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# BMJ Open

**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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1 **Impact of red and processed meat and fibre intake on treatment**  
2 **outcome among patients with chronic inflammatory diseases:**  
3 *Protocol for a prospective cohort study on prognostic factors and*  
4 *personalised medicine*

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55 **ABSTRACT**

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

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

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3 77 **Ethics and dissemination:** The overarching goal of this project is to improve the lives of  
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5 78 patients suffering from CID, by providing evidence to support dietary recommendations  
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7  
8 79 likely to improve the clinical outcome. The study is approved by the local Ethics  
9  
10 80 Committee (S-20160124) and the local Data Agency (2008-58-035). The study findings will  
11  
12 81 be disseminated in peer-reviewed journals, via patient associations, and presented at  
13  
14 82 national and international conferences.

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18 83 **Trial Registration details:** ClinicalTrials.gov identifier: NCT03173144

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22 84 Keywords: biomarker; lifestyle; personalized medicine; patient related outcome measures  
23  
24 85 (PROMs); treatment outcome; western style diet (WSD)  
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#### 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- $\alpha$
- 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

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## 88 INTRODUCTION

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

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

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3 112 prospectively collected lifestyle data, such as European Investigation into Cancer and  
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5 113 Nutrition (EPIC) Study and the Nurses' Health Study (NHS)<sup>20-34</sup>.

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8 114 In light of the large impact from the environment on the disease development mirrored  
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10 115 by the increasing incidence<sup>5 10</sup>, it seems that the environment, including lifestyle, may  
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12 116 influence treatment response. Accordingly, many patients ask their health care  
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14 117 professionals about lifestyle recommendations that can improve the outcome of TNFi.  
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### 19 119 **Evidence-Based Research**

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23 120 In an attempt to increase value and reduce waste in research, no new studies should be  
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25 121 done without a systematic review of existing evidence<sup>35</sup>. In a recent systematic review  
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27 122 investigating the current knowledge on the impact of diet on TNFi response in IBD<sup>36</sup>, it was  
28  
29 123 concluded that an evidence-based dialogue on the impact of diet on TNFi treatment  
30  
31 124 response for clinical use is scarce. Similarly, to the best of our knowledge, only few large  
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33 125 prospective studies have assessed effects of lifestyle on anti-TNF treated CID patients <sup>37</sup>.  
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35  
36 126 One prospective study compared partial enteral nutrition (16 patients), exclusive enteral  
37  
38 127 nutrition (22 patients), and anti-TNF (52 patients) therapy in 90 paediatric patients. There  
39  
40 128 were no significant differences in clinical response rates between the three treatments;  
41  
42 129 however, the rate of patients that achieved a faecal calprotectin  $\leq 250$   $\mu\text{g/g}$  was higher  
43  
44 130 among the anti-TNF treated patients than the other treatment arms<sup>38</sup>.  
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49 131 More recently, potential lifestyle factors for further investigation in relation to TNFi  
50  
51 132 therapy among CID patients were identified<sup>39</sup>. In order to explore different hypotheses, we  
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53 133 included studies that may be subject to recall bias, and bias introduced by lifestyle changes  
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55 134 due to the disease itself; among identified factors were smoking, physical activities, and  
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3 135 intake of Western style diet<sup>39</sup>. In fact, we have proposed a model whereby a diet high in  
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5 136 meat and low in fibres may impact inflammation and anti-TNF treatment<sup>36</sup> (Figure 1).  
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8 137 Following the previous evidence provided, we set out to prospectively identify  
9  
10 138 lifestyle factors that support achievement of optimal treatment outcome. The ultimate aim  
11  
12 139 is to improve the quality of life of the individual CID patient by providing feasible advice  
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14 140 such as dietary recommendations for improved treatment outcome.  
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## 20 21 22 142 **Aims and hypotheses** 23

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25 143 The primary aim of this prospective cohort study is to investigate whether treatment  
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27 144 outcomes across conditions differ between various predefined lifestyle factors. The main  
28  
29 145 hypothesis is that '*Diets high in fibre AND low in red and processed meat are associated with an*  
30  
31 146 *improved treatment outcome*'. Secondary aims are to investigate whether and to what extent  
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33 147 lifestyle-associated biomarkers have prognostic value for differentiating responders from  
34  
35 148 non-responders based on both disease-specific and generic treatment outcomes.  
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3 150 **METHODS AND ANALYSIS**  
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6 151 **Design**  
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10 152 The BELIEVE study is a prospective cohort study with focus on disease activity after (14-16  
11  
12 153 weeks) of initiating TNFi. The primary endpoint will be assessed at week 14-16 after  
13  
14 154 initiation of TNFi, and is defined based on specific CID condition; where a A: Responder  
15  
16 155 according to the specific criteria described below (incl. drug-continuation) or B:  
17  
18 156 Non-responder (incl. drug-discontinuation). Whether a patient will discontinue therapy is  
19  
20 157 assumed to be based on a certain degree of shared decision making between the patient  
21  
22 158 and physician supported by principles from national guidelines for each CID as  
23  
24 159 recommended in the respective national guidelines <sup>40</sup> and laboratory data.  
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33 161 **Setting**  
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36 162 The study took place at the 1) Department of Gastroenterology and Hepatology, Aalborg  
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38 163 University Hospital; 2) Department of Hepatology and Gastroenterology, Aarhus  
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40 164 University Hospital; 3) Diagnostic Centre, Silkeborg Regional Hospital; 4) Department of  
41  
42 165 Internal Medicine, Herning Regional Hospital; 5) Department of Gastroenterology, Herlev  
43  
44 166 Hospital; 6) Organ Centre, Hospital of Southern Jutland; 7) Department of  
45  
46 167 Gastroenterology Hospital of South West Jutland; 8) Department of Medical  
47  
48 168 Gastroenterology, Department of Rheumatology, Department of Dermatology and Allergy  
49  
50 169 Centre, and Department of Ophthalmology, Odense University Hospital will be included  
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52 170 from 1<sup>st</sup> of April 2017 and until 31<sup>th</sup> of Marts 2019 or until a minimum of 100 patients with  
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171 IBD, 100 patients with RA, and 120 patients with axSpA, PsA, PsO, HS and NiU are

172 achieved.

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#### 174 **Patient characteristics and eligibility criteria**

175 Inclusion criteria: patients  $\geq 18$  years with CID assigned for initiation of TNFi therapy for

176 the first time and able to read and understand Danish. Exclusion criteria: patients that

177 previously have received biological treatment and patients not mentally able to answer the

178 questionnaire.

179 Clinical data (Table 1) consist of personal data, data on health and disease, lifestyle,

180 laboratory measurements, and disease activity scores including patient-reported outcome

181 measures (PROMs), clinical assessments, and laboratory data. Each participant will fill out

182 validated questionnaires on disease activity, quality of life, and lifestyle using an electronic

183 link. Studies have revealed electronic questionnaires to be comparable to paper-based in

184 relation to the outcomes (i.e. PROMs)<sup>41 42</sup>.

