BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018166
Article Type:	Protocol
Date Submitted by the Author:	09-Jun-2017
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Primary Subject Heading:	Medical management
Secondary Subject Heading:	Nutrition and metabolism, Dermatology, Gastroenterology and hepatology, Pharmacology and therapeutics, Rheumatology
Keywords:	lifestyle AND chronic inflammatory disease, biomarker AND lifestyle, personalized medicine, patient related outcome measures, treatment outcome, western style diet

Impact of red and processed meat and fibre intake on treatment outcome among patients with chronic inflammatory diseases:

Protocol for a prospective cohort study on prognostic factors and personalised medicine

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ABSTRACT

Introduction: Chronic inflammatory diseases (CID) - including inflammatory bowel diseases (Crohn's disease and ulcerative colitis), rheumatic conditions (rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis), inflammatory skin diseases (psoriasis, hidradenitis suppurativa) and non-infectious uveitis are treated with biologics targeting the pro-inflammatory molecule tumour necrosis factor (TNF)-α inhibitors (i.e. referred to as TNFi). Up to one third of the patients do, however, not respond to biologics and lifestyle factors are assumed to affect the treatment outcome. However, little is known on the effects of dietary lifestyle as a prognostic factor (possibly enabling personalised medicine). The overall aim of this multidisciplinary collaborative study is to identify dietary lifestyle factors that could support individualised forecasting of optimised treatment outcome.

***Methods and analysis*:** This prospective cohort study will enrol CID patients assigned for TNFi. At baseline (Pre-treatment), patient characteristics are assessed using patient-reported outcome measures, clinical assessments on disease activity, quality of life, and lifestyle together with registry data on comorbidity as well as concomitant medication. Follow-up will be conducted at week 14-16 after treatment initiation (according to the current Danish standards). Evaluation of a successful treatment outcome response will - for each disease - be based on established primary and secondary endpoints (including disease-specific core outcome sets); the major outcome of the analyses will be to detect differences in treatment outcome between patients with specific lifestyle characteristics.

Ethics and dissemination: The overarching goal of this project is to improve the lives of patients suffering from CID, by providing evidence to support dietary recommendations likely to improve the clinical outcome. The study is approved by the local Ethics Committee (S-20160124) and the local Data Agency (2008-58-035). The study findings will be disseminated in peer-reviewed journals, via patient associations, and presented at national and international conferences.

Trial Registration details: ClinicalTrials.gov identifier: NCT03173144

Keywords: biomarker; lifestyle; personalized medicine; patient related outcome measures (PROMs); treatment outcome; western style diet (WSD)

Strengths and limitations of this study

- This study includes a number of diseases that are treated with drugs targeting the pro-inflammatory cytokine tumour necrosis factor-α
- All evaluations are performed as part of a prospectively designed cohort study by established disease-specific scoring systems
- As comparison across diseases is limited by disease-specific scoring systems additional response criteria (e.g. quality of life and disability) are also used for analyses

INTRODUCTION

Chronic inflammatory diseases (CID), including inflammatory bowel diseases (IBD) (of which Crohn's disease [CD] and ulcerative colitis [UC] are the two most common entities), rheumatic conditions (rheumatoid arthritis [RA], axial spondyloarthropathy [axSpA], psoriatic arthritis [PsA]), skin diseases (psoriasis [PsO], hidradenitis suppurativa [HS]), and eye disease (non-infectious uveitis [NiU]), are diseases of the immune system that are managed with biological agents targeting (by inhibiting) the pro-inflammatory cytokine TNF (i.e. TNFi).

CIDs have a large and negative impact on the individual patient as well as the society (diminished work capacity as well as health expenses for therapies). CIDs are recurring, lifelong illnesses of potentially early onset that substantially affect the life quality of the patients and their families[1-4]. In addition, they are rather frequent; IBD affects up to 0.5 % of the population in the Western world[5] and RA and PsO have global prevalences of 0.3-1.0% and 1.5%, respectively[6 7]. Furthermore, the disease burden is predicted to rise dramatically due to growth in population, increasing aging, and increasing disease incidence[8-10]. Therefore, in the future, a large and increasing challenge will be put on the health care system, as more patients will need treatment. The diseases may have overlapping symptoms[11]. For example, some patients with UV and AS may experience bowel symptoms, and some patients with IBD may develop eye, joint and skin symptoms. The diseases are rather complex diseases with both genetic and environmental factors involved in the disease development. Hence, the CIDs share some genetic and environmental predisposing factors whereas other susceptibility factors differ between the diseases[12]. The genetic architecture of CIDs has previously been investigated by large international consortia[13-19]. Further, environmental factors have been investigated in large cohorts with

prospectively collected lifestyle data, such as European Investigation into Cancer and Nutrition (EPIC) Study and the Nurses' Health Study (NHS)[20-34].

In light of the large impact from the environment on the disease development mirrored by the increasing incidence[5 10], it seems that the environment, including lifestyle, may influence treatment response. Accordingly, many patients ask their health care professionals about lifestyle recommendations that can improve the outcome of TNFi.

Evidence-Based Research

In an attempt to increase value and reduce waste in research, no new studies should be done without a systematic review of existing evidence[35]. In a recent systematic review investigating the current knowledge on the impact of diet on TNFi response in IBD[36], it was concluded that an evidence-based dialogue on the impact of diet on TNFi treatment response for clinical use is scarce. Similarly, to the best of our knowledge, only few large prospective studies have assessed effects of lifestyle on anti-TNF treated CID patients [37]. One prospective study compared partial enteral nutrition (16 patients), exclusive enteral nutrition (22 patients), and anti-TNF (52 patients) therapy in 90 paediatric patients. There were no significant differences in clinical response rates between the three treatments; however, the rate of patients that achieved a faecal calprotectin ≤250 μg/g was higher among the anti-TNF treated patients than the other treatment arms[38].

More recently, potential lifestyle factors for further investigation in relation to TNFi therapy among CID patients were identified[39]. In order to explore different hypotheses, we included studies that may be subject to recall bias, and bias introduced by lifestyle changes due to the disease itself; among identified factors were smoking, physical activities, and

intake of Western style diet[39]. In fact, we have proposed a model whereby a diet high in meat and low in fibres may impact inflammation and anti-TNF treatment[36] (Figure 1).

Following the previous evidence provided, we set out to prospectively identify lifestyle factors that support achievement of optimal treatment outcome. The ultimate aim is to improve the quality of life of the individual CID patient by providing feasible advice such as dietary recommendations for improved treatment outcome.

Aims and hypotheses

The primary aim of this prospective cohort study is to investigate whether treatment outcomes across conditions differ between various predefined lifestyle factors. The main hypothesis is that *'Diets high in fibre AND low in red and processed meat are associated with an improved treatment outcome'*. Secondary aims are to investigate whether and to what extent lifestyle-associated biomarkers have prognostic value for differentiating responders from non-responders based on both disease-specific and generic treatment outcomes.

METHODS AND ANALYSIS

Design

The BELIEVE study is a prospective cohort study with focus on disease activity after (14-16 weeks) of initiating TNFi. The primary endpoint will be assessed at week 14-16 after initiation of TNFi, and is defined based on specific CID condition; where a A: Responder according to the specific criteria described below (incl. drug-continuation) or B: Non-responder (incl. drug-discontinuation). Whether a patient will discontinue therapy is assumed to be based on a certain degree of shared decision making between the patient and physician supported by principles from national guidelines for each CID as recommended in the respective national guidelines [40] and laboratory data.

Setting

The study took place at the 1) Department of Gastroenterology and Hepatology, Aalborg University Hospital; 2) Department of Hepatology and Gastroenterology, Aarhus University Hospital; 3) Diagnostic Centre, Silkeborg Regional Hospital; 4) Department of Internal Medicine, Herning Regional Hospital; 5) Department of Gastroenterology, Herlev Hospital; 6) Organ Centre, Hospital of Southern Jutland; 7) Department of Gastroenterology Hospital of South West Jutland; 8) Department of Medical Gastroenterology, Department of Rheumatology, Department of Dermatology and Allergy Centre, and Department of Ophthalmology, Odense University Hospital will be included from 1st of April 2017 and until 31th of Marts 2019 or until a minimum of 100 patients with

IBD, 100 patients with RA, and 120 patients with axSpA, PsA, PsO, HS and NiU are achieved.

Patient characteristics and eligibility criteria

Inclusion criteria: patients >=18 years with CID assigned for initiation of TNFi therapy for the first time and able to read and understand Danish. Exclusion criteria: patients that previously have received biological treatment and patients not mentally able to answer the questionnaire.

Clinical data (Table 1) consist of personal data, data on health and disease, lifestyle, laboratory measurements, and disease activity scores including patient-reported outcome measures (PROMs), clinical assessments, and laboratory data. Each participant will fill out validated questionnaries on disease activity, quality of life, and lifestyle using an electronic link. Studies have revealed electronic questionnaries to be comparable to paper-based in relation to the outcomes (i.e. PROMs)[41 42].

Primary and secondary endpoints

Primary endpoint: The predefined primary endpoint will be the proportion of patients with clinical response to therapy at first clinical followup (i.e. week 14-16 according to Danish standard):

- Crohn's disease: clinical remission, defined as Harvey and Bradshaw Index (HBI) of 4 or less[43]

- Ulcerative colitis: clinical remission, defined as Mayo Clinic Score of 2 or less (with no individual subscore of >1)[44]
- Rheumatoid arthritis: clinical response, defined as at least 20% improvement according to the criteria of the American College of Rheumatology (ACR20)[45]
- Axial spondyloarthritis: clinical response, defined as at least 20% improvement in Assessment of Spondyloarthritis International Society (ASAS20)[46 47]
- Psoriatic arthritis: clinical response, defined as at least 20% improvement according to the criteria of the American College of Rheumatology (ACR20)[48]
- Psoriasis: clinical response, defined as at least 75% improvement in Psoriasis Area and Severity Index (PASI 75)[49]
- Hidradenitis suppurativa: clinical response, defined as at least a 50% reduction in the abscess and inflammatory-nodule count, with no increase in abscess or draining-fistula counts (HiSCR response)[50]
- Non-Infectious Uveitis: clinical response, defined as those who did not have a treatment failure (treatment failure will be based on assessment of new inflammatory lesions, best corrected visual acuity, anterior chamber cell grade, and vitreous haze grade)[51]

Key secondary outcomes: Major secondary outcomes include, where available disease-specific outcome measures, covering core outcome sets as well as generic health-related quality of life (HRQoL) and disability at endpoint (first clinical followup; i.e., week 14-16 according to Danish standard):

Crohn's disease: STRIDE (Abdominal pain, Diarrhoea, Altered bowel habit, SES-CD [Presence of ulcers, Ulcerated Surface, Affected surface, Presence of narrowings, Number of affected segments], Alterations of cross-sectional imaging [MR, CT, UL][Only when endoscopy cannot adequately evaluate inflammation]), HBI (General well-being, Abdominal pain, Number of liquid stools per day, Abdominal Mass, Extraintestinal Manifestations [Abscess, fistulas, fissures, arthralgia, uveitis, erythema nodosum, pyoderma gangrenosum, mouth ulcera]), Physician global assessment, Number of draining fistulas, Corticosteroid-Free Remission, Concomitant medication

Ulcerative Colitis: STRIDE (Rectal bleeding, Altered bowel habit, Endoscopic remission [Mayo endoscopic subscore of 0-1]), Mayo Clinical Score (Mayo endoscopic subscore, Stools, Rectal bleeding, Physicians global assessment), Mayo "normal mucosal appearance", Mayo clinical response, SCCAI (Bowel frequency [day], Bowel frequency [night], Urgency of defecation, Blood in Stool, General well-being, Extracolonic features), Physician global assessment, Corticosteroid-Free Remission, Concomitant l medication

Rheumatoid Arthritis: Tender joints, Swollen joints, Pain, Physician global assessment, Patient global assessment, HAQ-DI, C-Reactive protein, DAS28-CRP, Simplified Disease Activity Index (SDAI)

Axial Spondyloarthropathy: BASFI, BASDAI, BASMI, Total score for back pain, Physician global assessment, Patient global assessment, C-Reactive protein

Psoriatic Arthritis: Tender joints, Swollen joints, Psoriatic Arthritis Pain, Physician global assessment, Patient global assessment, HAQ-DI, C-Reactive protein, DAS28-CRP, Simplified Disease Activity Index (SDAI), PASI

Psoriasis: PASI, Physician global assessment, Patient global assessment, Psoriatic Arthritis Pain, Dermatology Life Quality Index (DLQI) Total Score.

