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Predicting mucosal inflammation in IBD patients using patient-reported symptom scores and a faecal calprotectin home test: protocol for a multicentre prospective validation study

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ABSTRACT

Introduction Crohn's disease and ulcerative colitis are chronic inflammatory bowel diseases (IBD) with a relapsing-remitting nature. With adequate non-invasive prediction of mucosal inflammation, endoscopies can be prevented and treatment optimised earlier for better disease control. We aim to validate and recalibrate commonly used patient-reported symptom scores combined with a faecal calprotectin (FC) home test as non-invasive diagnostic tool for remote monitoring of IBD, both in daily practice and in a strict trial setting. Endoscopy will be used as the gold standard.

Methods and analysis In this multicentre prospective validation study, adult IBD patients are asked to fill out questionnaires regarding disease activity (Monitor IBD At Home, mobile Health Index, Manitoba IBD Index, IBD control and patient-HBI/patient-Simple Clinical Colitis Activity Index), perform a FC home test and collect a stool sample for routine laboratory FC measurement, before the start of the bowel preparation for the ileocolonoscopy. Endoscopic disease activity will be scored according to the simplified endoscopic score for Crohn's disease (CD) for CD patients or Ulcerative Colitis Endoscopic Index for Severity and Mayo Endoscopic Subscore for ulcerative colitis patients. The main study outcome is the diagnostic test accuracy of the various patient-reported scores to assess mucosal inflammation in combination with a FC home test.

Ethics and dissemination This study is approved by the Medical Research Ethics Committee of azM/UM in Maastricht dated 03 March 2021 (METC 20–085) and is monitored by the Clinical Trial Centre Maastricht according to Good Clinical Practice guidelines. Written informed consent will be obtained from all patients. Study results will be published in international peer-reviewed medical journals.

Trial registration number NCT05886322

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first direct comparison of multiple patient-reported outcome measures (PROMs) combined with a faecal calprotectin (FC) home test, using the gold standard ileocolonoscopy as a reference.
⇒ The difference between daily clinical practice and strict trial setting is taken into account in the cut-offs of the endoscopic scores defining mucosal inflammation.
⇒ A limitation of this study is that the recalibrated PROMs are not externally validated.
⇒ A limitation of this study is the probability of intra-individual variability in FC testing.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory diseases characterised by a relapsing-remitting course and together are referred to as inflammatory bowel disease (IBD). Up to 0.5% of the general population in the Western World are diagnosed with IBD,[1] and the prevalence continues to rise.[2 3] The growing prevalence, lack of curative treatment and early onset in life lead to a large impact of IBD on healthcare systems[4] and patients' quality of life.[5]

Recurrent mucosal inflammation or chronic subclinical inflammation can lead to irreversible bowel damage.[6 7] Monitoring of IBD is aimed at early recognition of mucosal inflammation, so treatment can be optimised to prevent disease progression.[8] Ileocolonoscopy remains the gold standard to evaluate mucosal inflammation.[9] During endoscopy, inflammation can be quantified using various scores, such as the simplified endoscopic score for CD (SES-CD)[10] or the Ulcerative Colitis Endoscopic Index for Severity (UCEIS)[11] and Mayo Endoscopic Subscore (MES) for UC. However, ileocolonoscopy is an invasive, time-consuming, expensive and

potentially harmful procedure and thus not suitable for frequent monitoring.

The ideal monitoring test is non-invasive, affordable, simple to conduct and detects (imminent) disease activity. Moreover, it should be suitable for remote monitoring, since visits to the outpatient department are time-consuming and burdensome for both patients and healthcare providers when patients are in stable comprehensive remission, based on objective measures of disease activity and patient-reported outcome measures (PROMs).[12] Remote monitoring might reduce strain on healthcare systems[13] and reduce potential harm for immunocompromised patients, such as during the COVID-19 pandemic.

Several clinical disease activity indices have been developed. Classic symptom-based scores such as the Crohn's disease activity index, Harvey Bradshaw Index (HBI) and Simple Clinical Colitis Activity Index (SCCAI) were initially validated against physician global assessment and have been found to correlate poorly with endoscopic disease activity.[14 15] These scores are clinician-reported and include data from physical examination and/or laboratory test, and are not suitable for remote monitoring. PROMs that can be used for remote monitoring are the Monitor IBD At Home (MIAH) score,[16] mobile Health Index (mHI),[17] patient-HBI[18] and patient-SCCAI.[19] These PROMs measure self-reported disease activity based on indicators that are important to physicians.[20] In monitoring of IBD, assessment of subjective disease control might provide additional valuable information, since a perception gap between physicians and patients concerning disease activity frequently occurs, and subjective perceived control is associated with quality of life.[21] For this, the IBD-control[22] and Manitoba IBD Index (MIBDI)[23] can be used, since these represent outcomes that matter most to IBD patients and were developed and validated according to the guidelines of the Food and Drug Administration and Oxford Patient-Reported Outcome Measurement group but were not tested relative to endoscopy. Of the other PROMs, the MIAH score and mHI were validated against endoscopy, but the validity of the other PROMs to predict mucosal inflammation remains unclear.