185

#### 186 **Primary and secondary endpoints**

187 *Primary endpoint:* The predefined primary endpoint will be the proportion of patients with

188 clinical response to therapy at first clinical followup (i.e. week 14-16 according to Danish

189 standard):

190 • Crohn's disease: clinical remission, defined as Harvey and Bradshaw Index (HBI) of

191 4 or less<sup>43</sup>

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3 192 • Ulcerative colitis: clinical remission, defined as Mayo Clinic Score of 2 or less (with  
4  
5 193 no individual subscore of >1)<sup>44</sup>  
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9 194 • Rheumatoid arthritis: clinical response, defined as at least 20% improvement  
10  
11 195 according to the criteria of the American College of Rheumatology (ACR20)<sup>45</sup>  
12  
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14 196 • Axial spondyloarthritis: clinical response, defined as at least 20% improvement in  
15  
16 197 Assessment of Spondyloarthritis International Society (ASAS20)<sup>46 47</sup>  
18  
19  
20 198 • Psoriatic arthritis: clinical response, defined as at least 20% improvement according  
21  
22 199 to the criteria of the American College of Rheumatology (ACR20)<sup>48</sup>  
23  
24  
25  
26 200 • Psoriasis: clinical response, defined as at least 75% improvement in Psoriasis Area  
27  
28 201 and Severity Index (PASI 75)<sup>49</sup>  
29  
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31  
32 202 • Hidradenitis suppurativa: clinical response, defined as at least a 50% reduction in  
33  
34 203 the abscess and inflammatory-nodule count, with no increase in abscess or  
35  
36 204 draining-fistula counts (HiSCR response)<sup>50</sup>  
37  
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39  
40 205 • Non-Infectious Uveitis: clinical response, defined as those who did not have a  
41  
42 206 treatment failure (treatment failure will be based on assessment of new  
43  
44 207 inflammatory lesions, best corrected visual acuity, anterior chamber cell grade, and  
45  
46 208 vitreous haze grade)<sup>51</sup>  
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51 209 *Key secondary outcomes:* Major secondary outcomes include, where available disease-specific  
52  
53 210 outcome measures, covering core outcome sets as well as generic health-related quality of  
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55 211 life (HRQoL) and disability at endpoint (first clinical followup; i.e., week 14-16 according to  
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57 212 Danish standard):  
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4 213 Crohn's disease: STRIDE (Abdominal pain, Diarrhoea, Altered bowel habit,  
5  
6 214 SES-CD [Presence of ulcers, Ulcerated Surface, Affected surface, Presence of  
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8  
9 215 narrowings, Number of affected segments], Alterations of cross-sectional imaging  
10  
11 216 [MR, CT, UL][Only when endoscopy cannot adequately evaluate inflammation]),  
12  
13  
14 217 HBI (General well-being, Abdominal pain, Number of liquid stools per day,  
15  
16  
17 218 Abdominal Mass, Extraintestinal Manifestations [Abscess, fistulas, fissures,  
18  
19 219 arthralgia, uveitis, erythema nodosum, pyoderma gangrenosum, mouth ulcera]),  
20  
21  
22 220 Physician global assessment, Number of draining fistulas, Corticosteroid-Free  
23  
24  
25 221 Remission, Concomitant medication  
26  
27  
28 222 Ulcerative Colitis: STRIDE (Rectal bleeding, Altered bowel habit, Endoscopic  
29  
30  
31 223 remission [Mayo endoscopic subscore of 0-1]), Mayo Clinical Score (Mayo  
32  
33 224 endoscopic subscore, Stools, Rectal bleeding, Physicians global assessment), Mayo  
34  
35  
36 225 "normal mucosal appearance", Mayo clinical response, SCCAI (Bowel frequency  
37  
38 226 [day], Bowel frequency [night], Urgency of defecation, Blood in Stool, General  
39  
40  
41 227 well-being, Extracolonic features), Physician global assessment, Corticosteroid-Free  
42  
43  
44 228 Remission, Concomitant medication  
45  
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47 229 Rheumatoid Arthritis: Tender joints, Swollen joints, Pain, Physician global  
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49  
50 230 assessment, Patient global assessment, HAQ-DI, C-Reactive protein, DAS28-CRP,  
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52  
53 231 Simplified Disease Activity Index (SDAI)  
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56 232 Axial Spondyloarthritis: BASFI, BASDAI, BASMI, Total score for back pain,  
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58  
59 233 Physician global assessment, Patient global assessment, C-Reactive protein  
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4 234 Psoriatic Arthritis: Tender joints, Swollen joints, Psoriatic Arthritis Pain, Physician  
5  
6 235 global assessment, Patient global assessment, HAQ-DI, C-Reactive protein,  
7  
8  
9 236 DAS28-CRP, Simplified Disease Activity Index (SDAI), PASI  
10  
11  
12 237 Psoriasis: PASI, Physician global assessment, Patient global assessment, Psoriatic  
13  
14 238 Arthritis Pain, Dermatology Life Quality Index (DLQI) Total Score.  
15  
16  
17  
18 239 Hidradenitis Suppurativa: Percentage of Participants who achieve Abscess and  
19  
20 240 Inflammatory Nodule (AN) Count of 0, 1, and 2, respectively, Patient's Global  
21  
22 241 Assessment of Skin Pain, Modified Sartorius Score  
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27 242 Non-Infectious Uveitis: New active, inflammatory chorioretinal or retinal vascular  
28  
29 243 lesions relative to Baseline, Inability to achieve  $\leq 0.5+$  or a 2-step increase relative to  
30  
31 244 best state achieved at all visits in anterior chamber cell grade or vitreous haze  
32  
33 245 grade, Worsening of best corrected visual acuity by  $\geq 15$  letters relative to best state  
34  
35 246 achieved.  
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40 247 *Exploratory secondary (tertiary) outcomes:* As exploratory outcomes we will use biological  
41  
42 248 measures, disease specific disease activity measures as individual measure and combined  
43  
44 249 in scores as well as changes of these (including those measured by physician/patients such  
45  
46 250 as patients' health related quality of life) at first clinical followup<sup>52</sup> (week 14-16) (Table 1).  
47  
48 251 Furthermore, change in use of concomitant medicine, steroid-free remission, serious  
49  
50 252 adverse events (e.g. hospitalisations), and surgery at first clinical followup<sup>52</sup> (week 14-16)  
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52 253 will be used (Table 1).  
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3 255 **Prognostic factors**  
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6 256 *Primary exposure variable:* For the primary prognostic model, the primary exposure variables  
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9 257 will be in prioritized order:

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11  
12 258 • Upper tertile (33.3% of the total sample) based on the ratio of fibre/meat intake is  
13 associated with better treatment outcome  
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15 259  
16  
17 260 • Low intake of red and processed meat (defined as below the lower tertile [33.3% of  
18 the total sample]) and high intake of dietary fibres (defined as those above the  
19  
20 261 the total sample]) are independently associated with better  
21  
22 262 upper tertile [33.3% of the total sample]) are independently associated with better  
23  
24 263 treatment outcome, and a potential interaction between them gives the best  
25  
26 264 treatment outcome.  
27  
28  
29

30  
31 265 *Other (exploratory) exposure variables:*  
32  
33

- 34  
35 266 • Lifestyle factors independently or combined (red and processed meat, vegetables,  
36  
37 267 dietary fibre, cereals, gluten, legumes, red wine, dairy products, physical activity,  
38  
39 268 smoking, total protein/ fat, protein/ fat from red and processed meat, glyceimic  
40  
41 269 index)  
42  
43  
44 270 • Pretreatment lifestyle-associated biomarkers  
45  
46 271 • Combinations of lifestyle factors and lifestyle-associated biomarkers  
47  
48 272 • Gene-environment interaction analyses  
49  
50 273 • Pretreatment levels of inflammatory molecules  
51  
52  
53  
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56 274  
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58

59 275 **Data management**  
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1  
2  
3 276 The electronic questionnaire is in Danish language and the participants will have access to  
4  
5 277 the questionnaire by an electronic link sent to their personal, electronic mailbox. All data  
6  
7  
8 278 will be stored in a secure research storage facility<sup>53</sup>. Information registered by clinicians and  
9  
10 279 technicians will occasionally be transferred from paper format to electronic format using  
11  
12  
13 280 either double entry of data or automated forms processing<sup>54</sup>.

