients with functional and organic abdominal pain: a fMRI study in IBS, UC and healthy volunteers. *Gut* 2015;64:418-27.

21. Zamani M, Alizadeh-Tabari S, Zamani V. Systematic review with meta-analysis: the prevalence of anxiety and depression in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 2019;50:132-43.

22. Althaus A, Broicher W, Wittkamp P, et al. Determinants and frequency of irritable bowel syndrome in a German sample. *Z Gastroenterol* 2016;54:217-25.

23. Ford AC, Lacy BE, Harris LA, et al. Effect of Antidepressants and psychological therapies in irritable bowel syndrome: An Updated Systematic Review and Meta-Analysis. *Am J Gastroenterol* 2019;114:21-39.

24. Laird KT, Tanner-Smith EE, Russell AC, et al. Short-term and long-term efficacy of psychological therapies for irritable bowel syndrome: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2016;14:937-47.e4.

25. Ljótsson B, Hesser H, Andersson E, et al. Mechanisms of change in an exposure-based treatment for irritable bowel syndrome. *J Consult Clin Psychol* 2013;81:1113-26.

For peer review only

26. Lackner JM, Jaccard J. Specific and common mediators of gastrointestinal symptom improvement in patients undergoing education/support vs. cognitive behavioral therapy for irritable bowel syndrome. *J Consult Clin Psychol* 2021;89:435-53.
27. Flik CE, Bakker L, Laan W, et al. Systematic review: The placebo effect of psychological interventions in the treatment of irritable bowel syndrome. *World J Gastroenterol* 2017;23:2223-33.
28. Windgassen S, Moss-Morris R, Chilcot J, et al. The journey between brain and gut: A systematic review of psychological mechanisms of treatment effect in irritable bowel syndrome. *British Journal of Health Psychology* 2017;22:701-36.
29. Radziwon CD, Lackner JM. Cognitive Behavioral Therapy for IBS: How useful, how often, and how does it work? *Curr Gastroenterol Rep* 2017;19:49.
30. Reme SE, Stahl D, Kennedy T, et al. Mediators of change in cognitive behaviour therapy and mebeverine for irritable bowel syndrome. *Psychol Med* 2011;41:2669-79.
31. Spiller R, Major G. IBS and IBD - separate entities or on a spectrum? *Nature reviews Gastroenterology & Hepatology* 2016;13:613-21.
32. Gracie DJ, Ford AC. IBS-like symptoms in patients with ulcerative colitis. *Clinical and experimental Gastroenterology* 2015;8:101-9.
33. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. *The American Journal Of Gastroenterology* 2012;107:1474.
34. Löwe B, Andresen V, Van den Bergh O, et al. Persistent SOMAtic symptoms ACROSS diseases — from risk factors to modification: scientific framework and overarching protocol of the interdisciplinary SOMACROSS research unit (RU 5211). *BMJ Open* 2022;12:e057596.
35. Löwe B, Andresen V, Fraedrich K, et al. Psychological outcome, fatigue, and quality of life after infection with shiga toxin-producing Escherichia coli O104. *Clin Gastroenterol Hepatol* 2014;12:1848-55.
36. Uhlenbusch N, Manthey C, Nestoriuc Y, et al. Psychosocial support for people with ulcerative colitis and irritable bowel syndrome: a feasibility study on need, focus and viability [Psychosoziale Unterstützung von Menschen mit Colitis ulcerosa und Reizdarmsyn-drom: eine Machbarkeitsstudie zu Bedarf, Fokus und Durchführbarkeit]. *Psychother Psych Med* 2022:1–10 (online ahead of print).
37. Betz C, Mannsdörfer K, Bischoff SC. [Validation of the IBS-SSS]. *Z Gastroenterol* 2013;51:1171-6.

For peer review only

38. Shedden-Mora MC, Pan Y, Heisig SR, et al. Optimizing expectations about cancer treatment: Results of the randomized controlled PSY-BREAST trial. *Clinical Psychology in Europe* 2020;2:e2695.

39. Pan Y, Meister R, Löwe B, et al. Non-concealed placebo treatment for menopausal hot flushes: Study protocol of a randomized-controlled trial. *Trials* 2019;20:508.

40. Pan Y, Heisig SR, von Blanckenburg P, et al. Facilitating adherence to endocrine therapy in breast cancer: stability and predictive power of treatment expectations in a 2-year prospective study. *Breast Cancer Research and Treatment* 2018;168:667-77.