However, monitoring disease activity based on symptoms alone is insufficient as ongoing mucosal inflammation can be present in the absence of symptoms, while, on the other hand, symptoms can persist when mucosal healing is reached.[16 24] Objective markers, such as faecal calprotectin (FC), are used as a proxy for endoscopy to monitor mucosal inflammation. FC reduction to an acceptable range has been added as a treatment target in the Selecting Therapeutic Targets in Inflammatory Bowel Disease-II recommendations.[8] In the hospital, FC is determined with an ELISA. This measurement is time-consuming and requires a high level of expertise. In the last years, FC home tests have been developed. FC home tests are cheaper, easier to perform, safe and suitable for remote monitoring.

The combination of a PROM and a FC home test might be the ideal way to non-invasively detect mucosal inflammation in IBD patients. With adequate screening for mucosal inflammation, endoscopies can be prevented and treatment can be timely optimised for better disease control. In this study, we aim to validate various PROMs combined with a FC home test for the detection of mucosal inflammation, relative to the gold standard endoscopy, both in daily clinical practice and in a strict trial setting.

METHODS AND ANALYSIS

Study aim

The main objectives of this study are to:

- Assess which PROM, with and without FC home test, best predicts mucosal inflammation, compared against the gold standard ileocolonoscopy.
- Recalibrate PROMs, that is, to identify the optimal cut-off values, with the FC home test to optimise prediction of mucosal inflammation, relative to the gold standard ileocolonoscopy.

The secondary objectives are to:

- Assess which PROM, with and without FC home test, best predicts mucosal inflammation in a strict trial setting, relative to the gold standard ileocolonoscopy.
- Recalibrate PROMs with the FC home test to optimise prediction of mucosal inflammation in a strict trial setting, relative to the gold standard ileocolonoscopy.
- Assess the association between histologic disease activity and self-assessment of IBD disease control and abdominal pain in IBD patients in (clinical and) endoscopic remission.
- Assess agreement between FC levels measured by FC home tests and by routine laboratory tests in the participating centres.

Study design

This is a multicentre prospective cohort study conducted in Maastricht University Medical Centre+ (MUMC+), Jeroen Bosch Hospital (JBH), Franciscus Gasthuis & Vlietland (FGV), Catharina Hospital Eindhoven (CHE) and Zuyderland Medical Centre (ZMC) in the Netherlands. The Standard Protocol Items: Recommendations for Interventional Trials checklist was followed (see online supplemental file 1).

Study population

Adult patients with an established diagnosis of CD or UC are eligible for participation if they are scheduled for an ileocolonoscopy or sigmoidoscopy (the latter only for UC) as part of routine care at the endoscopy ward of one of the participating centres and meet all of the following inclusion criteria:

- Established diagnosis of CD or UC according to the ECCO guidelines.[9]
- CD or UC patients scheduled for an ileocolonoscopy or UC patients scheduled for a sigmoidoscopy at the

Table 1 Cut-off values to determine the presence of mucosal inflammation

	Mucosal inflammation	No mucosal inflammation
Outcomes		
Pragmatic endoscopic scores	SES-CD > 6; UCEIS > 4; MES ≥ 2 Ulcera > 0.5 cm	SES-CD ≤ 6; UCEIS ≤ 4; MES ≤ 1 No ulcera > 0.5 cm
Strict endoscopic scores	SES-CD > 2; UCEIS > 1; MES ≥ 1	SES-CD ≤ 2; UCEIS ≤ 1; MES = 0
Predictors		
MIAH	CD: ≥3.62 UC: ≥3.54	CD: <3.62 UC: <3.54
mHI	CD: ≥6.38 UC: ≥3.2	CD: <6.38 UC: <3.2
Manitoba IBD Index	Experiencing symptoms constantly to occasionally	Experiencing infrequent symptoms or feeling well
IBD-control-8 IBD-VAS	<13 points <85 points	≥13 points ≥85 points
p-HBI	≥5	<5
p-SCCAI	≥5	<5
FC	CD: >100 µg/g UC: >250 µg/g	CD: ≤100 µg/g UC: ≤250 µg/g