14  
15  
16 281 No important risk for the participating patients is foreseen as a direct result of the  
17  
18  
19 282 project. The clinicians will handle the healthcare of included patients as normal. As a result  
20  
21  
22 283 of this, no Data Management Committee will be established.  
23

24  
25 284

## 26 27 28 285 **Statistical methods**

29  
30  
31 286 Prognostic factor research is developed to aid health care providers in estimating the  
32  
33  
34 287 probability or risk that a specific event will occur in the future (prognostic models), and  
35  
36  
37 288 should subsequently be able to inform decision making<sup>55</sup>. Conceptually, we define a good  
38  
39  
40 289 prognostic model as one that works satisfactorily (i.e. is truthful) for patients other than  
41  
42  
43 290 those from whose data it was derived<sup>56</sup>. We will use this rigorously designed, prospective  
44  
45  
46 291 cohort study to explore our ability to predict clinical response across the conditions  
47  
48  
49 292 included (Y=primary endpoint), and explore whether patients who are on a diet high in  
50  
51  
52 293 fibre AND low in red and processed meat (X=assessed at baseline) is an informative  
53  
54  
55 294 prognostic factor. Per default, the statistical models will include condition (any of the CID  
56  
57  
58 295 conditions included), and clinical centre (site #1 to #8) as fixed effects. Specific details will  
59  
60 296 be part of the final Statistical Analysis Plan (SAP). In terms of transparency, we will follow

1  
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3  
4 297 the guidance from the 'Transparent Reporting of a multivariable prediction model for Individual  
5  
6 298 Prognosis Or Diagnosis' (TRIPOD) for the reporting of the multivariable models<sup>57</sup>.

7  
8  
9 299 *Sample size considerations:* It is a well-known difficulty for exploratory prognostic factor  
10  
11 300 research studies like this, to formalize how many participants (i.e. their anticipated events)  
12  
13  
14 301 to include. In order to consider an adequate number of outcome events, we apply "the rule  
15  
16  
17 302 of thumb" that dictates that 10 outcome events are needed for each independent variable  
18  
19  
20 303 (possible predictors); we plan to enrol 320 patients in total, and anticipate that 50% of these  
21  
22 304 will experience a clinical response during the 14-16 week period after therapy with TNFi is  
23  
24  
25 305 initiated. With this in mind: Anticipating that we will see at least 160 events (i.e. clinical  
26  
27 306 responses among the 320 patients), we will have a reasonable power to explore the impact  
28  
29  
30 307 of as many as 16 independent (predictor) variables (including condition and clinical  
31  
32  
33 308 centre).

34  
35 309 If we focus on the contrast between groups, for a comparison of two independent  
36  
37 310 binomial proportions (those with high fibre AND low meat intake vs other) using Pearson's  
38  
39  
40 311 Chi-square statistic with a Chi-square approximation with a two-sided significance level of  
41  
42  
43 312 0.05 ( $P < 0.05$ ), a total sample size of 318 - assuming an "allocation ratio" of 1 to 2 - has an  
44  
45  
46 313 approximate power of 0.924 (i.e. >90% statistical power) if the anticipated proportions  
47  
48  
49 314 responding are 60% and 40%, respectively.

50  
51 315 All the statistical programming will be done in SAS, STATA or R, transparently  
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53  
54 316 reporting the source code used to analyse the data. All computational details will be  
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56  
57 317 available in the pre-specified SAP, which will be finalised before data collection is  
58  
59 318 complete. Our primary analysis set will be based on those observations that we have  
60

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3  
4 319 available at closure; i.e. we will consider 'Data as observed' to be our primary resource for  
5  
6 320 statistical inference. However, for the purpose of sensitivity, multiple sensitivity analyses  
7  
8  
9 321 will be performed to assess the robustness of the primary analyses, including analyses  
10  
11 322 based on the "Non-responder-imputation", and multiple-imputation analyses - which is  
12  
13 323 based on model-based approaches for missing data (these details will be available in the  
14  
15 324 final Statistical Analysis Plan). A simplistic "null responder imputation" would  
16  
17 325 represent a conservative base case, and is likely valid even if data is "missing not at  
18  
19 326 random"<sup>58</sup>, as it assumes and imply that the patients have had no improvement (or  
20  
21 327 worsening) since entering the study.  
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### 30 **Project organisation**

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34 330 The project is organised with a Clinical Research Group (CRG) and an Analytical Research  
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36 331 Group (ARG). The CRG includes specialists from the medical, gastroenterological,  
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38 332 rheumatological, dermatological and ophthalmological departments that are sampling the  
39  
40 333 cohort. The ARG will perform the analyses on the biological material.  
41  
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44 334 Furthermore, the project is organised with a steering committee (SC) (including  
45  
46 335 Professor Uffe Holmskov, Professor Jens Kjeldsen, Professor Torkell Ellingsen, and  
47  
48 336 Professor Vibeke Andersen) that is responsible for the scientific follow-up and will be  
49  
50 337 organising meetings for the involved parties. The PI has planned and organised the study  
51  
52 338 and has achieved the legal permissions. The whole group including clinicians and analysts  
53  
54 339 is responsible for the scientific results and the economy.  
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4 340 Collaboration between patients and health professionals on research projects is  
5  
6 341 relatively new<sup>59-61</sup>. Involvement of patients in research (patient research partners [PRPs])  
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8  
9 342 should result in patients' views e.g. on prioritising, being heard and incorporated.  
10  
11 343 Furthermore, individual patients and patient organisations may help in designing research  
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13 344 studies, preparing information material, discussing results, dissemination of results, and  
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15 345 recruitment of study participants. Recommendations include relevant support and  
16  
17 346 education of PRPs. With this initiative, we wanted to get experiences with including PRPs.  
18  
19 347 Thus this project builds on input from the Danish Colitis-Crohn Association, represented  
20  
21 348 by the director Charlotte Lindgaard Nielsen, the Danish Psoriasis Association, represented  
22  
23 349 by the director Lars Werner, and two individual RA patients from one of the involved  
24  
25 350 departments.  
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32  
33 351 The SC will hold telephone conferences every 2-4 weeks, and more often when  
34  
35 352 necessary, and face-to-face meetings 3-4 times per year. Among all participants, the SC will  
36  
37 353 organise telephone conferences every 2-4 weeks, and more often when necessary, and  
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39 354 face-to-face meetings at start-up and thereafter every year.  
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#### 46 356 **Perspectives**

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50 357 The use of prognosis research evidence at multiple stages is highly important on the  
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52 358 translational pathway toward improving patient outcome. Prognosis research include  
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54 359 various aspects of importance to health care professionals, enabling them to guide the  
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56 360 individual patient in terms of shared decision making via overall prognosis, knowledge on  
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3 361 important prognostic factors, prognostic models, and subsequently (from randomised trial  
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5 362 evidence) even stratified medicine<sup>55-62-64</sup>. We anticipate that the BELIEVE study will reveal  
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7  
8 363 prognostic factors of importance, such as whether the diet of the patient is likely to interfere  
9  
10 364 with the outcome of being prescribed a TNFi. Also hopefully, by combining various pheno-  
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12 365 and geno-type aspects into prognostic models, the BELIEVE might add value in terms of  
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14 366 potentially important “personalised medicine” further down the road.

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18 367 Interesting findings with the potential of having prognostic value will be sought  
19  
20 368 replicated in other prospective cohorts including a planned study of CID cases from the  
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22 369 Danish “Diet, Health and Cancer” cohort and potentially other cohorts with lifestyle data<sup>65</sup>  
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24  
25 370<sup>66</sup>.

### 26 27 28 29 371 **Dissemination of results to the public and scientifically**

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31  
32 372 The target journal for the primary outcome will be among the general medical journals,  
33  
34 373 because of its general implications (potentially) for family doctors. Subsequently, other  
35  
36 374 hypotheses will be analysed and manuscripts prepared (independently of the findings)  
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38 375 which will likely be submitted to specialty journals (e.g. nutritional journals and specific  
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40 376 journals for immunology, gastroenterology, rheumatology, dermatology, and  
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42 377 ophthalmology).