Hidradenitis Suppurativa: Percentage of Participants who achieve Abscess and Inflammatory Nodule (AN) Count of 0, 1, and 2, respectively, Patient's Global Assessment of Skin Pain, Modified Sartorius Score

Non-Infectious Uveitis: New active, inflammatory chorioretinal or retinal vascular lesions relative to Baseline, Inability to achieve ≤ 0.5+ or a 2-step increase relative to best state achieved at all visits in anterior chamber cell grade or vitreous haze grade, Worsening of best corrected visual acuity by ≥ 15 letters relative to best state achieved.

Exploratory secondary (tertiary) outcomes: As exploratory outcomes we will use biological measures, disease specific disease activity measures as individual measure and combined in scores as well as changes of these (including those measured by physician/patients such as patients' health related quality of life) at first clinical followup[52] (week 14-16) (Table 1). Furthermore, change in use of concomitant medicine, steroid-free remission, serious adverse events (e.g. hospitalisations), and surgery at first clinical followup[52] (week 14-16) will be used (Table 1).

Prognostic factors

Primary exposure variable: For the primary prognostic model, the primary exposure variables will be in prioritized order:

- Upper tertile (33.3% of the total sample) based on the ratio of fibre/meat intake is associated with better treatment outcome
- Low intake of red and processed meat (defined as below the lower tertile [33.3% of the total sample]) and high intake of dietary fibres (defined as those above the upper tertile [33.3% of the total sample]) are independently associated with better treatment outcome, and a potential interaction between them gives the best treatment outcome.

Other (exploratory) exposure variables:

- Lifestyle factors independently or combined (red and processed meat, vegetables, dietary fibre, cereals, gluten, legumes, red wine, dairy products, physical activity, smoking, total protein/ fat, protein/ fat from red and processed meat, glycemic index)
- Pretreatment lifestyle-associated biomarkers
- Combinations of lifestyle factors and lifestyle-associated biomarkers
- Gene-environment interaction analyses
- Pretreatment levels of inflammatory molecules

Data management

The electronic questionnaire is in Danish language and the participants will have access to the questionnaire by an electronic link sent to their personal, electronic mailbox. All data will be stored in a secure research storage facility[53]. Information registered by clinicians and technicians will occasionally be transferred from paper format to electronic format using either double entry of data or automated forms processing[54].

No important risk for the participating patients is foreseen as a direct result of the project. The clinicians will handle the healthcare of included patients as normal. As a result of this, no Data Management Committee will be established.

Statistical methods

Prognostic factor research is developed to aid health care providers in estimating the probability or risk that a specific event will occur in the future (prognostic models), and should subsequently be able to inform decision making [55]. Conceptually, we define a good prognostic model as one that works satisfactorily (i.e. is truthful) for patients other than those from whose data it was derived [56].We will use this rigorously designed, prospective cohort study to explore our ability to predict clinical response across the conditions included (Y=primary endpoint), and explore whether patients who are on a diet high in fibre AND low in red and processed meat (X=assessed at baseline) is an informative prognostic factor. Per default, the statistical models will include condition (any of the CID conditions included), and clinical centre (site #1 to #8) as fixed effects. Specific details will be part of the final Statistical Analysis Plan (SAP). In terms of transparency, we will follow

the guidance from the '*Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis*' (TRIPOD) for the reporting of the multivariable models[57].

Sample size considerations: It is a well-known difficulty for exploratory prognostic factor research studies like this, to formalize how many participants (i.e. their anticipated events) to include. In order to consider an adequate number of outcome events, we apply "the rule of thumb" that dictates that 10 outcome events are needed for each independent variable (possible predictors); we plan to enrol 320 patients in total, and anticipate that 50% of these will experience a clinical response during the 14-16 week period after therapy with TNFi is initiated. With this in mind: Anticipating that we will see at least 160 events (i.e. clinical responses among the 320 patients), we will have a reasonable power to explore the impact of as many as 16 independent (predictor) variables (including condition and clinical centre).

If we focus on the contrast between groups, for a comparison of two independent binomial proportions (those with high fibre AND low meat intake vs other) using Pearson's Chi-square statistic with a Chi-square approximation with a two-sided significance level of 0.05 ($P<0.05$), a total sample size of 318 - assuming an "allocation ratio" of 1 to 2 - has an approximate power of 0.924 (i.e. >90% statistical power) if the anticipated proportions responding are 60% and 40%, respectively.

All the statistical programming will be done in SAS, STATA or R, transparently reporting the source code used to analyse the data. All computational details will be available in the pre-specified SAP, which will be finalised before data collection is complete. Our primary analysis set will be based on those observations that we have

available at closure; i.e. we will consider 'Data as observed' to be our primary resource for statistical inference. However, for the purpose of sensitivity, multiple sensitivity analyses will be performed to assess the robustness of the primary analyses, including analyses based on the "Non-responder-imputation", and multiple-imputation analyses - which is based on model-based approaches for missing data (these details will be available in the final Statistical Analysis Plan). A simplistic "null responder imputation" would represent a conservative base case, and is likely valid even if data is "missing not at random" [58], as it assumes and imply that the patients have had no improvement (or worsening) since entering the study.

Project organisation

The project is organised with a Clinical Research Group (CRG) and an Analytical Research Group (ARG). The CRG includes specialists from the medical, gastroenterological, rheumatological, dermatological and ophthalmological departments that are sampling the cohort. The ARG will perform the analyses on the biological material.

Furthermore, the project is organised with a steering committee (SC) (including Professor Uffe Holmskov, Professor Jens Kjeldsen, Professor Torkell Ellingsen, and Professor Vibeke Andersen) that is responsible for the scientific follow-up and will be organising meetings for the involved parties. The PI has planned and organised the study and has achieved the legal permissions. The whole group including clinicians and analysts is responsible for the scientific results and the economy.

Collaboration between patients and health professionals on research projects is relatively new[59-61]. Involvement of patients in research (patient research partners [PRPs]) should result in patients' views e.g. on prioritising, being heard and incorporated. Furthermore, individual patients and patient organisations may help in designing research studies, preparing information material, discussing results, dissemination of results, and recruitment of study participants. Recommendations include relevant support and education of PRPs. With this initiative, we wanted to get experiences with including PRPs. Thus this project builds on input from the Danish Colitis-Crohn Association, represented by the director Charlotte Lindgaard Nielsen, the Danish Psoriasis Association, represented by the director Lars Werner, and two individual RA patients from one of the involved departments.

The SC will hold telephone conferences every 2-4 weeks, and more often when necessary, and face-to-face meetings 3-4 times per year. Among all participants, the SC will organise telephone conferences every 2-4 weeks, and more often when necessary, and face-to-face meetings at start-up and thereafter every year.

Perspectives

The use of prognosis research evidence at multiple stages is highly important on the translational pathway toward improving patient outcome. Prognosis research include various aspects of importance to health care professionals, enabling them to guide the individual patient in terms of shared decision making via overall prognosis, knowledge on

important prognostic factors, prognostic models, and subsequently (from randomised trial evidence) even stratified medicine [55 62-64]. We anticipate that the BELIEVE study will reveal prognostic factors of importance, such as whether the diet of the patient is likely to interfere with the outcome of being prescribed a TNFi. Also hopefully, by combining various pheno- and geno-type aspects into prognostic models, the BELIEVE might add value in terms of potentially important "personalised medicine" further down the road.

Interesting findings with the potential of having prognostic value will be sought replicated in other prospective cohorts including a planned study of CID cases from the Danish "Diet, Health and Cancer" cohort and potentially other cohorts with lifestyle data[65 66].

Dissemination of results to the public and scientifically

The target journal for the primary outcome will be among the general medical journals, because of its general implications (potentially) for family doctors. Subsequently, other hypotheses will be analysed and manuscripts prepared (independently of the findings) which will likely be submitted to specialty journals (e.g. nutritional journals and specific journals for immunology, gastroenterology, rheumatology, dermatology, and ophthalmology).

Authorship confers credit and has important academic, social, and financial implications, and therefore any authorship on manuscripts coming from BELIEVE study implies responsibility and accountability for published work. In difficult cases we intend to follow the recommendations from the International Committee of Medical Journal Editors (ICMJE) to ensure that contributors who have made substantive intellectual contributions

to a paper are given credit as authors, but also that contributors credited as authors understand their role in taking responsibility and being accountable for what is published.

The ICMJE criteria for authorship intend to distinguish authors from other contributors. based on the following 4 criteria: (*i*) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (*ii*) Drafting the work or revising it critically for important intellectual content; AND (*iii*) Final approval of the version to be published; AND (*iv*) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to the scientific reporting of results, major findings with translational implications will be communicated to health professionals, patient organisations, public health policy makers, and to the general public through various media and news activities.

Ethics

Written informed consent will be obtained from all participants before participation in the study. The project has been approved by The Regional Scientific Ethical Committee (S-20160124) and the Danish Data Protection Agency (2008-58-035). The procedures followed are in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Foundation

This project is part of a project that has received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 733100"(P. Rosenstiel, A. Franke, J. Raes, V. Andersen). Founding has furthermore been received from Odense Patient data Explorative Network (OPEN) (OP-332, V. Andersen), "Knud og Edith Eriksens Mindefond" (V. Andersen), Region of Southern Denmark (V. Andersen), University of Southern Denmark (V. Andersen, U. Holmskov). The Parker Institute, Bispebjerg and Frederiksberg Hospital (R. Christensen, B. Heitmann) is supported by a core grant from the Oak Foundation (OCAY-13-309).

Author Contributions: V. Andersen, B. Heitmann and R. Christensen wrote the first draft and all authors read and commented the manuscript. All authors accepted the final submitted version.