CD, Crohn's disease; FC, faecal calprotectin; IBD, inflammatory bowel diseases; IBD-VAS, Inflammatory Bowel Disease-Visual Analogue Scale; MES, Mayo Endoscopic Subscore; mHI, mobile Health Index; MIAH, Monitor IBD At Home; p-HBI, patient-HBI; p-SCCAI, patient-SCCAI; SES-CD, simplified endoscopic score for CD; UC, ulcerative colitis; UCEIS, Ulcerative Colitis Endoscopic Index for Severity.

endoscopy ward of one of the participating centres (regardless of indication)
- Aged 18 years or older
- Smartphone with internet access (for use of FC home test).

Patients will be excluded if they meet any of the following criteria:
- Unclassified IBD
- Ileostomy, colostomy, ileoanal pouch anastomosis or ileorectal anastomosis
- Isolated upper gastrointestinal CD or isolated perianal disease
- Insufficient knowledge of Dutch language.

Recruitment of patients started in June 2022 in MUMC+, in October 2022 in JBH and FGV, and is expected to start in May 2024 in CZE and ZMC. The first patient was included in MUMC+ on 7 June 2022. At the time of submission (2 June 2023), we have included 113 patients, and full inclusion is expected in June 2025.

Outcomes

The primary outcome is the predictive value of different PROMs, with and without FC home test, for identifying mucosal inflammation in daily clinical practice, defined as an SES-CD >6 for CD, and MES ≥2 or UCEIS >4 for UC or ulcers >0.5 cm for both. For the secondary outcome of mucosal inflammation in a strict trial setting, the cut-offs are, respectively, an SES-CD >2 for CD and UCEIS >1 or MES ≥1 for UC (table 1). The PROM that provides the highest net benefit in decision curve analysis (see below) is deemed best. If biopsies are taken, the association between clinical symptoms, subjective disease control and histologic disease activity score will be assessed in patients in endoscopic remission. Additionally, the agreement between the FC levels measured by the home test and by the laboratory test will be assessed.

Predictors

The PROMs used in this study are the MIAH score, mHI, MIBDI, IBD-control, and the patient-reported HBI and SCCAI. The MIAH score and mHI are validated against endoscopy, whereas the other PROMs have only been validated against conventional clinical disease outcomes. See table 1 for the previously published cut-offs for the PROMs and FC that will be used to predict mucosal inflammation in the clinical practice and strict trial settings.[16–19 22 23] Moreover, the questions on stool frequency and rectal bleeding for UC patients, and stool frequency and abdominal pain for CD patients, will be used to determine disease activity according to the patient-reported outcome (PRO-2).

Study procedures

Eligible IBD patients will be invited to participate in this study at the IBD outpatient department or with an invitation letter. After signing an informed consent form, patients will receive one FC home test, one faecal container with a spatula and a link to the online questionnaires. Patients are asked to fill out the PROMs, perform the FC home test and collect a faecal sample 1 to 2 days before they start bowel preparation for endoscopy. Basic demographic and disease-specific data are collected at the time of colonoscopy.

Before the start of the bowel preparation, all patients fill out online questionnaires via Castor, consisting of the MIAH, mHI, p-HBI for CD or p-SCCAI for UC, IBD-control and MIBDI. In addition, the Bristol stool chart and questions regarding the ease of use of the FC home test are completed.

FC is measured by SmarTest (Preventis, Germany) and by routine laboratory test. SmarTest is a FC immunological test combined with a smartphone application. On the same day as filling out the questionnaires, patients will

measure FC using a SmarTest home test. Furthermore, patients collect a faecal sample of the same stool for measurement of FC by the local routine laboratory test, that is, by EliA Calprotectin test (Thermo Fisher Scientific) on the Phadia 250 in MUMC+ and FGV, QUANTA Flash Calprotectin (Inova Diagnostics) on BIO FLASH in JBH and DiaSorin LIAISON Calprotectin Assay in ZMC and CHE.