41. Nestoriuc Y, von Blanckenburg P, Schuricht F, et al. Is it best to expect the worst? Influence of patients' side-effect expectations on endocrine treatment outcome in a 2-year prospective clinical cohort study. *Ann Oncol* 2016;27:1909-15.

42. Kirsch I. Response expectancy theory and application: A decennial review. *Appl Prev Psychol* 1997;6:69-79.

43. Schwarzer R. Optimism, Vulnerability, and self-beliefs as health-related cognitions: A systematic overview. *Psychol Health Med* 1994;9:161–80.

44. Cameron LDL, H. The self-regulation of health and illness behavior: New York: Routledge 2003.

45. Laferton JA, Kube T, Salzmann S, et al. Patients' Expectations Regarding Medical Treatment: A Critical Review of Concepts and Their Assessment. *Front Psychol* 2017;8:233.

46. Volz MS, Farmer A, Siegmund B. Reduction of chronic abdominal pain in patients with inflammatory bowel disease through transcranial direct current stimulation: a randomized controlled trial. *Pain* 2016;157:429-37.

47. Ishaque SM, Khosruzzaman SM, Ahmed DS, et al. A randomized placebo-controlled clinical trial of a multi-strain probiotic formulation (Bio-Kult(R)) in the management of diarrhea-predominant irritable bowel syndrome. *BMC Gastroenterology* 2018;18:71.

48. Kroenke K, Spitzer RL, Williams JB, et al. The Patient Health Questionnaire somatic, anxiety, and depressive symptom scales: a systematic review. *Gen Hosp Psychiatry* 2010;32:345-59.

49. Walmsley RS, Ayres RC, Pounder RE, et al. A simple clinical colitis activity index. *Gut* 1998;43:29-32.

50. de Jong MJ, Huibregtse R, Masclee AAM, et al. Patient-Reported outcome measures for use in clinical trials and clinical practice in inflammatory bowel diseases: A Systematic Review. *Clin Gastroenterol Hepatol* 2018;16:648-63.e3.

For peer review only

51. Hiller W, Rief W. Internationale Skalen für Hypochondrie: Deutschsprachige Adaptation des Whiteley-Index (WI) und der Illness Attitude Scales (IAS). Göttingen: Hogrefe 2004.

52. Toussaint A, Hüsing P, Kohlmann S, et al. Detecting DSM-5 somatic symptom disorder: criterion validity of the Patient Health Questionnaire-15 (PHQ-15) and the Somatic Symptom Scale-8 (SSS-8) in combination with the Somatic Symptom Disorder - B Criteria Scale (SSD-12). *Psychol Med* 2020;50:324-33.

53. Rief W, Burton C, Frostholm L, et al. Core outcome domains for clinical trials on somatic symptom disorder, bodily distress disorder, and functional somatic syndromes: european network on somatic symptom disorders recommendations. *Psychosom Med* 2017;79:1008-15.

54. Alberts J, Löwe B, Glahn MA, et al. Development of the generic, multidimensional Treatment Expectation Questionnaire (TEX-Q) through systematic literature review, expert surveys and qualitative interviews. *BMJ Open* 2020;10:e036169.

55. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in Medicine* 2011;30:377-99.

56. Flik CE, van Rood YR, de Wit NJ. Systematic review: knowledge and educational needs of patients with irritable bowel syndrome. *Eur J Gastroenterol Hepatol* 2015;27:367-71.

57. Kohlmann S, Lehmann M, Eisele M, et al. Depression screening using patient-targeted feedback in general practices: study protocol of the German multicentre GET.FEEDBACK.GP randomised controlled trial. *BMJ Open* 2020;10:e035973.