Conflicts of Interest:

All authors declare no conflict of interest. However, the following authors declare: B. Heitmann has received funding from "MatPrat" the information office for Norwegian egg and meat; L. Hvid is in the advisory board for Abbvie A/S; J. Fallingborg is in the advisory boards for AbbVie A/S, MSD Denmark, Takeda Pharma A/S and Ferring Pharmaceuticals A/S; V. Andersen receives compensation for consultancy and for being a member of the advisory board from MSD Denmark (Merck) and Janssen A/S. The funding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

Table 1. Collection of patient characteristics, outcome measures and explanatory variables

Variable	Pre	Week 14-16
***Clinical data*[1]:**		
Gender (w, m)	X	
Age (years)	X	
Diagnosis (disease)	X	
Year of diagnosis (year)[2]	X	
Education (level)[3]	X	
Menopause (year)	X	
Comorbidity (diseases, Charlson index)	X	
Medication (predefined choices)	X	X
Diet (FFQ)[3] (predefined choices)	X	
Changes in diet (predefined choices)		X
Non-dietary lifestyle factors[3] (predefined choices)	X	X
***Investigations*:**		
Height (cm)	X	
Weight (kg)	X	X

Body mass index (kg/cm^2)	X	X
Routine blood analyses[4]	X	X
Endoscopy[5]	X	X
***Biological samples*[6]:**		
Fasting blood samples	X	X
Faeces samples	X	X
Urine samples	X	X
Biopsies[5]	X	X
Crohn's disease (CD)		
Disease location (predefined choices)	X	
Prior operations (y/n, description)	X	
Disease behaviour (fistulising, luminal)	X	
Perianal involvement (y/n)	X	
STRIDE – (y/n)	n.a.	X
Abdominal pain (y/n)	X	X
Diarrhoea (y/n)	X	X
Altered bowel habit (y/n)	X	X
SES-CD (score)	X	X
Presence of ulcers (score)	X	X

Ulcerated surface (score)	X	X
Affected surface (score)	X	X
Presence of narrowings (score)	X	X
Number of affected segments (score)	X	X
Alterations of cross-sectional imaging (MR, CT, UL) (y/n)[7]	X	X
HBI index (score)	X	X
***HBI of 4 or less (y/n)**	**X**	**X**
General well-being (score)	X	X
Abdominal pain (score)	X	X
No. of liquid stools per day (N)	X	X
Abdominal mass (score)	X	X
Manifestations (abscess, fistulas, fissures, arthralgia, uveitis, erythema nodosum, pyoderma gangrenosum, mouth ulcers, one point for each) (N)	X	X
Physician Global Assessment (score)	X	X
Physician Global Assessment (0–100 mm VAS)	X	X
Patient Global Assessment (0–100 mm VAS)	X	X
Corticosteroid-free remission[8] (y/n)		X
Concomitant medication (y,n, predefined choices)	X	X
Number of draining fistulas (fistulising CD)	X	X

Ulcerative Colitis (UC)		
Disease location (predefined choices)	X	
Prior operations (y/n, description)	X	
STRIDE criteria (y/n)	n.a.	X
Rectal bleeding (y/n)	X	X
Altered bowel habit (y/n)	X	X
Endoscopic remission (Mayo endoscopic subscore of 0-1)	X	X
***Mayo Clinical Score of 2 or less with no individual subscore of >1**	**X**	**X**
Mayo "normal mucosal appearance" (y/n)	X	X
Mayo clinical response[9] (y/n)	X	X
Mayo clinical score (score)	X	X
Mayo endoscopic subscore (score)	X	X
Stools (score)	X	X
Rectal bleeding (score)	X	X
Physician Global Assessment (score)	X	X
*Mayo Clinical Score of 2 or less with no individual subscore of >1	X	X
Mayo "normal mucosal appearance" (y/n)	X	X
Mayo clinical response[9] (y/n)	X	X
SCCAI (score)	X	X
Bowel frequency (day) (score)	X	X
Bowel frequency (night) (score)	X	X

Urgency of defecation (score)	X	X
Blood in stool (score)	X	X
General well-being (score)	X	X
Extracolonic features (1 per manifestation)	X	X
Physician Global Assessment (0–100 mm VAS)	X	X
Patient Global Assessment (0–100 mm VAS)	X	X
Corticosteroid-free remission[8] (y/n)		X
Concomitant medication (y,n, predefined choices)	X	X
Rheumatoid arthritis (RA)		
Positive for anti–CCP/RF (y/n)	X	
Swollen-joint count (of 28/66 joints examined)	X	X
Tender-joint count (of 28/68 joints examined)	X	X
DAS28-CRP (score)	X	X
Simplified Disease Activity Index (SDAI) (score)	X	X
***ACR20 (y/n)**	**n.a.**	**X**
ACR50 (y/n)	n.a.	X
ACR70 (y/n)	n.a.	X
EULAR good or moderate response (y/n)	n.a.	X
Low Disease Activity (DAS28 <3.2)	n.a.	X
DAS28 Remission (DAS28 <2.6)	n.a.	X

Physician Global Assessment (0-100 mm VAS)	X	X
Patient Global Assessment (0-100 mm VAS)	X	X
Patient assessment of pain (0-100 mm VAS)	X	X
HAQ-DI	X	X
HAQ (score)	X	X
Axial spondyloarthropathy (axSpA)		
Positive for HLA-B27 (y/n)	X	
BASDAI (score)	X	X
BASFI (score)	X	X
BASMI (score)		
Total score for back pain (0–100 mm VAS)	X	X
Patient global assessment of disease activity (0-100 mm VAS)	X	X
Patient assessment of pain (0-100 mm VAS)	X	X
Physician Global Assessment (0-100 mm VAS)	X	X
***ASAS20 (y/n)**	**n.a.**	**X**
ASAS40 (y/n)	n.a.	X
ASAS Partial response (y/n)	n.a.	X
ASAS5/6 response (y/n)	n.a.	X
Psoriatic arthritis (PsA)		

Dactylitis (y/n)	X	X
Enthesitis (y/n)	X	X
PASI (score)	X	X
PASI 75 response (y/n)	n.a.	X
PASI 90 response (y/n)	n.a.	X
***ACR20**	**n.a.**	**X**
Swollen-joint count (of 28/66 joints examined)	X	X
Tender-joint count (of 28/68 joints examined)	X	X
DAS28-CRP (score)	X	X
Patient Global Assessment of disease activity (0-100 mm VAS)	X	X
Patient Assessment of PsA pain (0-100 mm VAS)	X	X
Physician Global Assessment (0-100 mm VAS)	X	X
Simplified Disease Activity Index (SDAI)	X	X
HAQ-DI	X	X
HAQ (score)	X	X
Psoriasis (PsO)		
Psoriatic arthritis (y/n)	X	X
PASI (score)	X	X
***PASI75 response (y/n)**	**n.a.**	**X**
PASI90 response (y/n)	n.a.	X

Patient Global Assessment of disease activity (0-100 mm VAS)	X	X
Patient Assessment of PsA pain (0-100 mm VAS)	X	X
Physician Global Assessment (0-100 mm VAS)	X	X
DLQI (score)	X	X
Hidradenitis Suppurativa (HS)		
***HiSCR response**	**n.a.**	**X**
Hurley stage[10] (score)	X	X
Previous systemic treatment (y/n, description)	X	
Prior surgery (y/n, description)	X	
Lesion counts (N)	X	X
Total no. of abscesses and inflammatory nodules (N)	X	X
No. of abscesses (N)	X	X
No. of inflammatory nodules (N)	X	X
No. of draining fistulas (N)	X	X
Modified Sartorius score (score)	X	X
Percentage of Participants who achieve Abscess and Inflammatory Nodule (AN) Count of 0, 1, and 2, respectively	X	X
Patient Global Assessment of skin pain (score)	X	X
DLQI (score)	X	X

Non-infectious Uveitis (NiU)		
SUN (score)	X	X
***Uveitis treatment failure (y/n)**	**n.a.**	**X**
New active, inflammatory chorioretinal or retinal vascular lesions relative to Baseline (y/n)	X	X
Inability to achieve ≤ 0.5+ or a 2-step increase relative to best state achieved at all visits in anterior chamber cell grade or vitreous haze grade (y/n)	X	X
Worsening of best corrected visual acuity by ≥ 15 letters relative to best state achieved (y/n)	X	X
Health-related quality of Life[11]	***X***	***X***
SF12 (score)	X	X
SHS (score)	X	X
Physician Global Assessment (0–100 mm VAS)	X	X
Patient Global Assessment (0–100 mm VAS)	X	X
ROME-III (score)	X	X
NYHA (score)	X	X
Cont. anti-TNF treatment (y/n, predefined choices for stopping if no)	X	X
Adverse events		

Discontinuation due to adverse events (y/n)		X
Serious adverse event (y/n)		X
Death (y/n)		X
Occurrence of surgery (y/n)		X
Occurrence of hospital admission (y/n)		X
Occurrence of disease-related complication (y/n)		X
***Laboratory*[4]**		
CRP (mg/l)[12]	X	X

***Primary endpoint for the individual diseases**

[1]Data will be collected using a questionnaire, local and National registries.

[2]Registry data will be retrieved from the Danish registries using the Danish individual civil registration number (CPR) including BIO-IBD[67], DANBIO[68], DERMBIO[69] (database on IBD, RA, HS, axSpA, PsA, and PsO patients on biological therapy), the National Patient Registry (e.g. comorbidity), registries on medication and use of receipts, local laboratory databases (laboratory data) and the electronic patient records (side effects).

[3]Lifestyle (dietary and non-dietary) will be registered using a validated food-frequency questionnaire (FFQ) that includes food items and a photographic food atlas of picture series of portion sizes will be used to assess intake of food groups, such as meat and dairy, and calculate total energy, fiber, protein, fat sugar and carbohydrate intakes as well as glycemic index and load. In addition, questions on non-diet lifestyle factors (smoking, physical

activity, alcohol consumption and use of over-the counter medicine [use of probiotics, pre-probiotics, painkillers, laxatia, and anti-diarrhoea agents]) as well as educational level and year of menopause (women) are included[70]. The follow-up questionnaire is identical to the initial questionnaire apart from the questions on food items that only contains questions on changes of diet since the last questionnaire.

[4]Routine blood analyses include C-reactive protein (CRP), haemoglobin, erythrocyte count, haematocrit, erythrocyte mean cell volume (MCV), mean cell hemoglobin (MCH) and mean cell haemoglobin concentration (MCHC), leucocyte count, differential count, thrombocytes, albumin, K+ potassium, Na+ sodium, creatinine, coagulation factor II+VII+X, alanine amino transferase (ALAT), alkaline phosphatase, gamma-glutamyl transferase (GGT), haemoglobin glycation (Hb1Ac), lipids (cholesterol, high density, low density cholesterol), and transglutaminase.

[5]Only IBD patients

[6]From all participants, blood, urine, and faeces are sampled. In addition, from IBD patients, intestinal biopsies are sampled. In selected cases, additional biological material on participants from this study may be retrieved from the Patobank and the Danish Biobank. The samples will be collected adhering to the Sample PRE-analytical Code (SPREC) and Biospecimen Reporting for Improved Study Quality (BRISQ) guidelines, using Standard Operational Procedure (SOPs) describing and logging primary container, centrifugation conditions, centrifugation parameters and storage conditions[71 72]. The biological material will be stored at OPEN (biological material from OUH) or at SHS (biological material from

the other hospitals).

[7]Only CD patients when endoscopy cannot adequately evaluate inflammation.

[8]Corticosteroid-free remission. Clinical remission in patients using oral corticosteroids at baseline (Pre) that have discontinued corticosteroids and are in clinical remission at first follow-up.