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48 378 Authorship confers credit and has important academic, social, and financial implications,  
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50 379 and therefore any authorship on manuscripts coming from BELIEVE study implies  
51  
52 380 responsibility and accountability for published work. In difficult cases we intend to follow  
53  
54 381 the recommendations from the International Committee of Medical Journal Editors  
55  
56 382 (ICMJE) to ensure that contributors who have made substantive intellectual contributions  
57  
58  
59  
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3  
4 383 to a paper are given credit as authors, but also that contributors credited as authors  
5  
6  
7 384 understand their role in taking responsibility and being accountable for what is published.  
8  
9  
10 385 The ICMJE criteria for authorship intend to distinguish authors from other contributors.  
11  
12  
13 386 based on the following 4 criteria: (i) Substantial contributions to the conception or design of  
14  
15  
16 387 the work; or the acquisition, analysis, or interpretation of data for the work; AND (ii)  
17  
18 388 Drafting the work or revising it critically for important intellectual content; AND (iii) Final  
19  
20  
21 389 approval of the version to be published; AND (iv) Agreement to be accountable for all  
22  
23  
24 390 aspects of the work in ensuring that questions related to the accuracy or integrity of any  
25  
26 391 part of the work are appropriately investigated and resolved.  
27  
28

29 392 In addition to the scientific reporting of results, major findings with translational  
30  
31 393 implications will be communicated to health professionals, patient organisations, public  
32  
33  
34 394 health policy makers, and to the general public through various media and news activities.  
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37 395

40 396 **Ethics**

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43 397 Written informed consent will be obtained from all participants before participation in the  
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45  
46 398 study. The project has been approved by The Regional Scientific Ethical Committee  
47  
48 399 (S-20160124) and the Danish Data Protection Agency (2008-58-035). The procedures  
49  
50 400 followed are in accordance with the ethical standards of the responsible committee on  
51  
52  
53 401 human experimentation (institutional and national) and with the Helsinki  
54  
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56 402 Declaration of 1975, as revised in 2000.  
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58  
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4

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6  
7  
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9  
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13  
14 409 Eriksens Mindefond" (V. Andersen), Region of Southern Denmark (V. Andersen),  
15  
16  
17 410 University of Southern Denmark (V. Andersen, U. Holmskov). The Parker Institute,  
18  
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20  
21  
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23  
24

25 413  
26  
27

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29  
30 415 and all authors read and commented the manuscript. All authors accepted the final  
31  
32 416 submitted version.  
33  
34

35 417  
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38 418 **Conflicts of Interest:**  
39

40  
41 419 All authors declare no conflict of interest. However, the following authors declare: B.  
42  
43 420 Heitmann has received funding from "MatPrat" the information office for Norwegian egg  
44  
45 421 and meat; L. Hvid is in the advisory board for Abbvie A/S; J. Fallingborg is in the advisory  
46  
47 422 boards for AbbVie A/S, MSD Denmark, Takeda Pharma A/S and Ferring Pharmaceuticals  
48  
49 423 A/S; V. Andersen receives compensation for consultancy and for being a member of the  
50  
51 424 advisory board from MSD Denmark (Merck) and Janssen A/S. The funding sponsors had  
52  
53 425 no role in the design of the study; in the collection, analyses, or interpretation of data; in the  
54  
55 426 writing of the manuscript, and in the decision to publish the results.  
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**Table 1. Collection of patient characteristics, outcome measures and explanatory**

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**variables**

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

Body mass index (kg/cm <sup>2</sup> )	X	X
Routine blood analyses <sup>4</sup>	X	X
Endoscopy <sup>5</sup>	X	X
<b>Biological samples<sup>6</sup>:</b>		
Fasting blood samples	X	X
Faeces samples	X	X
Urine samples	X	X
Biopsies <sup>5</sup>	X	X
<b>Crohn's disease (CD)</b>		
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) <sup>7</sup>	X	X
HBI index (score)	X	X
<b>*HBI of 4 or less (y/n)</b>	<b>X</b>	<b>X</b>
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 <sup>8</sup> (y/n)		X
Concomitant medication (y,n, predefined choices)	X	X
Number of draining fistulas (fistulising CD)	X	X

<b><i>Ulcerative Colitis (UC)</i></b>		
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
<b>*Mayo Clinical Score of 2 or less with no individual subscore of &gt;1</b>	<b>X</b>	<b>X</b>
Mayo "normal mucosal appearance" (y/n)	X	X
Mayo clinical response <sup>9</sup> (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
<b>*Mayo Clinical Score of 2 or less with no individual subscore of &gt;1</b>	<b>X</b>	<b>X</b>
Mayo "normal mucosal appearance" (y/n)	X	X
Mayo clinical response <sup>9</sup> (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 <sup>8</sup> (y/n)		X
Concomitant medication (y,n, predefined choices)	X	X
<b><i>Rheumatoid arthritis (RA)</i></b>		
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
<b>*ACR20 (y/n)</b>	<b>n.a.</b>	<b>X</b>
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
<b><i>Axial spondyloarthritis (axSpA)</i></b>		
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
<b>*ASAS20 (y/n)</b>	<b>n.a.</b>	<b>X</b>
ASAS40 (y/n)	n.a.	X
ASAS Partial response (y/n)	n.a.	X
ASAS5/6 response (y/n)	n.a.	X
<b><i>Psoriatic arthritis (PsA)</i></b>		

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
<b>*ACR20</b>	<b>n.a.</b>	<b>X</b>
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
<b><i>Psoriasis (PsO)</i></b>		
Psoriatic arthritis (y/n)	X	X
PASI (score)	X	X
<b>*PASI75 response (y/n)</b>	<b>n.a.</b>	<b>X</b>
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
<i>Hidradenitis Suppurativa (HS)</i>		
<b>*HiSCR response</b>	<b>n.a.</b>	<b>X</b>
Hurley stage <sup>10</sup> (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



<i>Non-infectious Uveitis (NiU)</i>		
SUN (score)	X	X
<b>*Uveitis treatment failure (y/n)</b>	<b>n.a.</b>	<b>X</b>
New active, inflammatory chorioretinal or retinal vascular lesions relative to Baseline (y/n)	X	X
Inability to achieve $\leq 0.5+$ 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 $\geq 15$ letters relative to best state achieved (y/n)	X	X
<i>Health-related quality of Life<sup>11</sup></i>	<b>X</b>	<b>X</b>
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
<i>Adverse events</i>		

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
<i>Laboratory</i> <sup>4</sup>		
CRP (mg/l) <sup>12</sup>	X	X

**\*Primary endpoint for the individual diseases**

<sup>1</sup>Data will be collected using a questionnaire, local and National registries.

<sup>2</sup>Registry data will be retrieved from the Danish registries using the Danish individual civil registration number (CPR) including BIO-IBD<sup>67</sup>, DANBIO<sup>68</sup>, DERMBIO<sup>69</sup> (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).