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TABLE

Table 1: Therapeutic topics of the experimental intervention 1 (GUT.EXPECT + SC)

1st Online-Session: Living with a chronic bowel disease
- Structured assessment of patient's illness related anxieties and dysfunctional symptom expectations - Psychoeducation on the biopsychosocial model and the significance of illness-related anxieties and symptom expectations - Guided imagery - Worksheets and homework
2nd Online-Session: Developing helpful thoughts
- Psychoeducation on the ABC model* - Cognitive restructuring of an individual illness related anxiety or dysfunctional symptom expectation - Development of an individual tool box - Worksheets and homework
3rd Online-Session: (Re)try behaviour
- Psychoeducation on the vicious circle of anxiety and avoidance and safety behaviours - Planning a behavioural experiment - Complementing the individual tool box - Worksheets and homework
Booster Online-Session
- Evaluation of the behavioural experiment - Recapitulation of the sessions - Dealing with difficulties - Deepening of the strategies learned - Summary of the tool box - Worksheets

*ABC model: According to the **ABC** model, initially introduced by Albert Ellis, an **A**ctivating event leads to potentially irrational **B**eliefs. These beliefs create emotional, behavioural, physical and cognitive **C**onsequences. The ABC model is a cognitive behavioural technique that can be used to restructure irrational beliefs and cognitions.

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FIGURE LEGENDS

Figure 1. Commonalities and differences between ulcerative colitis and irritable bowel syndrome

Figure 2. Hypothetical cross-disease model of pathomechanisms for persistent gastrointestinal symptoms in IBS and UC. Illness anxiety and dysfunctional expectations as hypothesised mechanisms of action for persistent gastrointestinal symptoms are marked in red.

Figure 3. Study design and outcome assessment. GUT.EXPECT = expectation management intervention; GUT.SUPPORT = supportive intervention

Figure 4. Anticipated flow of participants through the course of the study. *Outcomes after 6 and 12 months are secondary and were not included in the sample size estimation. GUT.EXPECT = expectation management intervention; GUT.SUPPORT = supportive intervention

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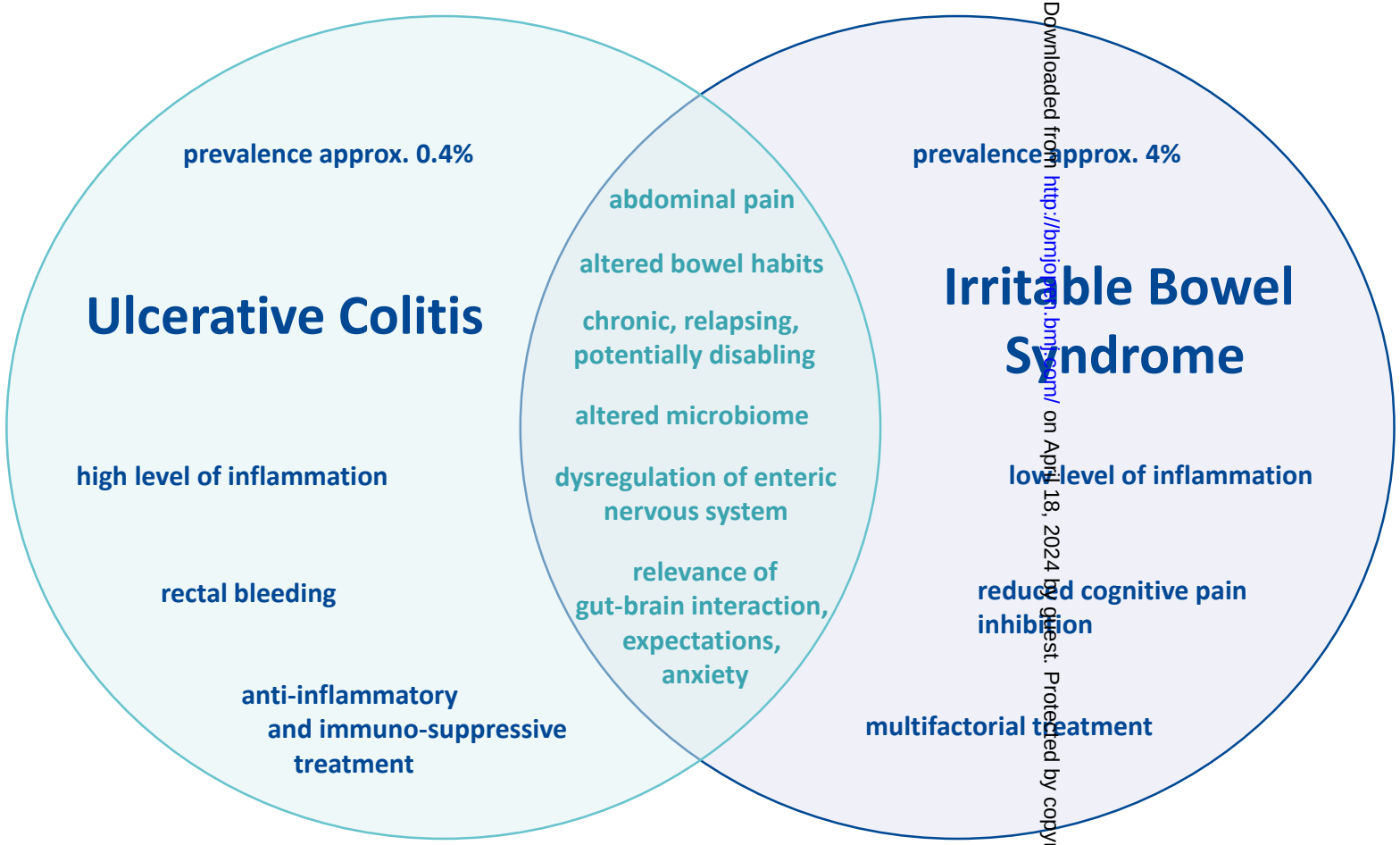