[9]A reduction in complete Mayo score of ≥3 points and ≥30% from baseline (or a partial Mayo score of ≥2 points and ≥25% from baseline, if the complete Mayo score was not performed at the visit) with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point

[10]Data for the Hurley stage reflect actual assessment. A patient's overall Hurley stage is the highest stage across all affected anatomical sites. Stage 1 is defined as localized formation of single or multiple abscesses without sinus tracts or scarring, stage II as recurrent abscesses (single or multiple) with sinus tract formation and scarring, and stage III as multiple abscesses with extensive, interconnected sinus tracts and scarring.

[11]All participants will be asked whether they have any complaints regarding or are known with diseases affecting the bowel, the skin, rheumatic complains etc. and if no to both questions they will not be asked to complete the relevant questionnaire.

[12]Biological response defined as a drop in CRP level of more than 25% or to normal level among patients with an elevated CRP before treatment (higher than normal range)[73].

Abbreviations; ACR, American College of Rheumatology; ASAS20/40, Assessment of Spondyloarthritis International Society; CRP, C-reactive Protein; DAS28, Disease Activity

Score: DLQI[74 75], Dermatology Life Quality Index; FFQ, Food frequency questionnaire; Harvey and Bradshaw Index, HBI; HiSCR[50], Hidradenitis Suppurativa Clinical Response; HAQ1, Health Assessment Questionnaire 1; NYHA, New York Heart Association, PASI, Psoriasis Area and Severity Index; SCCAI, Simple Clinical Colitis Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF12, Short Form Health Survey; SHS[76 77], Short Health Scale; SUN, Standardization of Uveitis Nomenclature for Reporting Clinical Data; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease [52]

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FIGURE LEGENDS

Figure 1. Hypothesis for effects of diet in relation to treatment effect

(Left) Low levels of fibre intake may promote microbial metabolism of mucus as the main energy source [36 78 79]. This will lead to decrease of the mucus layer. Further, degradation of mucus releases free sulphate which would then become available for utilisation by sulphate-reducing bacteria (like *Bilophila wadsworthia*) for microbial produced hydrogen sulphide[80]. In addition, high intake of food containing organic sulphur and sulphate additives, such as meat and processed meat, may increase the amount of sulphate for microbial produced hydrogen sulphide[81 82]. The resultant hydrogen sulphide from low intake of fibre and high intake of meat may reduce the disulphide bonds in the mucus network rendering the mucus layer penetrable to e.g. bacteria [80 83]. Then, microbial-associated molecular patterns (MAMPs) from microbes or contained in the diet may reach the epithelium and activate the pattern recognition receptors (PRR) such as Toll-like receptors (TLRs) on the enterocytes (intestinal epithelial cells, IEC), and next activate nuclear factor-kappa B (NFkB), type I interferon (IFN), and other inflammatory pathways. This leads to production of pro-inflammatory (tumour necrosis factor-α (TNF), interleukin (IL)-1β, IL-6, IFN, IL-17 etc.) and anti-inflammatory (primarily IL-10) cytokines and chemokines that will next activate innate lymphocytic cells (ILC) and other immune cells and the immune system in general[84 85]. There is some support for such a mechanism in CID, including findings of; high amounts of sulphate-reducing bacteria in UC patients[80 86], an association between the highest tertiles of carbohydrate-restricted diet and RA, in a nested case-control study among 386 individuals who developed RA and 1886 matched controls from the Swedish Västerbotten Intervention Program (VIP) cohort with prospectively sampled dietary survey[87], association of high fibre intake with low risk of CD among 170 776 participants from the prospective Nurses' Health Study I (NHSI)[22], association of high intake of red meat and total protein and risk of developing inflammatory polyarthritis in the population-based prospective cohort of 25 630 participants from the European Prospective Investigation of Cancer in Norfolk (EPIC-Norfolk)[34]. Finally, a prospective study of 191 UC patients in remission found that

high consumption of meat, particularly red and processed meat, protein, and alcohol, was associated with risk of relapse and that high sulphur or sulphate intakes may offer an explanation for the observed findings[88]. Additionally, support of the notation that diet may affect systemic immune response is provided by the finding that intake of low-glycemic index diet was found to lower secretion of TNF and IL-6 from stimulated peripheral blood mononuclear cells from obese humans[89]. **(Right)** Intake of high fibre and low meat may promote an effective mucosal barrier and support the effects of anti-TNF treatment outcome. Intake of soluble plant fibre has been found to block bacterial adhesion to gut enterocytes in animal and cell studies[90]. The genetic architecture of the individual may also impact the influence of lifestyle factors[14]. Hence, in order to provide lifestyle recommendations, we need to understand the effects of lifestyle on the immune system, and how lifestyle may improve the therapeutic outcome and reduce the need of medical treatment in the individual person. Information on diet and non-diet lifestyle exposures may be collected by using e.g. questionnaires and lifestyle-associated biomarkers or the combination of these methods [91-93]. Evidence-based biomarkers for lifestyle assessment are scarce [94-114] and mostly used for studies on healthy individuals [115-118].

Figure 2. Organisation and patients research partners (PRPs)

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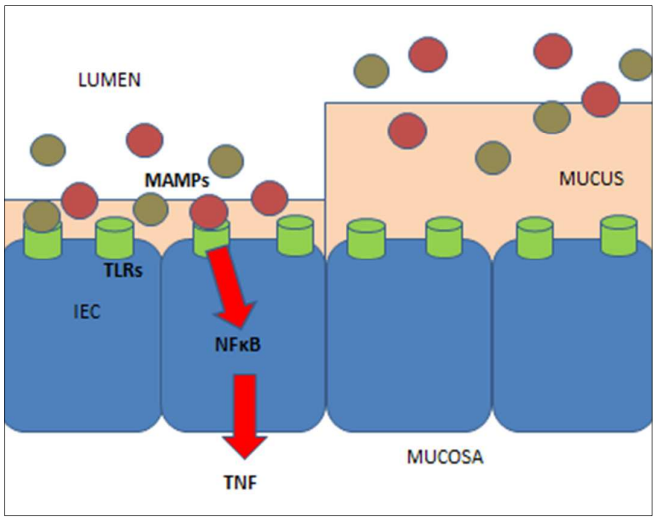

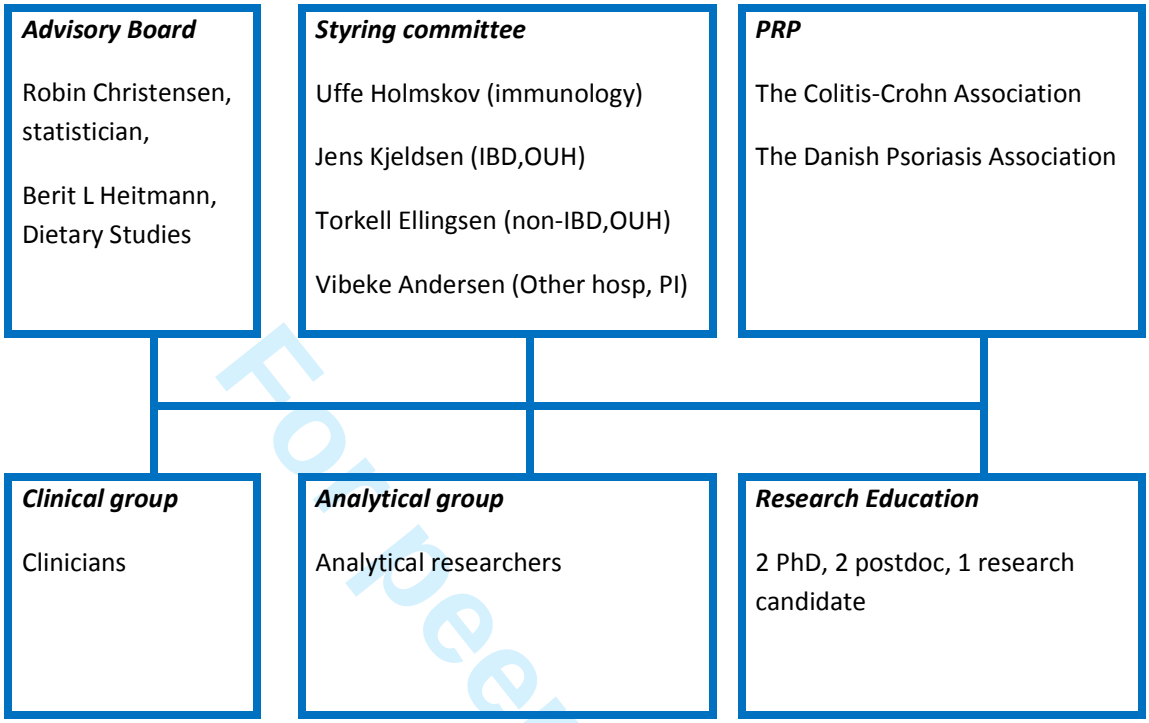

Areas of responsibility in parenthesis. **IBD-OUH**, sampling of IBD patients from Odense University Hospital (OUH); **non-IBD, OUH**, sampling of non-IBD patients from OUH; Other hosp, sampling of patients from other hospitals; PI, principal investigator

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_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_suppl_____
Funding	4	Sources and types of financial, material, and other support	_14_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	2 and 14_____
	5b	Name and contact information for the trial sponsor	___2_____
	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	_7-14_____
	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)	__7, 11- 14

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	__Figure 1____
	6b	Explanation for choice of comparators	__8_____
Objectives	7	Specific objectives or hypotheses	__6_____
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)	__7_____
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	___7_____
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)	____7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__7_____
	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)	___NA_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	___NA_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___NA_____
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	____8-10_____
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)	____7_____

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	__12_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___7_____
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	___NA_____
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	_____NA_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____NA_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__7_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__NA_____
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	___19_____
	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	__19_____

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	19
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	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	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)	12
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	NA
	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	NA
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	19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
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)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
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	NA
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	NA
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	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	suppl
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	19

*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.

BMJ Open

Impact of red and processed meat and fibre intake on treatment outcomes among patients with chronic inflammatory diseases: Protocol for a prospective cohort study of prognostic factors and personalised medicine

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-018166.R1
Article Type:	Protocol
Date Submitted by the Author:	29-Aug-2017
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Primary Subject Heading:	Medical management
Secondary Subject Heading:	Nutrition and metabolism, Dermatology, Gastroenterology and hepatology, Pharmacology and therapeutics, Rheumatology
Keywords:	lifestyle AND chronic inflammatory disease, biomarker AND lifestyle, personalized medicine, patient related outcome measures, treatment outcome, western style diet

Impact of red and processed meat and fibre intake on treatment outcomes among patients with chronic inflammatory diseases:

Protocol for a prospective cohort study of prognostic factors and personalised medicine

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ABSTRACT 300/300

Introduction: Chronic inflammatory diseases (CID) are frequently treated with biologic medications, specifically TNF inhibitors [TNFi]). These medications inhibit the pro-inflammatory molecule tumour necrosis factor (TNF)-α, which has been strongly implicated in the aetiology of these diseases. Up to one-third of patients do not, however, respond to biologics, and lifestyle factors are assumed to affect treatment outcomes. Little is known about the effects of dietary lifestyle as a prognostic factor that may enable personalised medicine. The primary outcome of this multidisciplinary collaborative study will be to identify dietary lifestyle factors that support optimal treatment outcomes.

