Statistical Analysis Plan

SOMA.GUT-RCT

Persistence of gastrointestinal symptoms in irritable bowel syndrome and ulcerative colitis: mechanisms and modifications

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Version history

Version	Date	Section number changed	Description/Changes made
1.0	19-SEP-2024		Final version, signed
0.9	18-SEP-2024	5.4	Mediation analysis revised
0.3	12-SEP-2024	5.4; various	Prefinal version: Mediation analysis updated; Proposed changes incorporated throughout the document
0.2	10-SEP-2024		Update after Review
0.1	03-MAY-2024		First draft

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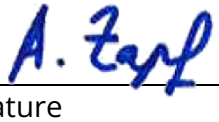

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Abbreviations

ACE-D	Adverse Childhood Experiences Qestionnaire
BFI-10	Big Five Inventory-10
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EFS	Evalued for Safety Set
ERQ	Emotion Regulation Questionnaire
FAS	full analysis set
FIML	full information maximum likelihood
IBS	Irritable bowel syndrome
IBS-SSS	irritable bowel syndrome severity scoring system
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-treat
NRS	Numeric rating scale
PANAS	Positive and Negative Affectivity Schedule
PHQ-15	Patient Health Questionnaire-15
PM	percentage mediated
PP	Per Protocol
PSS10	Perceived Stress Scale
RCT	Randomised Controlled Trial
SAP	Statistical Analysis Plan
SC	Standard Care
SCCAI	Simple Clinical Colitis Activity Index
SD	Standard Deviation
SSD-12	Somatic Symptom Disorder - B Criteria Scale
TAS-20	Toronto Alexithymia Scale
TE	treatment effect
TEX-Q	Treatment Expectation Questionnaire
TNF-α	tumor necrosis factor
UC	Ulcerative colitis
WI-7	Whiteley-Index Short version

1 Introduction

This Statistical Analysis Plan (SAP) is based on the published study protocol (Löwe, et al., 2022)[18] and follows the guideline for statistical analysis plans (Gamble, et al., 2017).[9]
Some points of the statistical methods and of the study design are already described in the study protocol. This Statistical Analysis Plan (SAP) aims to further specify the procedures and statistical methods applied during the final analysis of the study data.

1.1 Background and rationale

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.

1.2 Objectives

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.

2 Study Methods

2.1 Trial design

SOMA.GUT-RCT is a three-arm randomised controlled trial (RCT) in 117 patients with UC and 117 patients with IBS, totalling 234 patients. 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, to investigate further risk factors and to allow comparisons of risk factors across diseases. Thus, we will use the design of a three-arm randomised controlled trial, 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 1). 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.[16]

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.