The ileocolonoscopy used as a reference for mucosal inflammation in this study is part of standard care. Endoscopic activity will be assessed by a central reader per hospital using SES-CD for CD, and MES and UCEIS for UC. The cut-offs used in a strict trial setting are usually too strict for therapeutic decision-making in daily practice. Therefore, we will use pragmatic and strict endoscopic scores in this study, for use in daily clinical practice and in a strict trial setting, respectively. These cut-off values are based on expert opinions and recommendations.[8] If biopsies are taken, histologic activity will be scored by a blinded central pathologist according to the Geboes score and the Inflammatory Bowel Disease-Distribution, Chronicity, Activity (IBD-DCA) score.[25–27]

Sample size

For the primary objective of comparing PROMs for the prediction of mucosal inflammation, a power calculation is not appropriate as statistical testing and confidence intervals are not used when comparing decision curves.[16] For redeveloping PROMs, we need enough patients in both disease activity groups to estimate all coefficients of the longest PROM without overfitting. Using a rule of thumb, this translates to at least 10 times the number of coefficients for the IBD-control plus a coefficient for FC for a total of 90 patients with mucosal inflammation and 90 patients without, per disease type. Based on this information, we estimated that around 200 CD patients and 200 UC patients are needed, with an estimated prevalence of mucosal inflammation of 30–50%.[16] After including 300 patients, we plan to determine the actual prevalence of mucosal inflammation (using the pragmatic daily practice definition) per IBD type, so sample size can be adjusted if necessary.

Statistical analyses

Basic demographic and disease-specific data include sex, age, type of IBD, Montreal classification at diagnosis, disease duration, surgical history, current IBD medication, smoking status and the indication for colonoscopy or sigmoidoscopy. Descriptive statistics will be used to display these data. The frequency of categorical variables and the mean with SD or median with IQR of continuous variables will be reported.

Patients not undergoing their scheduled ileocolonoscopy or when it is not possible to determine the endoscopic disease activity score will be replaced by new subjects. This can occur when bowel preparation is inadequate or when the upper limit of inflammation is not reached during sigmoidoscopy.

Prediction of mucosal inflammation in daily clinical practice

The primary outcome is prediction of mucosal inflammation in daily clinical practice, for different PROMs and their cut-offs (table 1), both with and without a FC home test, compared against the gold standard ileocolonoscopy. Of these PROMs, we will assess diagnostic test accuracy (sensitivity, specificity, positive predictive value and negative predictive value), discrimination (c-statistic), calibration (intercept and slope) and net benefit through decision curve analysis.

Decision curve analysis

To determine the best PROM for predicting mucosal inflammation on ileocolonoscopy, we will use decision curve analysis.[28] This shows the net benefit of each PROM, combining the benefits of diagnosing mucosal inflammation versus the harms of doing an unnecessary colonoscopy, taking into account patient and provider preferences. Net benefit of screening with each PROM will be compared with doing an ileocolonoscopy in all and in no patients. This will be plotted over threshold probabilities of 0 to 50%. The threshold probability can be interpreted as the relative benefit of detecting mucosal inflammation versus the harm of doing an unnecessary colonoscopy. A threshold probability of 1% implies that diagnosing mucosal inflammation is 99 times more beneficial than avoiding a colonoscopy, while a threshold probability of 50% implies that avoiding a colonoscopy is as beneficial as diagnosing mucosal inflammation. In the standard case of decision curve analysis, patients are classified according to their predicted probability of the event and a probability cut-off that is equal to the threshold probability. In our case, however, not all PROMs calculate a predicted probability (IBD-control and MIBDI), while others already have a prespecified cut-off (MHI, MIAH, p-HBI and p-SCCAI). As such, we will use the cut-offs as defined in the literature (table 1) and plot net benefit of using these cut-offs over a range of threshold probabilities. This reflects the way the PROMs are used in clinical practice.

Redeveloping remote monitoring tool for IBD

We want to optimise PROMs with and without FC home test for screening for mucosal inflammation in daily clinical practice and in a strict trial setting. For each PROM, we will specify a logistic regression model with mucosal inflammation as the dependent variable in which we re-estimate a coefficient for each question in the PROM and FC if applicable. Penalised maximum likelihood will be used to improve external validity. Gold standard will be mucosal inflammation determined by the UCEIS for UC and SES-CD for CD. We will assess discrimination (c-statistic), calibration (intercept and slope) and clinical benefit (decision curve analysis) of using the recalibrated PROMs for screening of mucosal inflammation. Models will be internally validated using bootstrap optimism correction with 400 bootstrap samples, and optimism-corrected estimates will be reported.

Prediction of mucosal inflammation in a strict trial setting

We will determine the best PROM for predicting mucosal inflammation in a strict trial setting, using stricter cut-off values for endoscopic remission (table 1). Decision curve analysis will be used, as described above.