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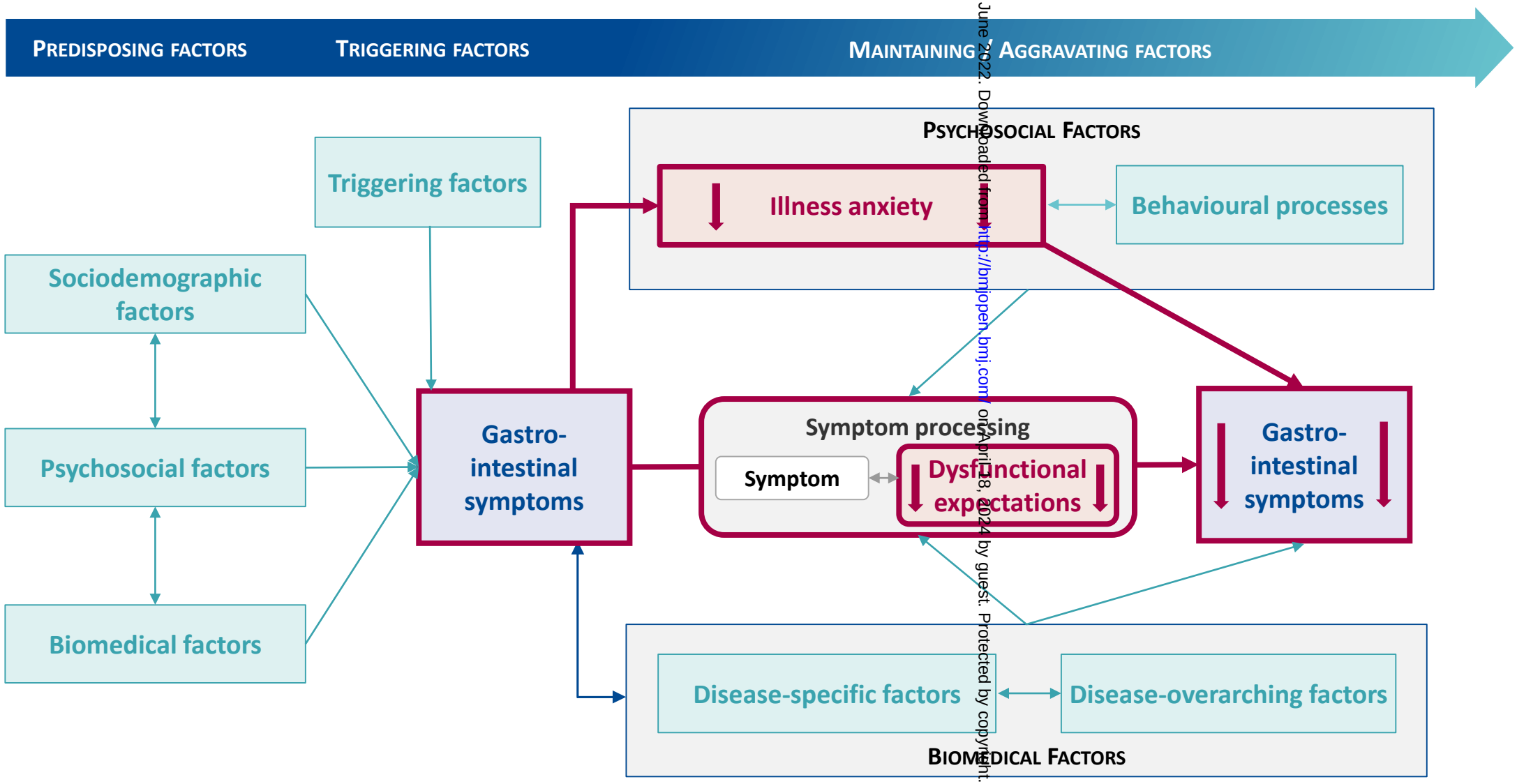