***Methods and analysis*:** This prospective cohort study will enrol 320 CID patients who are prescribed a TNFi between June 2017 and March 2019. Included among the CID patients will be patients with inflammatory bowel disease (Crohn's disease and ulcerative colitis), rheumatic disorders (rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis), inflammatory skin diseases (psoriasis, hidradenitis suppurativa) and non-infectious uveitis. At baseline (pre-treatment), patient characteristics will be assessed using patient-reported outcome measures, clinical assessments of disease activity, quality of life, and lifestyle, in addition to registry data on comorbidity and concomitant medication(s). In accordance with current Danish standards, follow-up will be conducted 14-16 weeks after treatment initiation. For each disease, evaluation of successful treatment response will be based on established primary and secondary endpoints, including disease-specific core outcome sets. The major outcome of the analyses will be to detect variability in treatment effectiveness between patients with different lifestyle characteristics.

Ethics and dissemination: The principle goal of this project is to improve the quality of life of patients suffering from CID by providing evidence to support dietary and other lifestyle recommendations that may improve clinical outcomes. The study is approved by the Ethics Committee (S-20160124) and the Danish Data Protecting Agency (2008-58-035). Study findings will be disseminated through peer-reviewed journals, patient associations, and presentations at international conferences.

Trial Registration details: ClinicalTrials.gov identifier: NCT03173144

Keywords: biomarker; lifestyle; personalized medicine; patient-reported outcome measures (PROMs); treatment outcome; Western-style diet (WSD)

Strengths and limitations of this study

- This study includes a number of diseases treated with biologics targeting the pro-inflammatory cytokine tumour necrosis factor-α
- All evaluations will be performed as part of a prospectively designed cohort study using established disease-specific scoring systems
- As comparisons between diseases are limited by disease-specific scoring systems, additional response criteria (e.g. quality of life and disability) will be used for analysis
- The sample size is limited

INTRODUCTION

Chronic inflammatory diseases (CID) are a diverse set of immunologic diseases that include inflammatory bowel disease (IBD) (Crohn's disease [CD] and ulcerative colitis [UC]), rheumatic conditions (rheumatoid arthritis [RA], axial spondyloarthropathy [axSpA], psoriatic arthritis [PsA]), inflammatory skin diseases (psoriasis [PsO], hidradenitis suppurativa [HS]), and eye disease (non-infectious uveitis [NiU]). The pro-inflammatory cytokine tumour necrosis factor α (TNF) is recognized to play an important role in the aetiology of these diseases. Correspondingly, biological agents that inhibit TNF, also known as TNF inhibitors (TNFi), are an important component of treatment. However, a large number of patients do not benefit from TNFi treatment[1].

CIDs have a large and negative impact on both individual patients and at a community level as a consequence of health-related workplace productivity loss and health system expense, which is largely influenced by the high cost of providing biologic medications[1]. CIDs are recurring, lifelong illnesses of potentially early onset that can substantially affect the life quality of patients and their families[2-5]. In addition, they are prevalent diseases with IBD affecting 0.5% of the population in the Western world[6], and RA and PsO affecting respectively 0.3-1.0% and 1.5% of the global population[7 8]. Furthermore, the disease burden, and hence health system burden, is predicted to rise dramatically due to population growth, aging demographics and increasing disease incidence[9-11].

The diseases may have overlapping symptoms[12]. For example, some patients with NiU and axSpA may experience bowel symptoms and some patients with IBD may develop extraintestinal manifestations (i.e. eye, joint, and skin symptoms). The diseases are rather complex with both genetic and environmental factors implicated in aetiology. While CIDs share some genetic and environmental predisposing factors, other susceptibility factors

differ[13]. The genetic architecture of CIDs has previously been investigated by large international consortia[14-20]. Similarly, environmental factors have been investigated in large cohorts with prospectively collected lifestyle data, such as the European Investigation into Cancer and Nutrition (EPIC) Study as well as the Nurses' Health Study (NHS)[21-35].

In light of the notable impact that environment factors play in disease development, which is further supported by the increasing incidence of these disease[6 11], it stands to reason that modifying environment factors such as lifestyle may influence treatment response. Accordingly, quite a few patients ask their health care professionals for lifestyle recommendations that can influence the effectiveness of treatment, and in particular the outcomes achieved with TNFi.

Evidence-based research

In an attempt to increase value and reduce waste in research, a systematic review of existing evidence was performed prior to embarking on this study[36]. In a recent systematic review examining the impact of diet on TNFi response in IBD[37], it was concluded that there is scarce evidence linking TNFi treatment response to specific dietary recommendations; hence, there is a clear research need. Similarly, only a few large prospective studies have assessed the effects of lifestyle on TNFi-treated CID patients[38]. One prospective study compared partial enteral nutrition (16 patients), exclusive enteral nutrition (22 patients), and TNFi (52 patients) therapy in 90 pediatric patients. There were no significant differences in clinical response rates between the three treatment arms, although the rate of patients that achieved a faecal calprotectin concentration of ≤250 μg/g was higher among the TNFi treated patients[39].

More recently, lifestyle factors, as they relate to TNFi therapy among CID patients, were identified as an area for further investigation[40]. In order to explore different hypotheses, we included studies that may be subject to recall bias or bias introduced by lifestyle changes due to the disease itself, e.g. smoking, physical activities, and intake of Western-style diet[40]. After reviewing these potential hypotheses, we proposed a model whereby a diet high in meat and low in fibres may impact inflammation and TNFi treatment[37] (Figure 1).

Based on previous evidence, we set out to prospectively identify dietary factors that support optimal TNFi treatment outcomes, with the ultimate aim of improving the quality of life of CID patients.

Aims and hypotheses

The primary aim of this prospective cohort study is to investigate whether treatment outcomes in CID patients vary with dietary differences. The main hypothesis is that *'Diets high in fibre AND low in red and processed meat are associated with improved treatment outcomes*'. Secondary aims are whether and to what extent lifestyle-associated biomarkers have prognostic value for differentiating responders from non-responders based on both disease-specific and generic treatment outcomes.

METHODS AND ANALYSES

Design

The BELIEVE study is a prospective cohort study that will examine disease activity after initiating TNFi treatment. The primary endpoint will be assessed 14-16 weeks after initiation of a TNFi and will be defined based on the specific CID condition. The cohort will be classified as responders (including those who continue with drug treatment) or non-responders (including those who discontinue drug treatment) based on the disease-specific criteria defined below. The decision to discontinue therapy is assumed to be based on a shared decision making process between patients and their physicians, and to be supported by principles outlined in disease-specific guidelines[41].

Setting

This multi-centre study reflects a collaboration between the following centres: 1) Department of Gastroenterology and Hepatology, Aalborg University Hospital; 2) Department of Hepatology and Gastroenterology, Aarhus University Hospital; 3) Diagnostic Centre, Silkeborg Regional Hospital; 4) Department of Internal Medicine, Herning Regional Hospital; 5) Department of Gastroenterology, Herlev Hospital; 6) Organ Centre, Hospital of Southern Jutland; 7) Department of Gastroenterology, Hospital of South West Jutland; 8) Department of Medical Gastroenterology, Department of Rheumatology, Department of Dermatology and Allergy Centre, and Department of Ophthalmology, Odense University Hospital. Study enrolment will take place between June 15, 2017 and

March 31, 2019, or until the study has enrolled a minimum of 100 patients with IBD, 100 patients with RA and 120 patients with axSpA, PsA, PsO, HS and NiU.

Patient characteristics and eligibility criteria

Inclusion criteria: patients ≥18 years with CID who are beginning TNFi therapy, and who have not previously received TNFi treatment, and who are able to read and understand Danish. Exclusion criteria: patients who have previously received a biological treatment and patients who by virtue of illiteracy or cognitive impairment are unable to complete the questionnaire.

Clinical data (Table 1) will include personal data, data on health and disease, dietary and non-dietary lifestyle information, laboratory measurements, and disease activity scores including patient-reported outcome measures (PROMs), clinical assessments, and laboratory data. Participants will complete validated questionnaires on disease activity, quality of life and lifestyle using an electronic link. Studies have revealed electronic questionnaires to be comparable to paper-based in relation to the outcomes (i.e. PROMs)[42 43].

Primary and secondary endpoints

Primary endpoint: The predefined primary endpoint will be the proportion of patients with a clinical response to therapy 14-16 weeks after treatment initiation. Below are the disease-specific definitions of clinical response to therapy:

- Crohn's disease: clinical remission, defined as Harvey-Bradshaw Index (HBI) of 4 or less[44]

- Ulcerative colitis: clinical remission, defined as Mayo Clinic Score of 2 or less (with no individual sub-score of >1)[45]

- Rheumatoid arthritis: clinical response, defined as at least a 20% improvement according to the criteria of the American College of Rheumatology (ACR20)[46]

- Axial spondyloarthritis: clinical response, defined as at least a 20% improvement according to the Assessment of Spondyloarthritis International Society (ASAS20)[47 48]

- Psoriatic arthritis: clinical response, defined as at least a 20% improvement according to the criteria of the American College of Rheumatology (ACR20)[49]

- Psoriasis: clinical response, defined as at least a 75% improvement in Psoriasis Area and Severity Index (PASI 75)[50]

- Hidradenitis suppurativa: clinical response, defined as at least a 50% reduction in the abscess and inflammatory-nodule count, with no increase in abscess or draining-fistula counts (HiSCR response)[51]

- Non-infectious uveitis: clinical response, defined as those who did not have a treatment failure (treatment failure will be based on assessment of new inflammatory lesions, best corrected visual acuity, anterior chamber cell grade, and vitreous haze grade)[52]

Key secondary outcomes: Major secondary outcomes, also to be measured 14-16 weeks after treatment initiation, include disease-specific outcome measures that cover core outcome

sets, the generic health-related quality of life (HRQoL) and disability at endpoint. Below are a list of disese-specific secondary outcomes.

- Crohn's disease: STRIDE (abdominal pain, diarrhea, altered bowel habit, SES-CD [presence of ulcers, ulcerated surface, affected surface, presence of narrowing, number of affected segments], alterations of cross-sectional imaging [MR, CT, ultrasound][only when endoscopy cannot adequately evaluate inflammation]), HBI (general well-being, abdominal pain, number of liquid stools per day, abdominal Mass, extraintestinal manifestations [abscess, fistulas, fissures, arthralgia, uveitis, erythema nodosum, pyoderma gangrenosum, mouth ulcers]), physician global assessment, number of draining fistulas, corticosteroid-free remission, concomitant medication.

- Ulcerative colitis: STRIDE (rectal bleeding, altered bowel habit, endoscopic remission [Mayo endoscopic sub-score of 0-1]), Mayo Clinical Score (Mayo endoscopic sub-score, stools, rectal bleeding, physician global assessment), Mayo "normal mucosal appearance", Mayo clinical response, SCCAI (bowel frequency [day], bowel frequency [night], urgency of defecation, blood in stool, general well-being, extracolonic features), physician global assessment, corticosteroid-free remission, concomitant medication.

- Rheumatoid arthritis: Tender joints, Swollen joints, pain, physician global assessment, patient global assessment, health assessment Questionnaire (HAQ), C-reactive protein, DAS28-CRP, simplified disease activity index (SDAI).