<sup>3</sup>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

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4 activity, alcohol consumption and use of over-the counter medicine [use of probiotics,  
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6 pre-probiotics, painkillers, laxatia, and anti-diarrhoea agents]) as well as educational level  
7  
8 and year of menopause (women) are included<sup>70</sup>. The follow-up questionnaire is identical to  
9  
10 the initial questionnaire apart from the questions on food items that only contains  
11  
12 questions on changes of diet since the last questionnaire.  
13  
14

15  
16  
17 <sup>4</sup>Routine blood analyses include C-reactive protein (CRP), haemoglobin, erythrocyte  
18  
19 count, haematocrit, erythrocyte mean cell volume (MCV), mean cell hemoglobin (MCH)  
20  
21 and mean cell haemoglobin concentration (MCHC), leucocyte count, differential count,  
22  
23 thrombocytes, albumin, K<sup>+</sup> potassium, Na<sup>+</sup> sodium, creatinine, coagulation factor II+VII+X,  
24  
25 alanine amino transferase (ALAT), alkaline phosphatase, gamma-glutamyl transferase  
26  
27 (GGT), haemoglobin glycation (Hb1Ac), lipids (cholesterol, high density, low density  
28  
29 cholesterol), and transglutaminase.  
30  
31  
32

33  
34  
35 <sup>5</sup>Only IBD patients  
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38 <sup>6</sup>From all participants, blood, urine, and faeces are sampled. In addition, from IBD patients,  
39  
40 intestinal biopsies are sampled. In selected cases, additional biological material on  
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42 participants from this study may be retrieved from the Patobank and the Danish Biobank.  
43  
44 The samples will be collected adhering to the Sample PRE-analytical Code (SPREC) and  
45  
46 Biospecimen Reporting for Improved Study Quality (BRISQ) guidelines, using Standard  
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48 Operational Procedure (SOPs) describing and logging primary container, centrifugation  
49  
50 conditions, centrifugation parameters and storage conditions<sup>71 72</sup>. The biological material  
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52 will be stored at OPEN (biological material from OUH) or at SHS (biological material from  
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4 the other hospitals).

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7 <sup>7</sup>Only CD patients when endoscopy cannot adequately evaluate inflammation.

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12 <sup>8</sup>Corticosteroid-free remission. Clinical remission in patients using oral corticosteroids at  
13 baseline (Pre) that have discontinued corticosteroids and are in clinical remission at first  
14 follow-up.

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22 <sup>9</sup>A reduction in complete Mayo score of  $\geq 3$  points and  $\geq 30\%$  from baseline (or a partial  
23 Mayo score of  $\geq 2$  points and  $\geq 25\%$  from baseline, if the complete Mayo score was not  
24 performed at the visit) with an accompanying decrease in rectal bleeding subscore of  $\geq 1$   
25 point or absolute rectal bleeding subscore of  $\leq 1$  point

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

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

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53 <sup>12</sup>Biological response defined as a drop in CRP level of more than 25% or to normal level  
54 among patients with an elevated CRP before treatment (higher than normal range)<sup>73</sup>.

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58 Abbreviations; ACR, American College of Rheumatology; ASAS20/40, Assessment of  
59 Spondyloarthritis International Society; CRP, C-reactive Protein; DAS28, Disease Activity  
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4 Score: DLQI<sup>74, 75</sup>, Dermatology Life Quality Index; FFQ, Food frequency questionnaire;  
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6 Harvey and Bradshaw Index, HBI; HiSCR<sup>50</sup>, Hidradenitis Suppurativa Clinical Response;  
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8 HAQ1, Health Assessment Questionnaire 1; NYHA, New York Heart Association, PASI,  
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10 Psoriasis Area and Severity Index; SCCAI, Simple Clinical Colitis Activity Index; SES-CD,  
11  
12 Simple Endoscopic Score for Crohn's Disease; SF12, Short Form Health Survey; SHS<sup>76, 77</sup>,  
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14 Short Health Scale; SUN, Standardization of Uveitis Nomenclature for Reporting Clinical  
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16 Data; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease <sup>52</sup>  
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3 431 **FIGURE LEGENDS**  
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5 432 **Figure 1. Hypothesis for effects of diet in relation to treatment effect**  
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8 433 **(Left)** Low levels of fibre intake may promote microbial metabolism of mucus as the main  
9  
10 434 energy source<sup>36 78 79</sup>. This will lead to decrease of the mucus layer. Further, degradation of mucus  
11  
12 435 releases free sulphate which would then become available for utilisation by sulphate-reducing  
13  
14 436 bacteria (like *Bilophila wadsworthia*) for microbial produced hydrogen sulphide<sup>80</sup>. In addition, high  
15  
16 437 intake of food containing organic sulphur and sulphate additives, such as meat and processed meat,  
17  
18 438 may increase the amount of sulphate for microbial produced hydrogen sulphide<sup>81 82</sup>. The resultant  
19  
20 439 hydrogen sulphide from low intake of fibre and high intake of meat may reduce the disulphide  
21  
22 440 bonds in the mucus network rendering the mucus layer penetrable to e.g. bacteria<sup>80 83</sup>. Then,  
23  
24 441 microbial-associated molecular patterns (MAMPs) from microbes or contained in the diet may reach  
25  
26 442 the epithelium and activate the pattern recognition receptors (PRR) such as Toll-like receptors  
27  
28 443 (TLRs) on the enterocytes (intestinal epithelial cells, IEC), and next activate nuclear factor-kappa B  
29  
30 444 (NFkB), type I interferon (IFN), and other inflammatory pathways. This leads to production of  
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32 445 pro-inflammatory (tumour necrosis factor- $\alpha$  (TNF), interleukin (IL)-1 $\beta$ , IL-6, IFN, IL-17 etc.) and  
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34 446 anti-inflammatory (primarily IL-10) cytokines and chemokines that will next activate innate  
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36 447 lymphocytic cells (ILC) and other immune cells and the immune system in general<sup>84 85</sup>. There is some  
37  
38 448 support for such a mechanism in CID, including findings of; high amounts of sulphate-reducing  
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40 449 bacteria in UC patients<sup>80 86</sup>, an association between the highest tertiles of carbohydrate-restricted diet  
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42 450 and RA, in a nested case-control study among 386 individuals who developed RA and 1886 matched  
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44 451 controls from the Swedish Västerbotten Intervention Program (VIP) cohort with prospectively  
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46 452 sampled dietary survey<sup>87</sup>, association of high fibre intake with low risk of CD among 170 776  
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48 453 participants from the prospective Nurses' Health Study I (NHSI)<sup>22</sup>, association of high intake of red  
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50 454 meat and total protein and risk of developing inflammatory polyarthritis in the population-based  
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52 455 prospective cohort of 25 630 participants from the European Prospective Investigation of Cancer in  
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54 456 Norfolk (EPIC-Norfolk)<sup>34</sup>. Finally, a prospective study of 191 UC patients in remission found that  
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3 457 high consumption of meat, particularly red and processed meat, protein, and alcohol, was associated  
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5 458 with risk of relapse and that high sulphur or sulphate intakes may offer an explanation for the  
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7 459 observed findings<sup>88</sup>. Additionally, support of the notation that diet may affect systemic immune  
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9 460 response is provided by the finding that intake of low-glycemic index diet was found to lower  
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11 461 secretion of TNF and IL-6 from stimulated peripheral blood mononuclear cells from obese humans<sup>89</sup>.  
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14 462 **(Right)** Intake of high fibre and low meat may promote an effective mucosal barrier and support the  
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16 463 effects of anti-TNF treatment outcome. Intake of soluble plant fibre has been found to block bacterial  
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18 464 adhesion to gut enterocytes in animal and cell studies<sup>90</sup>. The genetic architecture of the individual  
19  
20 465 may also impact the influence of lifestyle factors<sup>14</sup>. Hence, in order to provide lifestyle  
21  
22 466 recommendations, we need to understand the effects of lifestyle on the immune system, and how  
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24 467 lifestyle may improve the therapeutic outcome and reduce the need of medical treatment in the  
25  
26 468 individual person. Information on diet and non-diet lifestyle exposures may be collected by using  
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28 469 e.g. questionnaires and lifestyle-associated biomarkers or the combination of these methods<sup>91-93</sup>.  
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31 470 Evidence-based biomarkers for lifestyle assessment are scarce<sup>94-114</sup> and mostly used for studies on  
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33 471 healthy individuals<sup>115-118</sup>.