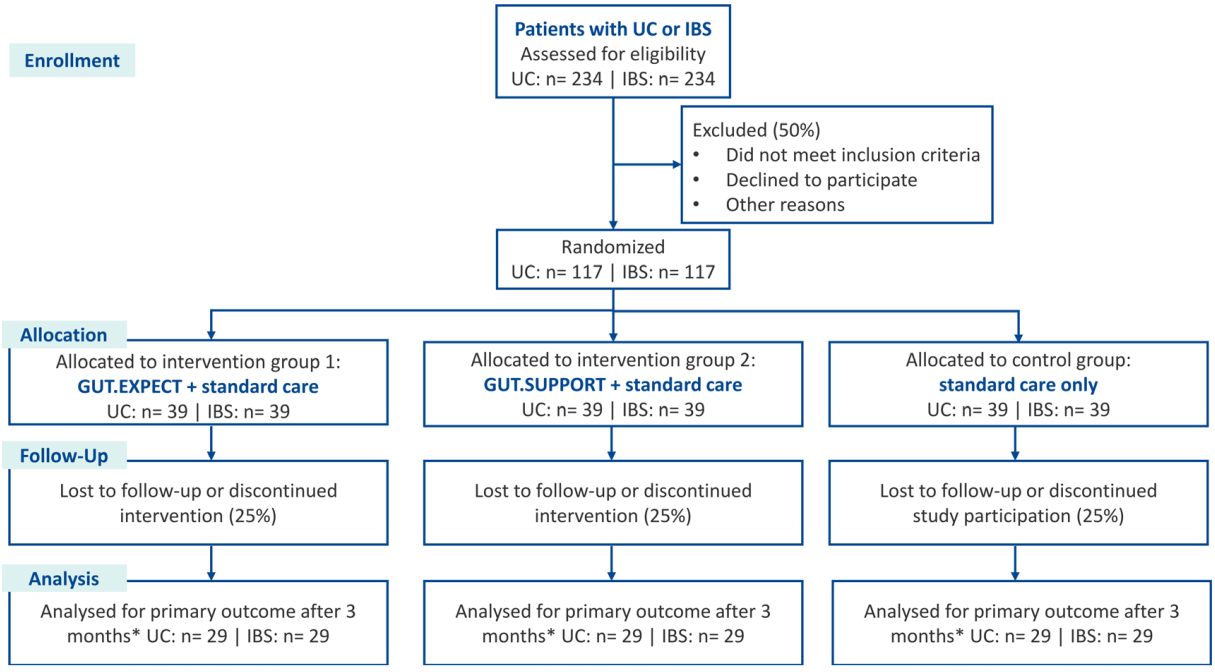

*Figure 1: Planned flow of participants through the course of the study. *Outcomes after 6 and 12 months are secondary and were not included in the sample size estimation. GUT.EXPECT, expectation management intervention; GUT.SUPPORT, supportive intervention*

2.2 Randomization

Patients were randomized in a 1:1:1 ratio using central block-wise randomization with variable block length to targeted expectation management and standard care, non-specific supportive treatment and standard care or to standard care only (control). The randomization is performed directly after baseline data collection.

2.3 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 irritable bowel syndrome severity scoring system (IBS-SSS).[11] 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 (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.

2.4 Framework

SOMA.GUT-RCT is planned to show that persistent gastrointestinal symptoms in UC and IBS can be improved by modifying dysfunctional symptom expectations and illness-related anxiety using expectation management strategies.

2.5 Statistical interim analyses and stopping guidance

No interim analyses will be conducted.

2.6 Timing of final analysis

The final analysis of the primary outcome will take place after the database has been reviewed for completeness and accuracy and database lock.

2.7 Timing of outcome assessments

The primary outcome was assessed at baseline and after 3 months follow-up. Secondary endpoints will be assessed at 6 weeks, 3 months, 6 months and 12 months after baseline.

3 Statistical Principles

3.1 Confidence intervals and *P* values

All applicable statistical tests will be two-sided and will be performed using a two-sided 5% significance level. Analyses of secondary outcomes will be performed exploratory, without adjustment for multiplicity. All confidence intervals presented will be 95% and two-sided.

3.2 Adherence and protocol deviations

At any point, patients in all three groups were able to quit the study.

3.3 Analysis populations

3.3.1 Full Analysis Set (FAS)

The primary analysis is based on the full analysis set (FAS). It is as complete as possible and as close as possible to the Intention-To-Treat (ITT) principle which includes all randomized patients, as belonging to their randomization arm, regardless of whether they refused therapy, or whether other protocol violations are known.

3.3.2 Intention to treat Population (ITT)

The primary analysis population is the ITT (intention to treat) population. The ITT population consists of all patients randomized.

3.3.3 Per Protocol population (PP)

The Per Protocol population includes all patients randomized who have no major protocol violation and for whom data is available from the follow-up measurement point.

Major protocol violations are any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with

the IEC/IRB -approved protocol that may affect the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

Major protocol violation includes ineligible participants who were included in the trial by mistake, and those for whom the intervention or other procedure differed from that outlined in the protocol, or failure of consent process. Major protocol violations can occur at different times of the study and are defined in Table 1

Table 1: Major protocol violations at different times of study

Upon Inclusion:	• IBS-SSS < 175 in the inclusion screening • IBS-SSS < 75 in the baseline assessment (may differ from the inclusion screening) • ROME IV criteria not fully met (IBS) • No validated diagnosis of UC or IBS (doctor's letter or UKE/IK-confirmation) • No guideline-appropriate treatment • Missing or incomplete study consent • Acute suicidality • Acute illness requiring treatment (except UC/IBS) • Psychotherapy in the last 3 months or currently starting psychotherapy • Insufficient German language skills • Significant cognitive deficits
At Baseline:	• Unreported SAE
At 6-week follow-up:	• 6-week follow-up completed before the 3rd intervention session (GUT.EXPECT, GUT.SUPPORT
At 3-month follow-up:	• More than 2 missing intervention sessions (GUT.EXPECT, GUT.SUPPORT) • Data collection takes place before the booster session (GUT.EXPECT, GUT.SUPPORT)
At 12-month follow-up:	• For IBS: missing telephone SKID interview, as the ROME IV criteria were not collected without it

3.3.4 Evaluated for Safety Set (EFS)

All randomized patients will be included into the Evaluated for Safety (EFS) set.