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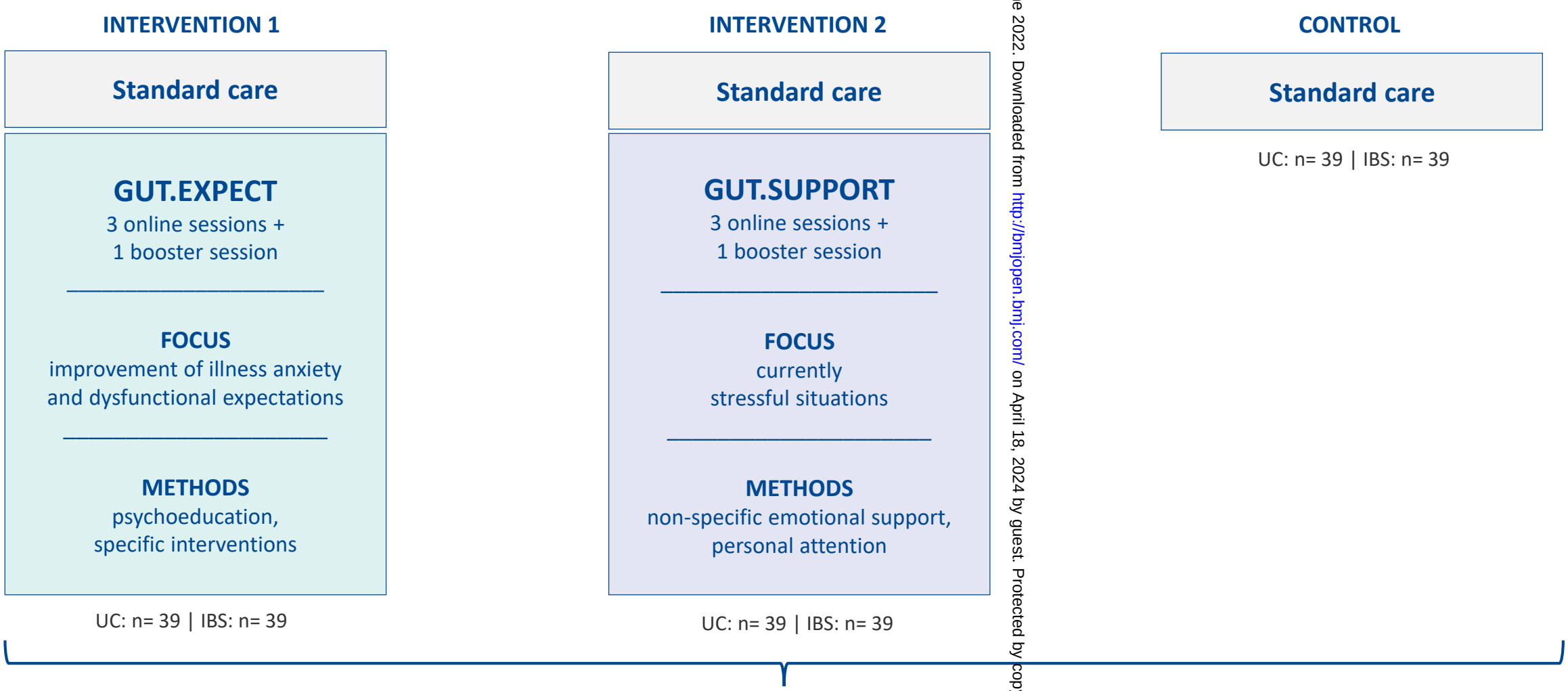