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37 472 **Figure 2. Organisation and patients research partners (PRPs)**  
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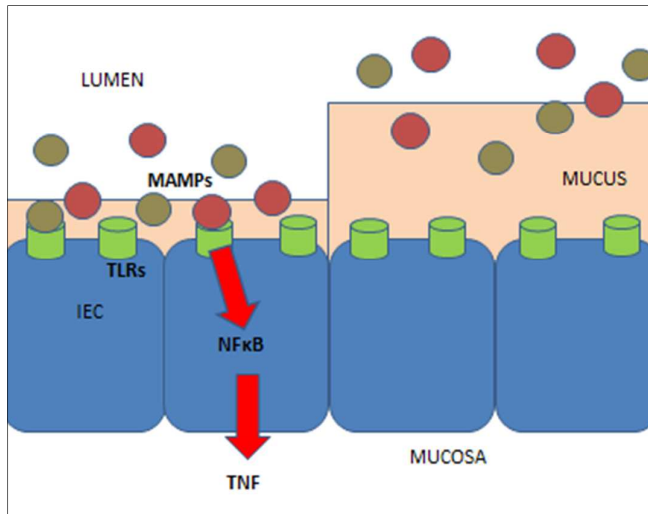
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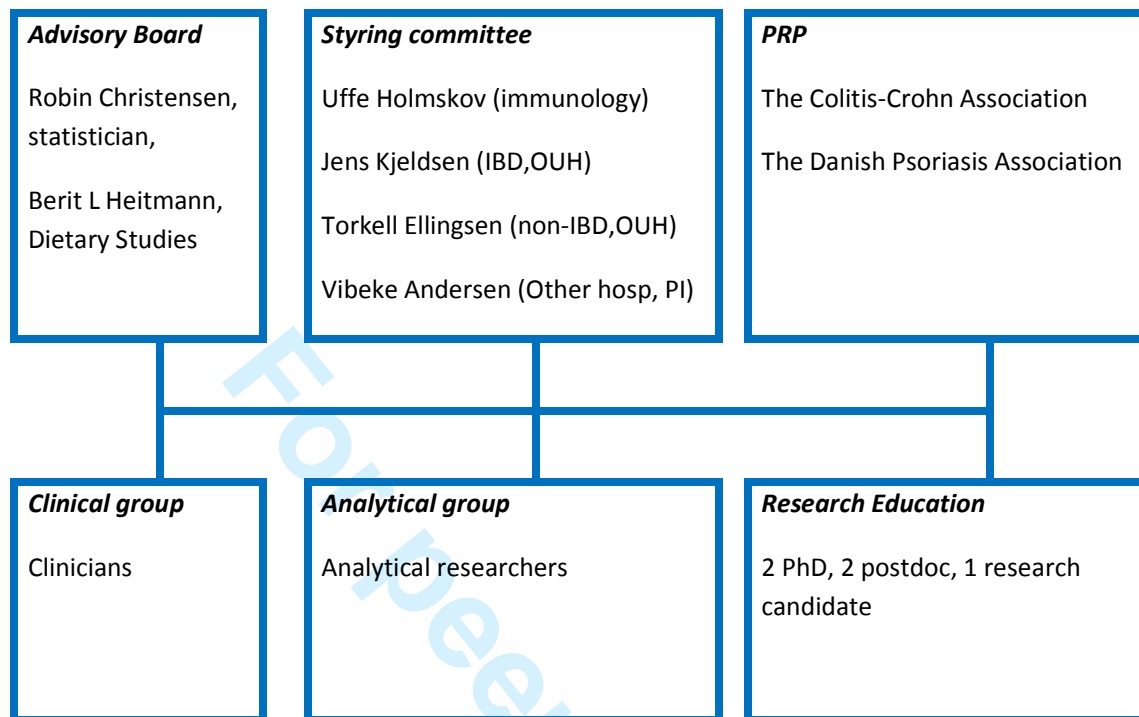
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Areas of responsibility in parenthesis. **IBD-OUH**, sampling of IBD patients from Odense University Hospital (OUH); **non-IBD, OUH**, sampling of non-IBD patients from OUH; Other hosp, sampling of patients from other hospitals; PI, principal investigator



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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
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

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49**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__

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3	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__
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6	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__7__
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### 8 **Methods: Assignment of interventions (for controlled trials)**

#### 9 Allocation:

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12	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__
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18	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__
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22	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	__NA__
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25	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__7__
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28		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	__NA__
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### 32 **Methods: Data collection, management, and analysis**

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34	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__
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39		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__
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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	___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___

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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___7___
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___NA___
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9	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___
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12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___14___
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15	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___
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18	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___NA___
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21	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___
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26		31b	Authorship eligibility guidelines and any intended use of professional writers	___NA___
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28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___NA___
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30	<b>Appendices</b>			
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32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__suppl__
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35	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___
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38 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 39 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 40 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.  
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# 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:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-018166.R1
Article Type:	Protocol
Date Submitted by the Author:	29-Aug-2017
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<b>Primary Subject Heading</b>:	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

SCHOLARONE™  
Manuscripts

BMJ

1 **Impact of red and processed meat and fibre intake on treatment**

2 **outcomes among patients with chronic inflammatory diseases:**

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

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57 **ABSTRACT 300/300**

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

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



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3 79 **Ethics and dissemination:** The principle goal of this project is to improve the quality of life  
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6 80 of patients suffering from CID by providing evidence to support dietary and other  
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8 81 lifestyle recommendations that may improve clinical outcomes. The study is approved by  
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10 82 the Ethics Committee (S-20160124) and the Danish Data Protecting Agency (2008-58-035).  
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12 83 Study findings will be disseminated through peer-reviewed journals, patient associations,  
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14 84 and presentations at international conferences.

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18 85 **Trial Registration details:** ClinicalTrials.gov identifier: NCT03173144  
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22 86 Keywords: biomarker; lifestyle; personalized medicine; patient-reported outcome  
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24 87 measures (PROMs); treatment outcome; Western-style diet (WSD)  
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#### Strengths and limitations of this study

- This study includes a number of diseases treated with biologics targeting the pro-inflammatory cytokine tumour necrosis factor- $\alpha$
- 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

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4 90 **INTRODUCTION**

5 91 Chronic inflammatory diseases (CID) are a diverse set of immunologic diseases that  
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8 92 include inflammatory bowel disease (IBD) (Crohn's disease [CD] and ulcerative colitis  
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10 93 [UC]), rheumatic conditions (rheumatoid arthritis [RA], axial spondyloarthritis  
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12 94 [axSpA], psoriatic arthritis [PsA]), inflammatory skin diseases (psoriasis [PsO], hidradenitis  
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14 95 suppurativa [HS]), and eye disease (non-infectious uveitis [NiU]). The pro-inflammatory  
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16 96 cytokine tumour necrosis factor  $\alpha$  (TNF) is recognized to play an important role in the  
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18 97 aetiology of these diseases. Correspondingly, biological agents that inhibit TNF, also  
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20 98 known as TNF inhibitors (TNFi), are an important component of treatment. However, a  
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22 99 large number of patients do not benefit from TNFi treatment<sup>1</sup>.

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27 100 CIDs have a large and negative impact on both individual patients and at a community  
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29 101 level as a consequence of health-related workplace productivity loss and health system  
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31 102 expense, which is largely influenced by the high cost of providing biologic medications<sup>1</sup>.  
32  
33 103 CIDs are recurring, lifelong illnesses of potentially early onset that can substantially affect  
34  
35 104 the life quality of patients and their families<sup>2-5</sup>. In addition, they are prevalent diseases with  
36  
37 105 IBD affecting 0.5% of the population in the Western world<sup>6</sup>, and RA and PsO affecting  
38  
39 106 respectively 0.3-1.0% and 1.5% of the global population<sup>7,8</sup>. Furthermore, the disease burden,  
40  
41 107 and hence health system burden, is predicted to rise dramatically due to population  
42  
43 108 growth, aging demographics and increasing disease incidence<sup>9-11</sup>.