4 Trial Population

4.1 Eligibility

The absolute and relative (%) frequencies of ineligible participants recruited, if any, will be reported, with reasons for ineligibility.

4.2 Recruitment

The CONSORT diagram in Figure 4 of the design paper (Löwe, et al., 2022)[18] will be updated with the actual recruitment figures.

4.3 Withdrawal/follow-up

The data of patients who have discontinued their participation in the study will be used if the patients have not objected to the use of their data. If patients discontinue treatment, efforts will be made to recruit them for further visits. We inquired causes for study withdrawal, reported them to the Data Safety & Monitoring Board (DSMB), and will report those in case of disclosure to clarify whether there are any differences between the intervention and control groups.

4.4 Baseline patient characteristics

Available baseline data consists of demographic data, medical history, and clinical information gathered in accordance with the goals of the overarching SOMACROSS research unit (see table 2 in (Löwe, et al., 2022)[16]) and the project-specific data

- Symptom duration
- disease duration
- IBS-SSS
- SCCAI
- time between symptom onset and diagnosis
- time since the last treatment appointment due to bowel complaints
- time until the next treatment appointment due to bowel complaints
- time since last treatment appointment with the gastroenterologist
- number of inpatient treatments due to bowel complaints
- medication taken due to bowel complaints
- active disease (flare-up yes/no; UC only)

- duration of flare-up (UC only)
- time since last flare-up (UC only)
- fecal calprotectin
- CRP

will be summarized by descriptive statistics for the ITT population.

Categorical data will be summarised by numbers and percentages. Continuous data will be summarised by mean, standard deviation, median, interquartile range and range. Number of available observations and number of missing observations will be presented.

5 Analysis

5.1 Outcome definitions

5.1.1 Primary outcome

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 IBS-SSS questionnaire, which is applicable in both IBS and UC and validated in English and German in various forms of intestinal diseases.[3;11;24] 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.[3]

5.1.2 Secondary outcomes

Secondary outcomes include changes between baseline and follow-up measurements in total somatic symptom severity (PHQ-15),[15] disease activity (Simple Clinical Colitis Activity Index, SCCAI),[6;25] time since last treatment and utilisation of medical treatment, adverse effects and satisfaction with the intervention. C-reactive protein, and faecal calprotectin will be assessed at baseline and the 3 months post-intervention assessment. In addition, for patients whose blood was collected at the UKE, interleukin-6 and tumor necrosis factor (TNF-α) will be assessed at both time points. Further secondary outcomes are illness-related anxiety (WI-7),[10] psychological burden related to somatic symptoms or associated

health concerns (SSD-12),[23] expectations of symptom severity, treatment outcome and coping with symptoms (TEX-Q; NRS).[1;19]

The PHQ-15, SSCAI, WI-7, SSD-12 and TEX-Q are scored according to their questionnaire specific manuals.

Additionally, we will apply joint SOMACROSS core instruments.[16] 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. Most of these additional data will be collected at baseline and at the follow-up assessments, with the exception of the ACE-D, BFI-10, PANAS, TAS-20, ERQ and PSS10 questionnaires which are only collected at baseline.

5.2 Analysis methods

5.2.1 Primary outcome

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 between disease and treatment group, this is more effective than analysing both disease conditions independently. If the overall comparison yields a significant F-statistic, pairwise comparisons can be performed without adjustment of the type 1 error because of the closure testing principle. This analysis will be performed using the FAS. In the case of significant F-statistic, we will report baseline adjusted means and their respective differences, including 95% confidence intervals.

5.2.2 Secondary outcomes

The secondary outcomes will be reported according to their respective scale.

Group differences of PHQ-15, SSCAI, C-reactive protein, and faecal calprotectin will also be analysed using analysis of covariance with underlying disease (UC vs IBS) and sex as additional factors. The same reasoning as for the primary outcome IBS-SSS applies.

All variables will be checked for skewness and if necessary appropriately transformed.