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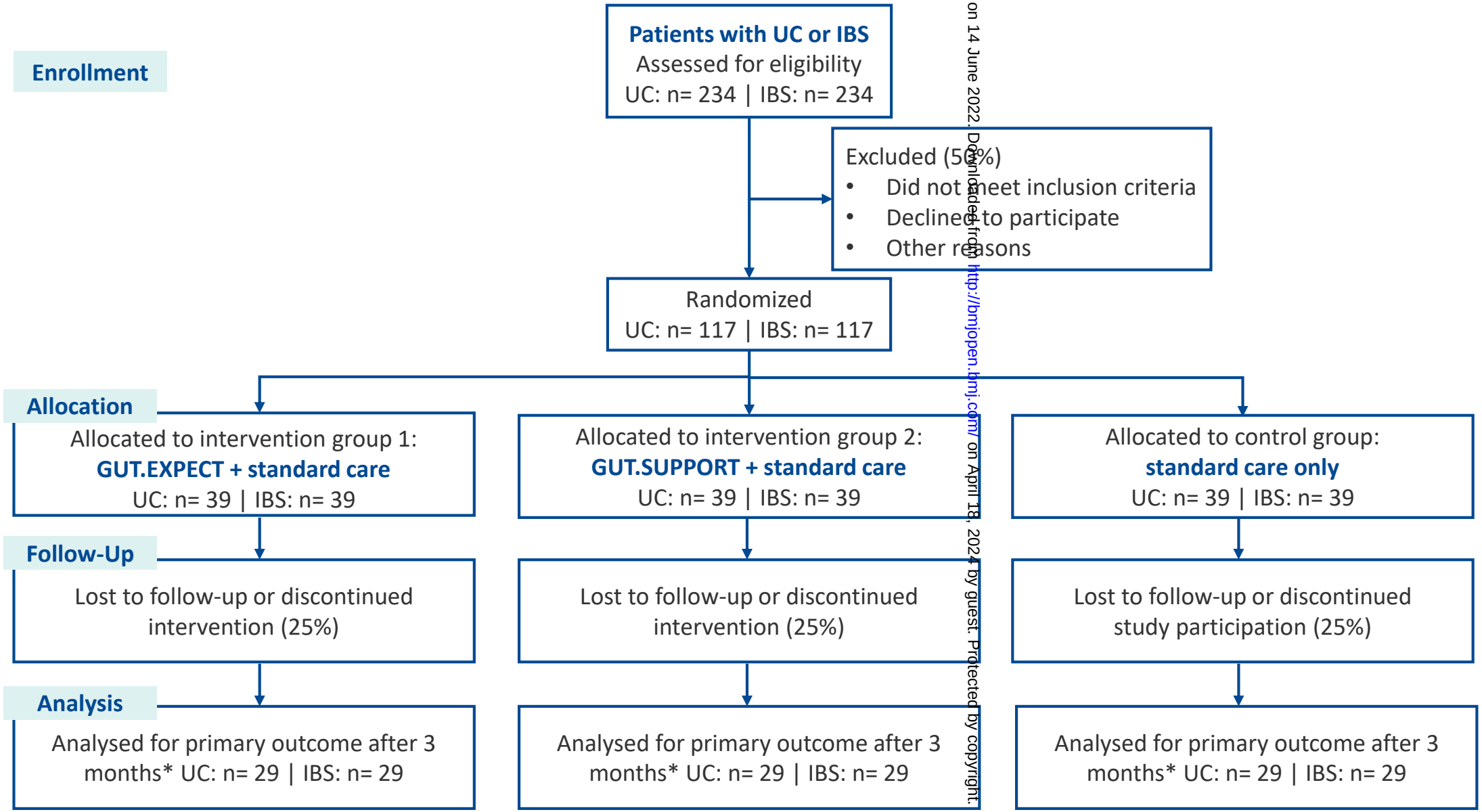

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 21
	5b	Name and contact information for the trial sponsor	22
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17, 18, 21

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-9
	6b	Explanation for choice of comparators	11-13
Objectives	7	Specific objectives or hypotheses	9, 10
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	11, 12
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12, 13, Table 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	17, 18
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	16
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11, 12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13, 14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11-14, Fig, 3, Fig 4

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11, 17
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11, 16, 17
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11, 16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	17, 18
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15, 16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15, 16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15, 16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17, 18, 21
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16-18
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17,18
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17, 18

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17, 18
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17, 18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	19
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	attached as a supplementary file
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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