

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

Bernd Löwe <sup>1</sup>, Yvonne Nestoriuc,<sup>2</sup> Viola Andresen,<sup>3</sup> Eik Vettorazzi,<sup>4</sup> Antonia Zapf,<sup>4</sup> Sina Hübener,<sup>5</sup> Kerstin Maehder,<sup>1</sup> Luisa Peters,<sup>1</sup> Ansgar W Lohse<sup>5</sup>

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For numbered affiliations see end of article.

## Correspondence to

Bernd Löwe; [b.loewe@uke.de](mailto:b.loewe@uke.de)

## 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, three-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 (SC, intervention 1), non-specific supportive treatment in addition to SC (intervention 2) or SC only (control). Both active intervention groups will comprise three individual online consultation sessions and a booster session after 3 months. The primary outcome is baseline to postinterventional change in gastrointestinal symptom severity.

**Ethics and dissemination** The study was approved by the Ethics Committee of the Hamburg Medical Association (2020-10198-B0-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. Furthermore, 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.

## 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 three-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 indicated no studies, which aim at alleviating persistent gastrointestinal symptoms in patients with ulcerative colitis and irritable bowel syndrome 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.

## 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

#### *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%–0.4% of the general population in Western Europe.<sup>1</sup> 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.<sup>2</sup> About 25% of UC patients develop persistent IBS-like symptoms even in endoscopic remission.<sup>3</sup> Notably, experimental placebo and nocebo studies indicate an important role of expectations and conditioning processes in the development and persistence of chronic gastrointestinal symptoms.<sup>4</sup>

#### *Psychological factors*

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

#### *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.<sup>11–14</sup> Recently, a review paper has nicely summarised the ‘power’ of expectations and conditioning processes in shaping gastrointestinal symptoms in gastrointestinal diseases.<sup>4</sup> 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

#### *Clinical presentation, aetiology and risk factors*

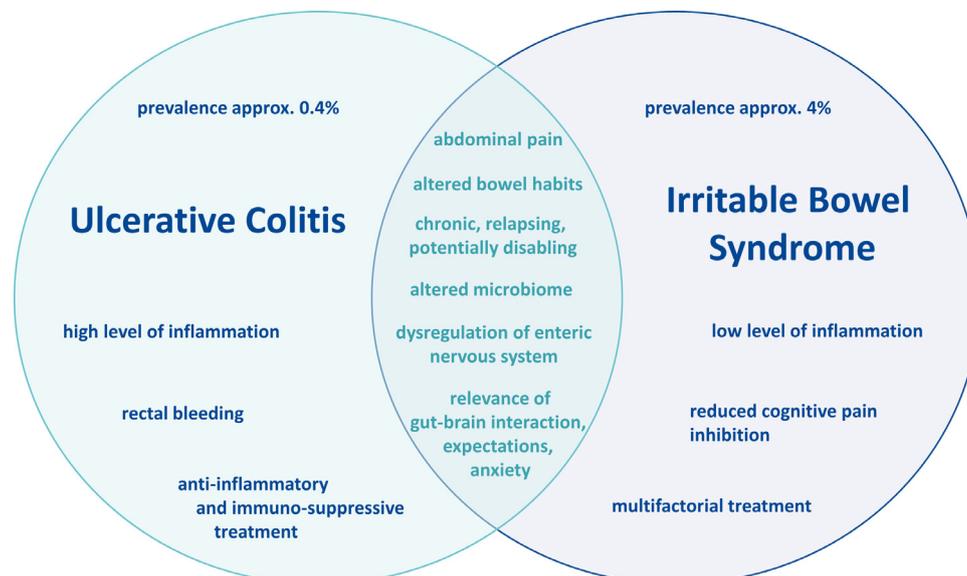
IBS is conceptualised as a disorder of gut–brain functions with complex and multifactorial aetiology<sup>15</sup> that has a worldwide prevalence of 4.1% (Rome IV criteria).<sup>16</sup> According to the Rome IV criteria, the main symptom of IBS is recurring abdominal pain associated with defecation and/or change in frequency of bowel movements and/or consistency of stool.<sup>17</sup> Patients experience substantial functional impairment and impaired quality of life.<sup>18</sup> 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.<sup>15,18–20</sup>

#### *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 with healthy subjects.<sup>21</sup> 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 with those without IBS.<sup>22</sup> Recent systematic reviews have found that both psychotherapy and antidepressants are effective in sustainably improving IBS symptoms and daily functioning.<sup>23,24</sup> Current research on the mechanisms of change in psychotherapy indicate that directly targeting gastrointestinal symptom-specific anxiety in particular seems promising.<sup>25,26</sup> 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.<sup>27,28</sup> For a detailed description of cognitive behavioural therapy (CBT) for IBS, we refer to a recent review.<sup>29</sup>

#### *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.<sup>30</sup> A systematic search in PubMed and the ICTRP indicated that so far no study has investigated



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

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.<sup>31</sup> 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.<sup>20–32</sup> Subjects with UC also have a higher likelihood of meeting IBS criteria than subjects without UC.<sup>32–33</sup> 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.