- Axial spondyloarthropathy: bath ankylosing spondylitis metrology index (BASMI), bath ankylosing spondylitis functional index (BASFI), bath ankylosing spondylitis disease activity index (BASDAI), total score for back pain, physician global assessment, patient global assessment, C-reactive protein.
- Psoriatic arthritis: tender joints, swollen joints, psoriatic arthritis pain, physician global assessment, patient global assessment, HAQ-DI, C-reactive protein, DAS28-CRP, simplified disease activity index (SDAI), PASI.
- Psoriasis: PASI, physician global assessment, patient global assessment, psoriatic arthritis pain, dermatology life quality index (DLQI) total Score.
- Hidradenitis suppurativa: percentage of participants who achieve abscess and inflammatory nodule (AN) count of 0, 1, and 2, respectively, patient's global assessment of skin pain, modified Sartorius score.
- Non-infectious uveitis: new active, inflammatory chorioretinal or retinal vascular lesions relative to baseline, inability to achieve ≤ 0.5+ or a 2-step increase relative to the best state achieved at all visits in anterior chamber cell grade or vitreous haze grade, worsening of best corrected visual acuity by ≥ 15 letters relative to best state achieved.

Exploratory secondary (tertiary) outcomes: Additional exploratory outcomes will include biological measures, disease-specific disease activity measures as individual measure and combined scores as well as changes of these (including those measured by physician/patients such as patients' health-related quality of life) at first clinical follow up[53]

(week 14-16) (Table 1). Other outcomes include changes in the use of concomitant medication, acheivement of steroid-free remission, serious adverse events such as hospitalisation, and the need for surgery at first clinical follow up (Table 1) [53].

Prognostic factors

Primary exposure variable: For the primary prognostic model, the primary exposure variables will be prioritized in the following order:

- The upper tertile of the sample (33.3% of the total sample), based on the ratio of fibre to meat intake, is associated with better treatment outcomes.
- The lower tertile of the sample (33.3% of the total sample) with respect to intake of red and processed meat, and the upper tertile of the sample (33.3% of the total sample) with respect to intake of dietary fibres, are independently associated with better treatment outcomes, and a potential interaction between them may further improve treatment outcomes.

Other (exploratory) exposure variables:

- Other lifestyle factors independently or combined (red and processed meat intake, vegetable intake, dietary fibre intake, cereal intake, gluten consumption, legume intake, red wine consumption, dairy product intake, amount of physical activity, smoking status, total protein/fat, protein/fat from red and processed meat, glycemic index)
- Pretreatment lifestyle-associated biomarkers

- Combinations of lifestyle factors and lifestyle-associated biomarkers
- Gene-environment interaction analyses
- Pretreatment levels of inflammatory molecules

Data management

The electronic questionnaire is in Danish. Participants will access the questionnaire by an electronic link which will be sent to their personal, electronic mailbox. All data will be stored in a secure research storage facility[54]. Information registered by clinicians and technicians will periodically be transferred from paper format to electronic format using either double entry of data or automated forms processing[55].

No patient risks are foreseen as a direct result of this project. Clinicians will treat enrolled patients in the same fashion as non-enrolled patients. As a consequence, no data monitoring committee will be established.

Statistical methods

Prognostic factor research was developed to aid healthcare providers in estimating the probability or risk that a specific event will occur in the future. Hence, it has the potential to inform clinical decision-making [56]. Conceptually, a good prognostic model is one that functions for patients other than those from whom the data was derived [57]. Our intention is to use data obtained from this rigorously designed, prospective cohort study to explore our

ability to predict clinical response across specific CID conditions (Y=primary endpoint) and to explore whether diets high in fibre AND low in red and processed meat (X=assessed at baseline) are an informative prognostic factor. Per default, the statistical models will include the specific CID condition and the clinical centre as fixed effects. Specific details will be part of the final statistical analysis plan (SAP). In terms of transparency, when reporting the multivariable models the study will adhere to guidelines from the '*Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis*' (TRIPOD).

Sample size considerations: Deciding sample size is a well-known difficulty with exploratory prognostic factor research studies. To obtain an adequate number of outcome events we apply "the rule of thumb" whereby 10 outcomes are needed for each independent variable. We plan to enrol 320 patients in total and we anticipate that 50% of these will experience a clinical response during the 14-16 week period after TNFi initiation[1]. With this in mind, and anticipating that we will see at least 160 events (i.e. clinical response among the 320 patients), the study is sufficiently power to explore the impact of as many as 16 independent variables including condition and clinical centre. Since using the "rule of thumb" method to justify sample size is a debated practice, we went one step further and estimated the statistical power to detect differences between two dietary groups. For the contrast between groups and for a comparison of two independent binomial proportions (those with high fibre AND low meat intake vs other) using Pearson's Chi-square statistic, with a Chi-square approximation, with a two-sided significance level of 0.05 ($P<0.05$), a total sample size of 318 - assuming an "allocation ratio" of 1 to 2 (one third) - has an

approximate power of 0.924 (i.e. >90% statistical power) if the anticipated proportions responding are 60% and 40% respectively.

Statistical programming will be done using the software SAS, STATA or R, with transparent reporting of the source code used to analyse the data. Computational details will be available in the pre-specified SAP. These will be finalised before data collection is complete. Our primary analysis set will be based on observations available at the time of study closure. In other words, we will consider 'Data as observed' to be our primary resource for statistical inference. However, for the purpose of sensitivity, multiple sensitivity analyses will be performed to assess the robustness of the primary analyses, including analyses based on the "Non-responder-imputation" and multiple-imputation analyses, which are based on model-based approaches for missing data (these details will be available in the final SAP). A simplistic "null responder imputation" would represent a conservative base case and is likely valid even if data is "missing not at random"[58], as it assumes, and implies that patients have not improved or have worsened after entering the study.

No interim analyses will be performed. All reported P values will be two-sided and by default these will not be adjusted for multiple comparisons. However, due to potential issues of multiplicity, as multiple statistical tests will be performed in the study, we will interpret "statistically significant" findings in the context of whether the 95% confidence interval (95%CI) excludes outcomes that could be perceived as clinically important. We will use the following consistent language to describe effects that might appear as chance findings: "*The prognostic factor appears to have little or no effect on the clinical outcome if the point*

estimate or the boundaries of the 95% CI lies between 0.80 and 1.25". Thus, despite an apparently statistically significant finding (P<0.05), a relative point estimate within the range of 0.80 and 1.25 will not be considered a clinically meaningful effect.

Strengths and limitations of the study

The food frequency questionnaire (FFQ) we use in the present study has been widely used in prospective cohort studies, including in European prospective investigations in the fields of oncology and chronic diseases[59 60]. It has been extensively used and evaluated in the Danish population, and results from different methods demonstrate consistency[61 62]. However, the FFQ is not without limits, in particular with respect to the lack of information on portion sizes[63 64]. We, therefore, modified the FFQ to capture information on portion size[63]. A second potential limitation relates to comprehensive questionnaire completion. However, in a pilot study of 10 hospital patients (50-70 years of age) the FFQ was completed within 40-50 minutes and no complaints were reported. The imprecision of the FFQ will lead to large confidence intervals. The result will most likely lead to null results (rather than type 2 errors). The disease groups are expected to vary in several aspects such as age, gender and body mass index (BMI). We will, however, be unable to determine the potential effect of selective diet reporting on responders and non-responders[65]. On the other hand, studies have suggested that dietary patterns are relatively stable among adults in the Danish population[66]. Due to study design and the limited number of participants, this study may not capture every lifestyle difference between responders and non-responders. Similarly, this study has only limited power to detect gene-environment

interactions. In order to avoid potential type 2 errors, it is important that the results are replicated in other well-characterized patient populations using prospectively sampled dietary information. To further evaluate the robustness of the results, study results would preferably be replicated in cohorts from other countries.

Project organisation

The study team is organised into three significant groups: a Clinical Research Group (CRG), an Analytical Research Group (ARG) (Figure 2) and a Steering Committee (SC). The CRG includes specialists from gastroenterology, rheumatology, dermatology and ophthalmology who will be implicated in the clinical care and assessment of study participants. The ARG will be responsible for performing laboratory analyses on the collected biological material. Finally, the SC -- whose members include Professor Uffe Holmskov, Professor Jens Kjeldsen, Professor Torkell Ellingsen, and Professor Vibeke Andersen -- are responsible for planning and organizing the study within the appropriate legal framework, facilitating meetings for the three study groups and for scientific follow-up. The group as a whole, including clinicians and analysts, is responsible for the scientific results and budget.

Collaboration between patients and health professionals on research projects is a relatively new phenomenon[67-69]. The involvement of patients in research (patient research partners [PRPs]) will ideally will give a stronger voice to patients' views on research,

specifically with respect to research priorities. Furthermore, individual patients and patient organisations can contribute to research study design, preparing educational material, discussing results, disseminating results, and recruiting study participants. Recommendations on incorporating PRPs into research study processes suggest that they should be provided with relevant support and education. With this initiative, we were keen to gain experience with PRPs. Thus, this project was built with input from the Danish Colitis-Crohn's Association, represented by its director Charlotte Lindgaard Nielsen, the Danish Psoriasis Association, represented by its director Lars Werner, and three individual RA patients from one of the participating clinical departments.

The SC will hold telephone conferences every 2-4 week, but more often when necessary, and face-to-face meetings 3-4 times per year. Among participants, the SC will organise telephone conferences every 2-4 weeks, again more often when necessary, and face-to-face meetings at the time of enrolment and every year thereafter until the conclusion of the study.

Perspectives

The use of prognosis research evidence at multiple stages is central to the process of translational research, with the ultimate goal of improving patient outcomes. Prognosis research includes various aspects of importance to healthcare professionals, enabling them to guide individual patients in terms of shared decision making via overall prognosis, knowledge on important prognostic factors or models and subsequently (from randomised

trial evidence) stratified medicine [56 70-72]. We anticipate that the BELIEVE study will reveal prognostic factors of importance, including whether the diet of the patient is likely to interfere with the outcome of being prescribed a TNFi treatment. Hopefully, by combining various phenotype and genotype aspects into the prognostic models, the BELIEVE study will add value to the long-term goal of achieving "personalised medicine".

We will seek to replicate findings that are identified as having prognostic value in other prospective cohorts, including from a planned study of CID cases from the Danish "Diet, Health and Cancer" cohort and potentially from other cohorts with lifestyle data[73 74].

Dissemination of results to the public and scientifically

The target journal for the primary outcome will be a general medical journal directed at family physicians. Family physicians see CID patients across the entire spectrum of disease. Moreover, lifestyle recommendations are an important element of general practice. Hence, although family physicians are not necessarily the primary decision-makers with respect to treatment of CID patients, a role more ably assumed by specialists, they have considerable influence on lifestyle decisions for CID patients. Subsequently, other hypotheses will be analysed and manuscripts prepared (independent of findings), with the intention of submitting additional articles to specialized journals in the areas of nutrition, immunology, gastroenterology, rheumatology, dermatology and ophthalmology.

Authorship confers credit and has important academic, social and financial implications, and therefore any authorship on manuscripts coming from the BELIEVE study is associated with responsibility and accountability for the published work. Thus we intend to follow the recommendations of the International Committee of Medical Journal Editors

(ICMJE) to ensure that contributors who have made substantive intellectual contributions to a paper are given credit as authors, but also that contributors credited as authors understand their role in taking responsibility and being accountable for the published work.