44  
45  
46  
47  
48 109 The diseases may have overlapping symptoms<sup>12</sup>. For example, some patients with NiU  
49  
50 110 and axSpA may experience bowel symptoms and some patients with IBD may develop  
51  
52 111 extraintestinal manifestations (i.e. eye, joint, and skin symptoms). The diseases are rather  
53  
54 112 complex with both genetic and environmental factors implicated in aetiology. While CIDs  
55  
56 113 share some genetic and environmental predisposing factors, other susceptibility factors  
57  
58  
59  
60

1  
2  
3 114 differ<sup>13</sup>. The genetic architecture of CIDs has previously been investigated by large  
4  
5 115 international consortia<sup>14-20</sup>. Similarly, environmental factors have been investigated in large  
6  
7  
8 116 cohorts with prospectively collected lifestyle data, such as the European Investigation into  
9  
10 117 Cancer and Nutrition (EPIC) Study as well as the Nurses' Health Study (NHS)<sup>21-35</sup>.

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

124

### 125 **Evidence-based research**

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

1  
2  
3 137 More recently, lifestyle factors, as they relate to TNFi therapy among CID patients,  
4  
5 138 were identified as an area for further investigation<sup>40</sup>. In order to explore different  
6  
7  
8 139 hypotheses, we included studies that may be subject to recall bias or bias introduced by  
9  
10 140 lifestyle changes due to the disease itself, e.g. smoking, physical activities, and intake of  
11  
12 141 Western-style diet<sup>40</sup>. After reviewing these potential hypotheses, we proposed a model  
13  
14 142 whereby a diet high in meat and low in fibres may impact inflammation and TNFi  
15  
16 143 treatment<sup>37</sup> (Figure 1).  
17  
18  
19

20 144 Based on previous evidence, we set out to prospectively identify dietary factors that  
21  
22 145 support optimal TNFi treatment outcomes, with the ultimate aim of improving the quality  
23  
24 146 of life of CID patients.  
25  
26  
27  
28 147

### 31 148 **Aims and hypotheses**

32  
33  
34 149 The primary aim of this prospective cohort study is to investigate whether treatment  
35  
36 150 outcomes in CID patients vary with dietary differences. The main hypothesis is that '*Diets*  
37  
38 151 *high in fibre AND low in red and processed meat are associated with improved treatment outcomes*'.  
39  
40  
41 152 Secondary aims are whether and to what extent lifestyle-associated biomarkers have  
42  
43 153 prognostic value for differentiating responders from non-responders based on both  
44  
45 154 disease-specific and generic treatment outcomes.  
46  
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48  
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3 156 **METHODS AND ANALYSES**  
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5

6 157 **Design**  
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9  
10 158 The BELIEVE study is a prospective cohort study that will examine disease activity after  
11  
12 159 initiating TNFi treatment. The primary endpoint will be assessed 14-16 weeks after  
13  
14 160 initiation of a TNFi and will be defined based on the specific CID condition. The cohort will  
15  
16 161 be classified as responders (including those who continue with drug treatment) or  
17  
18 162 non-responders (including those who discontinue drug treatment) based on the  
19  
20 163 disease-specific criteria defined below. The decision to discontinue therapy is assumed to  
21  
22 164 be based on a shared decision making process between patients and their physicians, and  
23  
24 165 to be supported by principles outlined in disease-specific guidelines<sup>41</sup>.  
25  
26  
27  
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30 166

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32  
33 167 **Setting**  
34  
35

36 168 This multi-centre study reflects a collaboration between the following centres: 1)  
37  
38 169 Department of Gastroenterology and Hepatology, Aalborg University Hospital; 2)  
39  
40 170 Department of Hepatology and Gastroenterology, Aarhus University Hospital; 3)  
41  
42 171 Diagnostic Centre, Silkeborg Regional Hospital; 4) Department of Internal Medicine,  
43  
44 172 Herning Regional Hospital; 5) Department of Gastroenterology, Herlev Hospital; 6) Organ  
45  
46 173 Centre, Hospital of Southern Jutland; 7) Department of Gastroenterology, Hospital of South  
47  
48 174 West Jutland; 8) Department of Medical Gastroenterology, Department of Rheumatology,  
49  
50 175 Department of Dermatology and Allergy Centre, and Department of Ophthalmology,  
51  
52 176 Odense University Hospital. Study enrolment will take place between June 15, 2017 and  
53  
54  
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1  
2  
3 177 March 31, 2019, or until the study has enrolled a minimum of 100 patients with IBD, 100  
4  
5 178 patients with RA and 120 patients with axSpA, PsA, PsO, HS and NiU.  
6  
7  
8

9 179

10  
11  
12 180 **Patient characteristics and eligibility criteria**  
13

14  
15  
16 181 Inclusion criteria: patients  $\geq 18$  years with CID who are beginning TNFi therapy, and who  
17  
18 182 have not previously received TNFi treatment, and who are able to read and understand  
19  
20 183 Danish. Exclusion criteria: patients who have previously received a biological treatment  
21  
22 184 and patients who by virtue of illiteracy or cognitive impairment are unable to complete the  
23  
24 185 questionnaire.  
25  
26  
27

28 186 Clinical data (Table 1) will include personal data, data on health and disease, dietary  
29  
30 187 and non-dietary lifestyle information, laboratory measurements, and disease activity scores  
31  
32 188 including patient-reported outcome measures (PROMs), clinical assessments, and  
33  
34 189 laboratory data. Participants will complete validated questionnaires on disease activity,  
35  
36 190 quality of life and lifestyle using an electronic link. Studies have revealed electronic  
37  
38 191 questionnaires to be comparable to paper-based in relation to the outcomes (i.e. PROMs)<sup>42</sup>  
39  
40  
41 192 <sup>43</sup>.  
42  
43  
44  
45

46 193

47  
48  
49 194 **Primary and secondary endpoints**  
50

51  
52  
53 195 *Primary endpoint:* The predefined primary endpoint will be the proportion of patients with a  
54  
55 196 clinical response to therapy 14-16 weeks after treatment initiation. Below are the  
56  
57 197 disease-specific definitions of clinical response to therapy:  
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59  
60

- 1  
2  
3 198 • Crohn's disease: clinical remission, defined as Harvey-Bradshaw Index (HBI) of 4 or  
4  
5 199 less<sup>44</sup>  
6  
7  
8  
9 200 • Ulcerative colitis: clinical remission, defined as Mayo Clinic Score of 2 or less (with  
10  
11 201 no individual sub-score of >1)<sup>45</sup>  
12  
13  
14 202 • Rheumatoid arthritis: clinical response, defined as at least a 20% improvement  
15  
16 203 according to the criteria of the American College of Rheumatology (ACR20)<sup>46</sup>  
17  
18  
19  
20 204 • Axial spondyloarthritis: clinical response, defined as at least a 20% improvement  
21  
22 205 according to the Assessment of Spondyloarthritis International Society (ASAS20)<sup>47 48</sup>  
23  
24  
25  
26 206 • Psoriatic arthritis: clinical response, defined as at least a 20% improvement  
27  
28 207 according to the criteria of the American College of Rheumatology (ACR20)<sup>49</sup>  
29  
30  
31  
32 208 • Psoriasis: clinical response, defined as at least a 75% improvement in Psoriasis Area  
33  
34 209 and Severity Index (PASI 75)<sup>50</sup>  
35  
36  
37  
38 210 • Hidradenitis suppurativa: clinical response, defined as at least a 50% reduction in  
39  
40 211 the abscess and inflammatory-nodule count, with no increase in abscess or  
41  
42 212 draining-fistula counts (HiSCR response)<sup>51</sup>  
43  
44  
45  
46 213 • Non-infectious uveitis: clinical response, defined as those who did not have a  
47  
48 214 treatment failure (treatment failure will be based on assessment of new  
49  
50 215 inflammatory lesions, best corrected visual acuity, anterior chamber cell grade, and  
51  
52 216 vitreous haze grade)<sup>52</sup>  
53  
54  
55

56 217 *Key secondary outcomes:* Major secondary outcomes, also to be measured 14-16 weeks after  
57  
58 218 treatment initiation, include disease-specific outcome measures that cover core outcome  
59  
60

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2  
3 219 sets, the generic health-related quality of life (HRQoL) and disability at endpoint. Below are  
4  
5 220 a list of disease-specific secondary outcomes.