#### 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:

##### 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

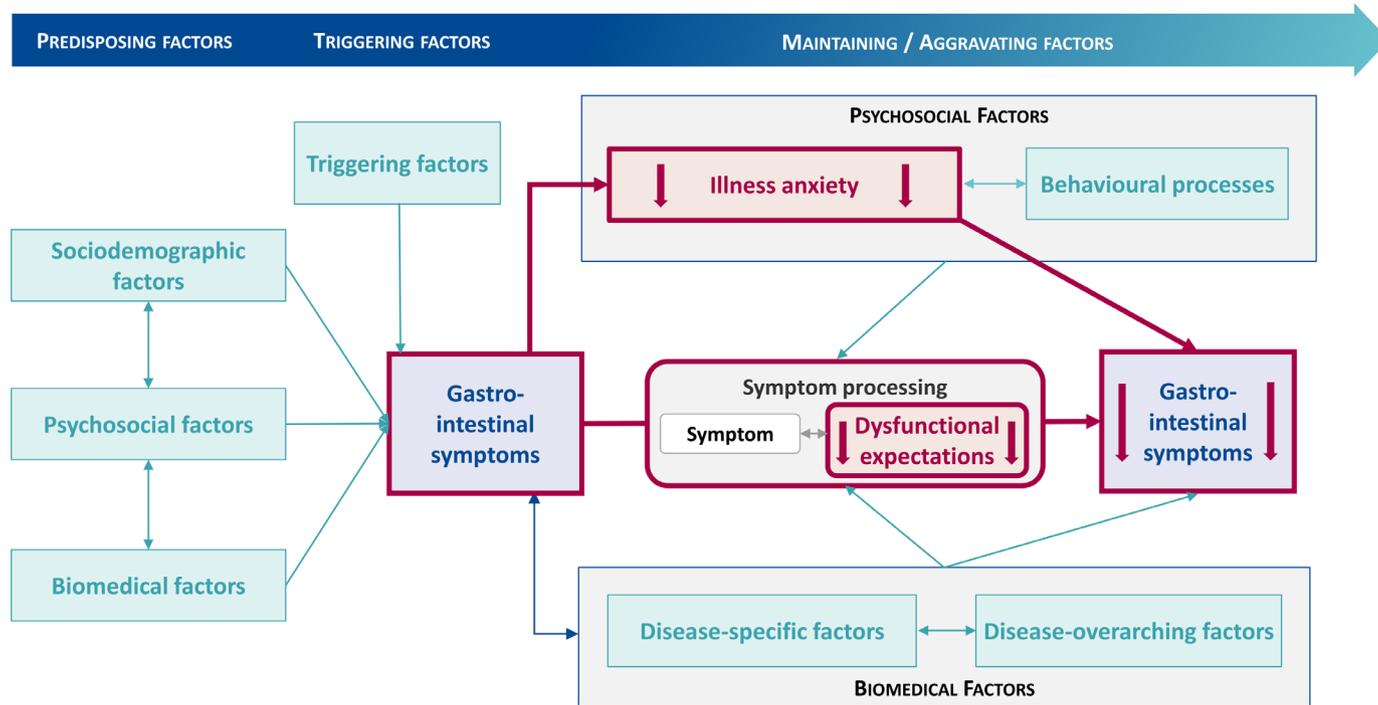
In addition to illness-related anxiety and dysfunctional symptom expectations, further biological, psychological and social factors contributing to the persistence of gastrointestinal symptoms in both UC and IBS can be identified.