The ICMJE criteria for authorship was designed to distinguish authors from other contributors based on the following 4 criteria: (*i*) substantial contributions to the conception or design of the work; or the acquisition, analysis or interpretation of data for the work; AND (*ii*) drafting the work or revising it critically for important intellectual content; AND (*iii*) final approval of the version to be published; AND (*iv*) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to the scientific reporting of results, major findings with translational implications will be communicated to health professionals, patient organisations, public health policy-makers and to the general public through various media and news activities.

Ethics

Written informed consent will be obtained from participants before participation in the study. The project has been approved by The Regional Scientific Ethical Committee (S-20160124) and the Danish Data Protection Agency (2008-58-035). The procedures followed are in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki

Declaration of 1975 with later amendments.

Funding

This project is part of a project that has received funding from the European Union's Horizon 2020 Research and Innovation Programme under grant agreement No 733100" (P. Rosenstiel, A. Franke, J. Raes, V. Andersen). Funding has furthermore been received from Odense Patient data Explorative Network (OPEN) (OP-332, V. Andersen), "Knud og Edith Eriksen's Mindefond" (V. Andersen), Region of Southern Denmark (V. Andersen), University of Southern Denmark (V. Andersen, U. Holmskov). The Parker Institute, Bispebjerg and Frederiksberg Hospital (R. Christensen, B. L. Heitmann) are supported by a core grant from the Oak Foundation (OCAY-13-309).

Acknowledgements

Lina A Knudsen and Mark Unger are thanked for English proofreading.

Author Contributions: VA, BLH, and RC wrote the first draft. All other authors, KWA, OHN, SBS, MJ, AB, LH, JG, JW, HG, UF, JAV, SGK, JF, SAGRM, TK, JB, JF, JFD, ABB, GLS, ST, NJF, IB, TBB, AS, EBS, AF, DE, PR, JR, MB, LW, CLN, HLM, ABN, TK, JK, UH, contributed to the conception and design of the study. All authors accepted the final submitted version.

Conflicts of Interest:

All authors declare no conflict of interest. However, the following authors declare: B. Heitmann has received funding from "MatPrat", the information office for Norwegian egg

475 and meat; L. Hvid is on the advisory board for Abbvie A/S; J. Fallingborg is on the advisory
476 boards for AbbVie A/S, MSD Denmark, Takeda Pharma A/S, and Ferring Pharmaceuticals
477 A/S; V. Andersen receives compensation for consultancy and for being a member of the
478 advisory board for MSD Denmark (Merck) and Janssen A/S. The funding sponsors had no
479 role in the design of the study; in the collection, analysis, or interpretation of data; in the
480 writing of the manuscript, or in the decision to publish the results.

481

482 **Table 1. Collection of patient characteristics, outcome measures, and explanatory**
483 **variables**

Variable	**Pre**	**Week 14-16**
***Clinical data*[1]:**		
Gender (F, M)	X	
Age (years)	X	
Diagnosis (disease)	X	
Onset of diagnosis (year)[2]	X	
Education (level)[3]	X	
Menopause (year)	X	
Comorbidity (diseases, Charlson index)	X	
Medication (predefined choices)	X	X
Diet (FFQ)[3] (predefined choices)	X	
Changes in diet (predefined choices)		X

Non-dietary lifestyle factors[3] (predefined choices)	X	X
***Investigations*:**		
Height (cm)	X	
Weight (kg)	X	X
Body mass index (kg/cm^2)	X	X
Routine blood analyses[4]	X	X
Endoscopy[5]	X	X
***Biological samples*[6]:**		
Fasting blood samples	X	X
Faeces samples	X	X
Urine samples	X	X
Biopsies[5]	X	X
Crohn's disease (CD)		
Disease location (predefined choices)	X	
Prior operations (y/n, description)	X	
Disease behaviour (fistulising, luminal)	X	
Perianal involvement (y/n)	X	
STRIDE – (y/n)	n.a.	X

Abdominal pain (y/n)	X	X
Diarrhoea (y/n)	X	X
Altered bowel habit (y/n)	X	X
SES-CD (score)	X	X
Presence of ulcers (score)	X	X
Ulcerated surface (score)	X	X
Affected surface (score)	X	X
Presence of narrowing (score)	X	X
Number of affected segments (score)	X	X
Alterations of cross-sectional imaging (MR, CT, UL) (y/n)[7]	X	X
HBI index (score)	X	X
***HBI of 4 or less (y/n)**	**X**	**X**
General well-being (score)	X	X
Abdominal pain (score)	X	X
No. of liquid stools per day (N)	X	X
Abdominal mass (score)	X	X
Manifestations (abscess, fistulas, fissures, arthralgia, uveitis, erythema nodosum, pyoderma gangrenosum, mouth ulcers, one point for each) (N)	X	X
Physician global assessment (score)	X	X
Physician global assessment (0–100 mm VAS)	X	X

Patient global assessment (0–100 mm VAS)	X	X
Corticosteroid-free remission[8] (y/n)		X
Concomitant medication (y/n, predefined choices)	X	X
Number of draining fistulas (fistulising CD)	X	X
Ulcerative colitis (UC)		
Disease location (predefined choices)	X	
Prior operations (y/n, description)	X	
STRIDE criteria (y/n)	n.a.	X
Rectal bleeding (y/n)	X	X
Altered bowel habit (y/n)	X	X
Endoscopic remission (Mayo endoscopic sub-score of 0-1)	X	X
*Mayo Clinical Score of 2 or less with no individual sub-score of >1	**X**	**X**
Mayo "normal mucosal appearance" (y/n)	X	X
Mayo clinical response[9] (y/n)	X	X
Mayo clinical score (score)	X	X
Mayo endoscopic sub-score (score)	X	X
Stools (score)	X	X
Rectal bleeding (score)	X	X
Physician global assessment (score)	X	X
SCCAI (score)	X	X

Bowel frequency (day) (score)	X	X
Bowel frequency (night) (score)	X	X
Urgency of defecation (score)	X	X
Blood in stool (score)	X	X
General well-being (score)	X	X
Extracolonic features (1 per manifestation)	X	X
Physician global assessment (0–100 mm VAS)	X	X
Patient global assessment (0–100 mm VAS)	X	X
Corticosteroid-free remission[8] (y/n)		X
Concomitant medication (y/n, predefined choices)	X	X
Rheumatoid arthritis (RA)		
Positive for anti–CCP/RF (y/n)	X	
Swollen-joint count (of 28/66 joints examined)	X	X
Tender-joint count (of 28/68 joints examined)	X	X
DAS28-CRP (score)	X	X
Simplified disease activity index (SDAI) (score)	X	X
***ACR20 (y/n)**	**n.a.**	**X**
ACR50 (y/n)	n.a.	X
ACR70 (y/n)	n.a.	X
EULAR good or moderate response (y/n)	n.a.	X

Low disease activity (DAS28 <3.2)	n.a.	X
DAS28 remission (DAS28 <2.6)	n.a.	X
Physician global assessment (0-100 mm VAS)	X	X
Patient global assessment (0-100 mm VAS)	X	X
Patient assessment of pain (0-100 mm VAS)	X	X
HAQ (score)	X	X
Axial spondyloarthropathy (axSpA)		
Positive for HLA-B27 (y/n)	X	
BASDAI (score)	X	X
BASFI (score)	X	X
BASMI (score)		
Total score for back pain (0–100 mm VAS)	X	X
Patient global assessment of disease activity (0-100 mm VAS)	X	X
Patient assessment of pain (0-100 mm VAS)	X	X
Physician global assessment (0-100 mm VAS)	X	X
***ASAS20 (y/n)**	**n.a.**	**X**
ASAS40 (y/n)	n.a.	X
ASAS partial response (y/n)	n.a.	X
ASAS5/6 response (y/n)	n.a.	X

Psoriatic arthritis (PsA)		
Dactylitis (y/n)	X	X
Enthesitis (y/n)	X	X
PASI (score)	X	X
PASI 75 response (y/n)	n.a.	X
PASI 90 response (y/n)	n.a.	X
***ACR20**	**n.a.**	**X**
Swollen-joint count (of 28/66 joints examined)	X	X
Tender-joint count (of 28/68 joints examined)	X	X
DAS28-CRP (score)	X	X
Patient global assessment of disease activity (0-100 mm VAS)	X	X
Patient assessment of PsA pain (0-100 mm VAS)	X	X
Physician global assessment (0-100 mm VAS)	X	X
Simplified disease activity index (SDAI)	X	X
HAQ (score)	X	X
Psoriasis (PsO)		
Psoriatic arthritis (y/n)	X	X
PASI (score)	X	X
*PASI75 response (y/n)	n.a.	X
PASI90 response (y/n)	n.a.	X

Patient global assessment of disease activity (0-100 mm VAS)	X	X
Patient assessment of PsA pain (0-100 mm VAS)	X	X
Physician global assessment (0-100 mm VAS)	X	X
DLQI (score)	X	X
Hidradenitis Suppurativa (HS)		
***HiSCR response**	**n.a.**	**X**
Hurley stage[10] (score)	X	X
Previous systemic treatment (y/n, description)	X	
Prior surgery (y/n, description)	X	
Lesion counts (N)	X	X
Total no. of abscesses and inflammatory nodules (N)	X	X
No. of abscesses (N)	X	X
No. of inflammatory nodules (N)	X	X
No. of draining fistulas (N)	X	X
Modified Sartorius score (score)	X	X
Percentage of participants who achieve abscess and inflammatory nodule (AN) count of 0, 1, and 2, respectively	X	X
Patient global assessment of skin pain (score)	X	X
DLQI (score)	X	X

Non-infectious uveitis (NiU)		
SUN (score)	X	X
***Uveitis treatment failure (y/n)**	**n.a.**	**X**
New active, inflammatory chorioretinal or retinal vascular lesions relative to baseline (y/n)	X	X
Inability to achieve ≤ 0.5+ or a 2-step increase relative to best state achieved at all visits in anterior chamber cell grade or vitreous haze grade (y/n)	X	X
Worsening of best corrected visual acuity by ≥ 15 letters relative to best state achieved (y/n)	X	X
Health-related quality of life[11]	***X***	***X***
SF12 (score)	X	X
SHS (score)	X	X
Physician global assessment (0–100 mm VAS)	X	X
Patient global assessment (0–100 mm VAS)	X	X
ROME-III (score)	X	X
NYHA (score)	X	X
Cont. anti-TNF treatment (y/n, predefined choices for stopping if no)	X	X
Adverse events		

Discontinuation due to adverse events (y/n)		X
Serious adverse event (y/n)		X
Death (y/n)		X
Occurrence of surgery (y/n)		X
Occurrence of hospital admission (y/n)		X
Occurrence of disease-related complication (y/n)		X
***Laboratory*[4]**		
CRP (mg/l)[12]	X	X

***Primary endpoint for the individual diseases**

[1]Data will be collected using a questionnaire as well as local and national registries.

[2]Registry data will be retrieved from the Danish registries using the Danish individual civil registration number (CPR) including BIO-IBD[75], DANBIO[76], DERMBIO[77] (database on IBD, RA, HS, axSpA, PsA, and PsO patients on biological therapy), the National Patient Registry (e.g. comorbidity), registries on medication and use of receipts, local laboratory databases (laboratory data) and the electronic patient records (side effects).