5.3 Missing data

If more than 5% of values are missing for the primary outcome, we will use multiple imputation in a sensitivity analysis. The number of imputations for multiple imputation will be chosen depending on the proportion of missing data according to (White, Royston, & Wood, 2011).[26]

5.4 Additional analyses

5.4.1 Mediation analysis

In order to analyse whether effects on persistent gastrointestinal symptoms resulted through changes in dysfunctional symptom expectations or illness-related anxiety, we will conduct causal mediation analyses. Mediation analyses will test whether in patients receiving GUT EXPECT, changes in the mediating variables at the 6 weeks' assessment predict a reduction in gastrointestinal symptom severity (IBS-SSS) at 3 months (primary outcome), 6 and 12 months. That is to say, the adjusted total treatment effect (TE) will be divided into the indirect effect, which describes the treatment effect on persistent gastrointestinal symptoms via the mediators, and the direct effect, which describes the treatment effect not mediated through the mediators. Subsequently, the percentage mediated (PM) can be estimated. Only potential mediator-outcome confounders need to be controlled for due to randomisation and a possible treatment-mediator interaction must be considered. To account for mediator-outcome confounding, we adjust generally for gender and diagnosis.

In our main mediation analysis given in Figure 2, we include expectations of symptom severity (EXP 2) and illness-related anxiety (SSD-12) at 6 weeks FU as mediating variables. We use linear structural equation model[27] to estimate the effect of the mediating variables on the IBS-SSS at 3 months and will repeat this anlaysis, when 6 and 12 month data is available.

The following sensitivity analyses are to be carried out to validate the results and investigate changes in the (in)direct effects and PM with regard to our main mediation model:

- additional adjusting for fecal calprotectin, IBS-SSS at baseline and duration of symptoms and, in a next step, for mediators at baseline (Figure 2)
- include an interaction between the treatment and the mediator(s)
- handling missing values by using the full information maximum likelihood (FIML) approach in the adjusted model with all confounders.

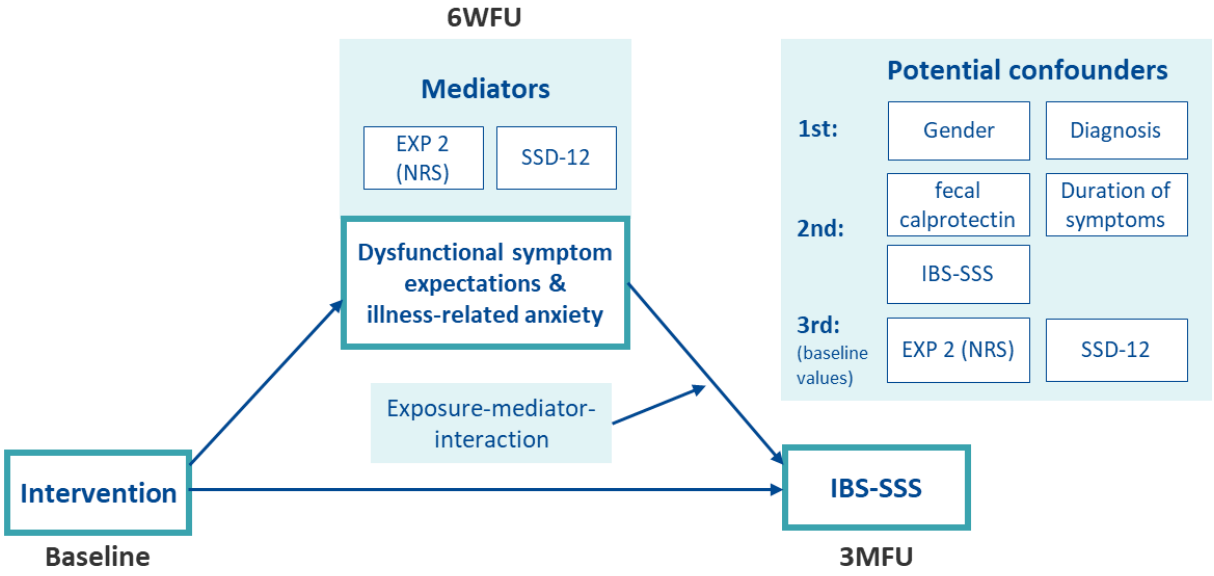

Figure 2: Main mediation analysis model

5.4.2 Subgroup analysis

Exploratory subgroup analyses aim at identifying subgroups which may especially benefit or do not respond well to the treatment groups offered, as measured by the reduction in gastrointestinal symptom severity (IBS-SSS). For this purpose, an ANCOVA for the IBS-SSS at 3 months as dependent variable will be performed in the ITT population, adjusted for the IBS-SSS at baseline and including group allocation as factor and the interaction between group and specified interaction variable. For each defined interaction variable, a separate ANCOVA model will be examined.