#### METHODS AND ANALYSIS

##### Study design

##### Study design and rationale

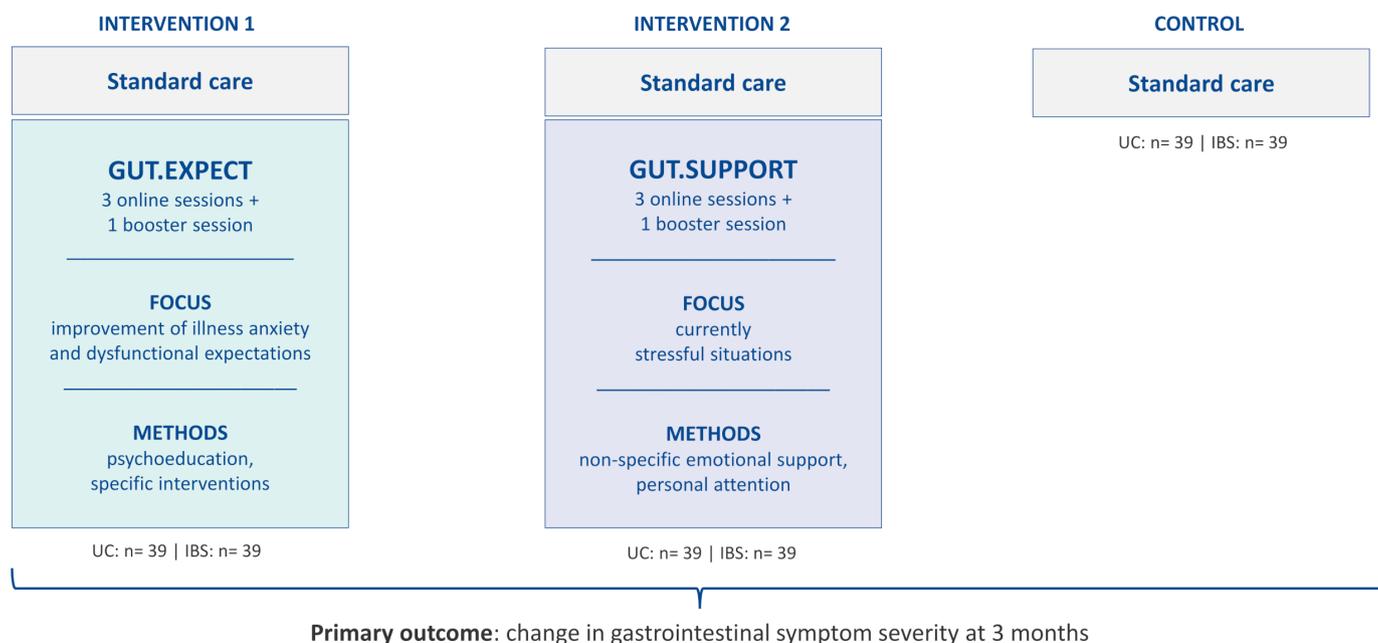
In order to identify the effect of a targeted modification of illness-related anxiety and dysfunctional symptom expectations on persistent gastrointestinal symptoms and to differentiate this effect from general modes of action, a randomised comparison between a specifically treated group, a group treated 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 with no intervention and to investigate objectives 2 and 3. Thus, we will use the design of a three-arm randomised controlled trial (RCT), in which 33% of each disease group will undergo targeted expectation management in addition



**Figure 2** Hypothetical cross-disease model of pathomechanisms for persistent gastrointestinal symptoms in ulcerative colitis and irritable bowel syndrome. Illness anxiety and dysfunctional expectations as hypothesised mechanisms of action for persistent gastrointestinal symptoms are marked in red.

to 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.<sup>34</sup>



**Figure 3** Study design and outcome assessment. GUT.EXPECT, expectation management intervention; GUT.SUPPORT, supportive intervention. UC, ulcerative colitis; IBS, irritable bowel syndrome

## Setting

For recruitment, we will use our outpatient clinics as well as our established network of cooperating gastroenterologists.<sup>19 22 35</sup> 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,<sup>36</sup> 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.<sup>36</sup> 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 IBS-Severity Scoring System (IBS-SSS ≥ 175),<sup>37</sup> 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.

## 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 SC. The manualised intervention primarily aims at optimising expectations about symptoms and treatment outcome and at reducing illness-related anxiety.<sup>19 28</sup> 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,<sup>12 38</sup> and other previous studies.<sup>11 39–41</sup> The theoretical basis of the intervention are the Response Expectancy Theory,<sup>42</sup> the Social Cognitive Theory,<sup>43</sup> the Common Sense Model of Self-Regulation of Health and Illness,<sup>44</sup> as well as the Integrative Model of Patients' Expectations Undergoing Medical Treatment.<sup>45</sup> The structure of the intervention in terms of length and online format is based on preferences expressed by patients in our feasibility study.<sup>36</sup> The intervention consists of three individual online video consultation sessions in intervals of 2 weeks each and a booster session after 3 months, with each session lasting 45 min. The cognitive-behavioural

## Box 1 Therapeutic topics of the experimental intervention 1 (GUT.EXPECT+SC)

### First Online-Session: Living with a chronic bowel disease

- ⇒ Structured assessment of patient's illness-related anxiety and dysfunctional symptom expectations.
- ⇒ Psychoeducation on the biopsychosocial model and the significance of illness-related anxiety and symptom expectations.
- ⇒ Worksheets and homework.