[3]Lifestyle (dietary and non-dietary) will be registered using a validated food-frequency questionnaire (FFQ) that includes food items, and a photographic food atlas of picture series of portion sizes will be used to assess intake of food groups, such as meat and dairy, and calculate total energy, fibre, protein, fat, sugar, and carbohydrate intakes as well as glycemic index and load. In addition, questions on non-diet lifestyle factors (smoking,

physical activity, alcohol consumption, and use of over-the-counter medicine [use of probiotics, prebiotics, painkillers, laxative, and anti-diarrhoea agents]) as well as educational level and year of menopause (female) are included[63]. The follow-up questionnaire is identical to the initial questionnaire apart from the questions on food items that only contain questions on changes of diet since the last questionnaire.

[4]Routine blood analyses include C-reactive protein (CRP), haemoglobin, erythrocyte count, haematocrit, erythrocyte mean cell volume (MCV), mean cell haemoglobin (MCH) and mean cell haemoglobin concentration (MCHC), leucocyte count, differential count, thrombocytes, albumin, K+ potassium, Na+ sodium, creatinine, coagulation factor II+VII+X, alanine aminotransferase (ALAT), alkaline phosphatase, gamma-glutamyl transferase (GGT), haemoglobin glycation (Hb1Ac), lipids (cholesterol, high density, low density cholesterol), and transglutaminase.

[5]Only IBD patients

[6]From all participants, blood, urine, and faeces are sampled. In addition, from IBD patients, intestinal biopsies are sampled. In selected cases, the additional biological material on participants from this study may be retrieved from the Patobank and the Danish Biobank. The samples will be collected adhering to the Sample PRE-analytical Code (SPREC) and Biospecimen Reporting for Improved Study Quality (BRISQ) guidelines, using standard operational procedures (SOPs) describing and logging primary container, centrifugation conditions, centrifugation parameters, and storage conditions[78 79]. The biological material will be stored in OPEN (biological material from OUH) or at SHS (biological material from

the other hospitals).

[7]Only CD patients when endoscopy cannot adequately evaluate inflammation.

[8]Corticosteroid-free remission. Clinical remission in patients using oral corticosteroids at baseline (Pre) that have discontinued corticosteroids and in clinical remission at first follow-up.

[9]A reduction in complete Mayo score of ≥3 points and ≥30% from baseline (or a partial Mayo score of ≥2 points and ≥25% from baseline, if the complete Mayo score was not performed at the visit) with an accompanying decrease in rectal bleeding sub-score of ≥1 point or absolute rectal bleeding sub-score of ≤1 point

[10]Data for the Hurley stage reflect actual assessment. A patient's overall Hurley stage is the highest stage across all affected anatomical sites. Stage 1 is defined as the localised formation of single or multiple abscesses without sinus tracts or scarring, stage II as recurrent abscesses (single or multiple) with sinus tract formation and scarring, and stage III as multiple abscesses with extensive, interconnected sinus tracts and scarring.

[11]All participants will be asked whether they have any complaints regarding or are known with diseases affecting the bowel, the skin, rheumatic complaints etc., and if no to both questions they will not be asked to complete the relevant questionnaire.

[12]Biological response defined as a drop in CRP level of more than 25% or to the normal level among patients with an elevated CRP before treatment (higher than normal range)[80].

Abbreviations: ACR, American College of Rheumatology; ASAS20/40, Assessment of Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease

Activity Index; BASFI (Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; DAS28, Disease activity score; DLQI[81 82], Dermatology Life Quality Index; FFQ, Food frequency questionnaire; HBI, Harvey-Bradshaw Index; HiSCR[51], Hidradenitis Suppurativa Clinical Response; HAQ, Health Assessment Questionnaire; NYHA, New York Heart Association; PASI, Psoriasis Area and Severity Index; SCCAI, Simple Clinical Colitis Activity Index; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF12, Short Form Health Survey; SHS[83 84], Short Health Scale; SUN, Standardization of Uveitis Nomenclature for Reporting Clinical Data; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease [53]

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FIGURE LEGENDS

Figure 1. Hypothesis for effects of diet in relation to treatment effect

(Left) Low levels of fibre intake may promote microbial metabolism of mucus as the main energy source [37 85 86]. This will lead to decrease of the mucus layer. Further, degradation of mucus releases free sulphate which would then become available for utilisation by sulphate-reducing bacteria (like *Bilophila wadsworthia*) for microbial produced hydrogen sulphide[87]. In addition, high intake of food containing organic sulphur and sulphate additives, such as meat and processed meat, may increase the amount of sulphate for microbial produced hydrogen sulphide[88 89]. The resultant hydrogen sulphide from low intake of fibre and high intake of meat may reduce the disulphide bonds in the mucus network rendering the mucus layer penetrable to e.g. bacteria [87 90]. Then, microbial-associated molecular patterns (MAMPs) from microbes or contained in the diet may reach the epithelium and activate the pattern recognition receptors (PRR) such as Toll-like receptors (TLRs) on the enterocytes (intestinal epithelial cells, IEC), and next activate nuclear factor-kappa B (NFkB), type I interferon (IFN), and other inflammatory pathways. This leads to production of pro-inflammatory (tumour necrosis factor-α (TNF), interleukin (IL)-1β, IL-6, IFN, IL-17 etc.), and anti-inflammatory (primarily IL-10) cytokines and chemokines that will next activate innate lymphocytic cells (ILC) and other immune cells and the immune system in general[91 92]. There is some support for such a mechanism in CID, including findings of; high amounts of sulphate-reducing bacteria in UC patients[87 93]; an association between the highest tertile of carbohydrate-restricted diet and RA, in a nested case-control study among 386 individuals who developed RA and 1886 matched controls from the Swedish Västerbotten Intervention Program (VIP) cohort with prospectively sampled dietary survey[94]; association of high fibre intake with low risk of CD among 170 776 participants from the prospective Nurses' Health Study I (NHSI)[23]; association of high intake of red meat and total protein and risk of developing inflammatory polyarthritis in the population-based prospective cohort of 25 630 participants from the European Prospective Investigation of Cancer in Norfolk (EPIC-Norfolk)[35]. Finally, a prospective study of 191 UC patients in remission found that

high consumption of meat, particularly red and processed meat, protein, and alcohol was associated with risk of relapse, and that high sulphur or sulphate intakes may offer an explanation for the observed findings[95]. Additionally, support of the notation that diet may affect systemic immune response is provided by the finding that intake of low-glycemic index diet was found to lower secretion of TNF and IL-6 from stimulated peripheral blood mononuclear cells from obese humans[96]. **(Right)** Intake of high fibre and low meat may promote an effective mucosal barrier and support the effects of outcome after drug targeting the pro-inflammatory molecule TNF (TNF inhibitors [TNFi]). Intake of soluble plant fibre has been found to block bacterial adhesion to gut enterocytes in animal and cell studies[97]. The genetic architecture of the individual may also impact the influence of lifestyle factors[15]. Hence, in order to provide lifestyle recommendations, we need to understand the effects of lifestyle on the immune system, and how lifestyle may improve the therapeutic outcome and reduce the need of medical treatment in the individual person. Information on diet and non-diet lifestyle exposures may be collected by using e.g. questionnaires and lifestyle-associated biomarkers or a combination of these methods [98-100]. Evidence-based biomarkers for lifestyle assessment are scarce [101-121] and mostly used for studies on healthy individuals [122-125].

Figure 2. Organisation and patient research partners

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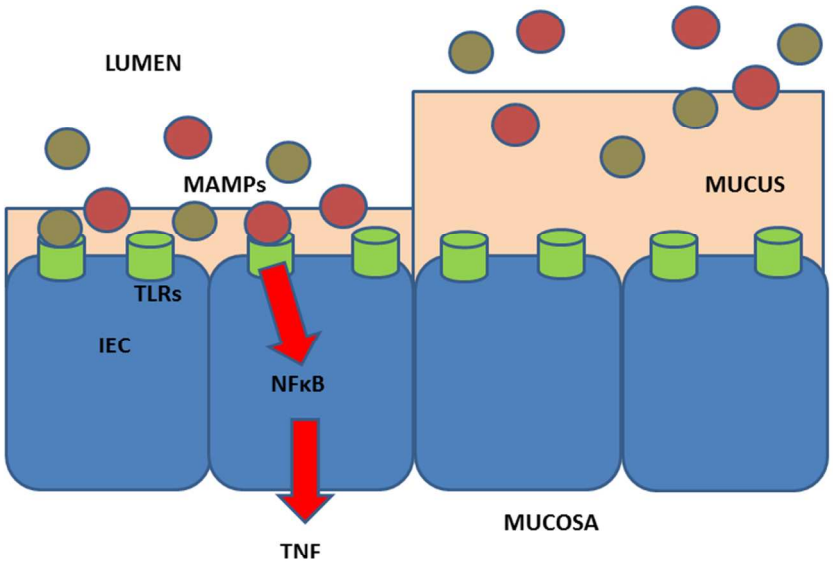

Figure 1. Hypothesis for effects of diet in relation to treatment effect

81x60mm (300 x 300 DPI)

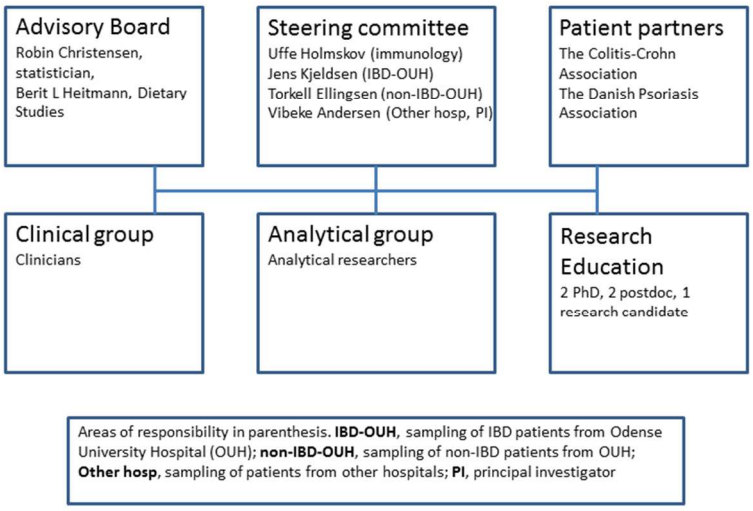

Figure 2. Organisation and patient research partners

81x60mm (300 x 300 DPI)

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_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	_suppl_____
Funding	4	Sources and types of financial, material, and other support	_14_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	2 and 14_____
	5b	Name and contact information for the trial sponsor	___2_____
	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	_7-14_____
	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)	__7, 11- 14

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	__Figure 1____
	6b	Explanation for choice of comparators	__8_____
Objectives	7	Specific objectives or hypotheses	__6_____
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)	__7_____
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	___7_____
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)	____7_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__7_____
	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)	___NA_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	___NA_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	___NA_____
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	____8-10_____
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)	____7_____

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	__12_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___7_____
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	___NA_____
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	_____NA_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____NA_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__7_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__NA_____
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	___19_____
	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	__19_____

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	19
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	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	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)	12
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	NA
	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	NA
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	19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
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)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
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	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
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	NA
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	NA
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	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	suppl
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	19

*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.