Interaction test p-values and. Subgroup-specific means and pairwise effect differences with 95% confidence intervals will be reported in the case of interaction tests with p values of less than 0·15 in accordance with the EMA guideline on the investigation of subgroups in confirmatory clinical trials[28]. The presented p-values will not be adjusted for multiple comparisons.

The following subgroup variables will be investigated in separate ANCOVA models regarding their potential interaction with the intervention groups with respect to the change in the IBS-SSS from baseline to 3 months:

Key subgroups

- Diagnosis (UC vs. IBS)
- Gender (female vs. male; diverse patients are exluded for this analysis)

Exploratory subgroups

- Age (young [≤first tercile] vs. middle aged vs. old [>third tercile])
- Migration background (none vs. 2nd generation [mother and/or father not born in Germany] vs. 1st generation [patient not born in Germany])
- Education (≤ 10 years in school vs. > 10 years in school)
- Duration of symptoms in years (<5 years vs 5-10 years vs >10 years)
- Baseline IBS-SSS none [0-74] vs mild [≥75-174] vs moderate [≥175 - 300] vs severe [>300] (this analysis will not be adjusted for baseline IBS-SSS)
- Somatic symptom severity (PHQ-15 categorical: <10 vs ≥10)
- Somatosensory Amplification (SSAS split at median (≤15 vs > 15))
- PHQ-15 categorical: <10 vs ≥10)
- GAD-7 categorical: <10 vs ≥10
- TAS-20 as 20-60 vs ≥ 61
- ERQ suppression split at median (≤3.25 vs > 3.25)
- SSD-12 < 24 vs ≥ 24
- Adverse childhood events (ACE-D: 0 vs. 1-3 vs. ≥ 4)
- BMI (< 18,5 vs. ≥ 18,5 to 24,9 vs. ≥ 25)
- Systemic inflammation (CRP: normal range [under detection limit and normal range up to < 5mg/l] vs. abnormal ≥ 5mg/l])
- Number of somatic comorbidities (0-1 vs. 2-3 vs. ≥ 4)
- for UC only:
    - Disease activity (: SCCAI 0-4 vs. ≥ 5)
    - Gastrointestinal inflammation (fecal calprotectin: normal range [under detection limit and normal range up to < 50µg/g] vs. abnormal ≥ 50 µg/g)

5.4.3 Regression analysis

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 linear multiple mixed regression analyses adjusted for the diagnostic group, while taking into account the number of predictors and sample size (estimated at baseline n=78 with n=39 for each UC and IBS).

Regression analyses will be conducted separately for IBS-SSS and PHQ-15 as outcome utilizing outcome data from 6 and 12 months' follow-up. Pre-specified predictors for both analyses are gender, age, IBS-SSS baseline score, depression (PHQ-9), anxiety (GAD-7), somatic symptom related cognitions, emotions and behaviours (SSD-12), expected symptom severity in 6 months (NRS) and fecal calprotectin.

To avoid bias, patients from the intervention groups will not be included in these analyses. 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 linear multiple mixed models 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 which include all randomized patients and timepoints in a comprehensive model to predict the course of IBS-SSS and PHQ-15. In order to account for unevenly spaced observations (i.e. 3 or 6 months) a spatial covariance structure will be used to model the longitudinal random effect.

5.5 Harms

To the best of our knowledge, there is no risk for serious adverse events caused by the application of expectation management interventions.[20;22] 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. Suicidal ideation, attempts and

potential suicides are also documented and reported. A possible association of these events with the interventions are discussed with the DSMB.

If serious adverse events do occur, they will be documented during the trial and will be reported to the Data Safety & Monitoring Board and to the primary ethics committee.

5.6 Statistical software

- STATA 14 or newer
- R 4.1.1 or newer
- SPSS 25.0 or newer

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