Association between abdominal pain and histological disease activity

Abdominal pain is frequently present in IBD patients in endoscopic remission,[29] and it is unknown whether this may be caused by mucosal nerve sensitisation due to ongoing low-grade mucosal inflammation (ie, histological activity) even when endoscopic remission is achieved. Therefore, the association between histologic activity and abdominal pain scores in IBD patients in endoscopic remission will be assessed. Abdominal pain will be assessed using the abdominal pain question from the p-HBI for CD and from the MIAH for UC. In addition, the association between histologic activity and poorly controlled IBD (ie, IBD-control <13/ visual analogue scale (VAS) <85) in patients in clinical (according to the PRO-2) and endoscopic remission will be assessed. Moreover, the prevalence of histologic activity in patients in clinical (according to the PRO-2) and endoscopic remission with well-controlled IBD (ie, IBD-control>13/VAS >85) will be assessed.

Agreement between FC home test and routine laboratory tests

We will determine the percentage of total agreement between the FC home test and routine laboratory tests to detect mucosal inflammation or remission. FC levels are measured in µg/g, but will, for agreement on mucosal inflammation, be treated as a dichotomous variable based on the predefined cut-off values (table 1). Cohen's kappa coefficient will be calculated, with the following interpretation: poor (<0), slight (0–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80) and almost perfect (0.81–0.99).

Additionally, the level of test agreement will be analysed by a Bland-Altman plot, showing the difference against the mean of the paired measurements of the FC home test and the laboratory test. Disagreements in the lower values of the tests (ie, below 500 µg/g) have a bigger impact than disagreements in the higher levels (ie, above 500 µg/g), since these disagreements can lead to misclassification of disease activity more easily.[30] The predefined acceptable limits of difference are set at +/−50 µg/g for the lower range (ie, below 500 µg/g) and+/−200 µg/g for the higher range (ie, above 500 µg/g).

Ethics and dissemination

The protocol has been approved by the Medical Research Ethics Committee of azM/UM in Maastricht dated 3 March 2021 (METC 20–085) and the latest amendment on 27 February 2023. This study will be conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice (GCP) guidelines and is monitored by the Clinical Trial Centre Maastricht. Approval of the institutional review board of the participating centres has been obtained, and written informed consent will be obtained from all patients.

All substantial changes to the protocol will be submitted as an amendment to the Medical Research Ethics Committee.

Publication

All study results will be published in international peer-reviewed medical journals, regardless of the nature of the outcome. First and last authors will depend on the specific contributions in each manuscript. Site principal investigators will be co-authors. Study results will also be presented at relevant national and international conferences.

Data deposition and curation

Data will be coded using consecutive numbers combined with the name of the participating site. A subject identification code list will be used to link the data to the subject. The coordinating investigator, those involved in the execution of the study, research monitors and the Health and Youth Care Inspectorate have access to the source data at the investigator site. This is necessary to make sure the research is correctly performed and reliable. Patient identification log, hospital records, informed consent forms, eCRFs and databases are kept for 15 years after completing the study. The data are always handled confidentially, in accordance with GCP guidelines and the protocol.

Patient and public involvement

Patients and public are not involved in recruitment or conduction of the study. The burden of participation was assessed by representatives of patient associations participating in the Medical Research Ethics Committee. In the development of PROMs (p-HBI, p-SCCAI and MIAH), patients were involved to assess the comprehensibility of the questionnaires. To incorporate the patients' perspective on disease control, we included the IBD-control and MIBDI.

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Contributors MP had the original idea for the study. LJ drafted the initial protocol. MP, LJ, ZM, TEHR, RLW, RCAvL and LB contributed to the protocol development and study design. RCAvL, LJ and LB planned the statistical analyses. LJ, MP, RCAvL, ZM, MR-C, LPLG, TEHR and RLW were involved in the initiation of the study at the local study sites and are involved in the conduct of the trial and acquisition of data. LJ led the writing of this manuscript. All authors contributed equally with comments and feedback to the conception and design of the study and the writing of this manuscript. All authors read and approved the final manuscript.

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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	1; attachment B1 (ABR-form)
	2b	All items from the World Health Organization Trial Registration Data Set	https://clinicaltrials.gov/ct2/show/NCT05886322
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	Attachment K3a, Clinical trial agreement
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1; attachment B1 (ABR-form)
	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	n/a

	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)	n/a
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	7-9
	6b	Explanation for choice of comparators	7-9
Objectives	7	Specific objectives or hypotheses	9
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	10
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)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14
	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)	n/a
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	n/a
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a

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	11-12
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)	12-14
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	10-11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	19
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	n/a
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	n/a
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
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	20
	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	n/a
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	20
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	16-17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-18
	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)	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	n/a
	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	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	15-16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
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)	21
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	19
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Attachment E1,E2 (informed consent form)
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	20-21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	n/a
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	20
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	20
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	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Restricted access
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attachment E1,E2 (in Dutch)

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.