### Second 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.
- ⇒ Guided imagery.
- ⇒ Worksheets and homework.

### Third 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.

techniques from the PSY-HEART and PSY-BREAST expectation modification interventions<sup>12 38</sup> 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 three intervention sessions and the booster session are shown in **box 1**. Homework will be 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.

### 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, that is, 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.<sup>34</sup>

## 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 postinterventional change in gastrointestinal symptom severity (3 months follow-up). Gastrointestinal symptom severity will be assessed using the IBS-SSS, which is applicable in both IBS and UC and validated in English and German in various forms of intestinal diseases.<sup>37 46 47</sup> On a scale of 0–500, 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.<sup>37</sup>

### Secondary outcomes

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

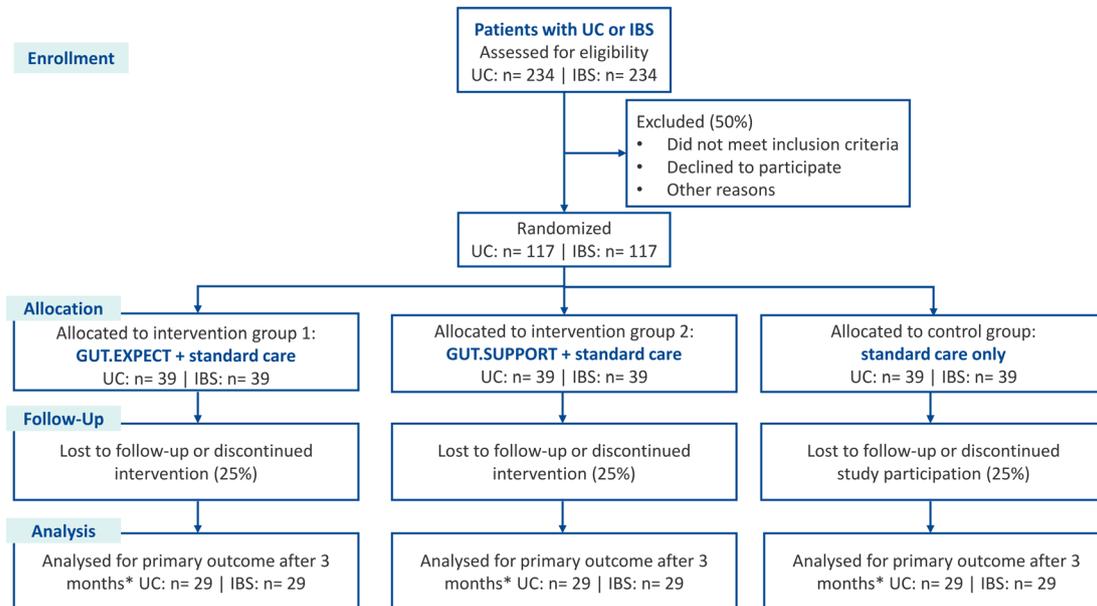
### Sample size

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 SD of 75 points on the IBS-SSS.<sup>47</sup> 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,<sup>19</sup> we assume a loss to follow-up between baseline and the primary outcome measurement (ie, 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.

### Statistical methods

The primary analysis and all prespecified 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.<sup>55</sup>

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)



**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; UC, ulcerative colitis; IBS, irritable bowel syndrome.

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 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 minimised 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 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.

#### Feasibility of recruitment

In our previous studies, we were able to successfully recruit patients within our network of cooperating gastroenterologists and clinics.<sup>19 22 35</sup> 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,<sup>36</sup> we enrolled n=35 patients within 1 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.<sup>10 56</sup> 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.<sup>12 38</sup> 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 (eg, 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 (eg, GETFEEDBACK.GP trial).<sup>57</sup> 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 non-compliant with ethical standards.

## Data Safety and Monitoring Board

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 with 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, deidentified 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 (eg, Systematised 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/](http://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.

#### Author affiliations

<sup>1</sup>Department of Psychosomatic Medicine and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

<sup>2</sup>Department of Psychology, Helmut Schmidt University, University of the Federal Armed Forces, Hamburg, Germany

<sup>3</sup>Medical Clinic, Israelitic Hospital, Hamburg, Germany

<sup>4</sup>Department of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

<sup>5</sup>Department of Medicine I, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

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#### ORCID iD

Bernd Löwe <http://orcid.org/0000-0003-4220-3378>

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