- 6  
7  
8  
9 221 • Crohn's disease: STRIDE (abdominal pain, diarrhea, altered bowel habit, SES-CD  
10  
11 222 [presence of ulcers, ulcerated surface, affected surface, presence of narrowing,  
12  
13 223 number of affected segments], alterations of cross-sectional imaging [MR, CT,  
14  
15 224 ultrasound][only when endoscopy cannot adequately evaluate inflammation]),  
16  
17 225 HBI (general well-being, abdominal pain, number of liquid stools per day,  
18  
19 226 abdominal Mass, extraintestinal manifestations [abscess, fistulas, fissures,  
20  
21 227 arthralgia, uveitis, erythema nodosum, pyoderma gangrenosum, mouth ulcers]),  
22  
23 228 physician global assessment, number of draining fistulas, corticosteroid-free  
24  
25 229 remission, concomitant medication.
- 26  
27  
28  
29  
30  
31  
32  
33 230 • Ulcerative colitis: STRIDE (rectal bleeding, altered bowel habit, endoscopic  
34  
35 231 remission [Mayo endoscopic sub-score of 0-1]), Mayo Clinical Score (Mayo  
36  
37 232 endoscopic sub-score, stools, rectal bleeding, physician global assessment), Mayo  
38  
39 233 "normal mucosal appearance", Mayo clinical response, SCCAI (bowel frequency  
40  
41 234 [day], bowel frequency [night], urgency of defecation, blood in stool, general  
42  
43 235 well-being, extracolonic features), physician global assessment, corticosteroid-free  
44  
45 236 remission, concomitant medication.
- 46  
47  
48  
49  
50  
51  
52  
53 237 • Rheumatoid arthritis: Tender joints, Swollen joints, pain, physician global  
54  
55 238 assessment, patient global assessment, health assessment Questionnaire (HAQ),  
56  
57 239 C-reactive protein, DAS28-CRP, simplified disease activity index (SDAI).  
58  
59  
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2  
3  
4 240 • Axial spondyloarthritis: bath ankylosing spondylitis metrology index  
5  
6 241 (BASMI), bath ankylosing spondylitis functional index (BASFI), bath ankylosing  
7  
8  
9 242 spondylitis disease activity index (BASDAI), total score for back pain, physician  
10  
11 243 global assessment, patient global assessment, C-reactive protein.  
12  
13  
14 244 • Psoriatic arthritis: tender joints, swollen joints, psoriatic arthritis pain, physician  
15  
16  
17 245 global assessment, patient global assessment, HAQ-DI, C-reactive protein,  
18  
19 246 DAS28-CRP, simplified disease activity index (SDAI), PASI.  
20  
21  
22  
23 247 • Psoriasis: PASI, physician global assessment, patient global assessment, psoriatic  
24  
25 248 arthritis pain, dermatology life quality index (DLQI) total Score.  
26  
27  
28  
29 249 • Hidradenitis suppurativa: percentage of participants who achieve abscess and  
30  
31 250 inflammatory nodule (AN) count of 0, 1, and 2, respectively, patient's global  
32  
33 251 assessment of skin pain, modified Sartorius score.  
34  
35  
36  
37 252 • Non-infectious uveitis: new active, inflammatory chorioretinal or retinal vascular  
38  
39 253 lesions relative to baseline, inability to achieve  $\leq 0.5+$  or a 2-step increase relative to  
40  
41 254 the best state achieved at all visits in anterior chamber cell grade or vitreous haze  
42  
43 255 grade, worsening of best corrected visual acuity by  $\geq 15$  letters relative to best state  
44  
45 256 achieved.  
46  
47  
48  
49  
50  
51 257 *Exploratory secondary (tertiary) outcomes:* Additional exploratory outcomes will include  
52  
53 258 biological measures, disease-specific disease activity measures as individual measure and  
54  
55 259 combined scores as well as changes of these (including those measured by  
56  
57  
58 260 physician/patients such as patients' health-related quality of life) at first clinical follow up<sup>53</sup>  
59  
60

1  
2  
3 261 (week 14-16) (Table 1). Other outcomes include changes in the use of concomitant  
4  
5 262 medication, achievement of steroid-free remission, serious adverse events such as  
6  
7  
8 263 hospitalisation, and the need for surgery at first clinical follow up (Table 1)<sup>53</sup>.  
9  
10

11 264

12  
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14  
15 265 **Prognostic factors**

16  
17  
18 266 *Primary exposure variable:* For the primary prognostic model, the primary exposure variables  
19  
20 267 will be prioritized in the following order:

- 21  
22  
23  
24 268 • The upper tertile of the sample (33.3% of the total sample), based on the ratio of  
25  
26 269 fibre to meat intake, is associated with better treatment outcomes.  
27  
28  
29 270 • The lower tertile of the sample (33.3% of the total sample) with respect to intake of  
30  
31 271 red and processed meat, and the upper tertile of the sample (33.3% of the total  
32  
33 272 sample) with respect to intake of dietary fibres, are independently associated with  
34  
35 273 better treatment outcomes, and a potential interaction between them may further  
36  
37 274 improve treatment outcomes.  
38  
39  
40

41  
42 275 *Other (exploratory) exposure variables:*

- 43  
44  
45  
46 276 • Other lifestyle factors independently or combined (red and processed meat intake,  
47  
48 277 vegetable intake, dietary fibre intake, cereal intake, gluten consumption, legume  
49  
50 278 intake, red wine consumption, dairy product intake, amount of physical activity,  
51  
52 279 smoking status, total protein/fat, protein/fat from red and processed meat, glycemic  
53  
54 280 index)  
55  
56  
57 281 • Pretreatment lifestyle-associated biomarkers  
58  
59  
60

- 1  
2  
3  
4 282 • Combinations of lifestyle factors and lifestyle-associated biomarkers  
5  
6 283 • Gene-environment interaction analyses  
7  
8  
9 284 • Pretreatment levels of inflammatory molecules  
10  
11  
12 285

13  
14  
15 286 **Data management**  
16

17  
18  
19 287 The electronic questionnaire is in Danish. Participants will access the questionnaire by an  
20  
21 288 electronic link which will be sent to their personal, electronic mailbox. All data will be  
22  
23 289 stored in a secure research storage facility<sup>54</sup>. Information registered by clinicians and  
24  
25 290 technicians will periodically be transferred from paper format to electronic format using  
26  
27 291 either double entry of data or automated forms processing<sup>55</sup>.  
28  
29  
30

31  
32 292 No patient risks are foreseen as a direct result of this project. Clinicians will treat  
33  
34 293 enrolled patients in the same fashion as non-enrolled patients. As a consequence, no data  
35  
36 294 monitoring committee will be established.  
37  
38  
39

40 295

41  
42  
43 296 **Statistical methods**  
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46  
47 297 Prognostic factor research was developed to aid healthcare providers in estimating the  
48  
49 298 probability or risk that a specific event will occur in the future. Hence, it has the potential to  
50  
51 299 inform clinical decision-making<sup>56</sup>. Conceptually, a good prognostic model is one that  
52  
53 300 functions for patients other than those from whom the data was derived<sup>57</sup>. Our intention is  
54  
55 301 to use data obtained from this rigorously designed, prospective cohort study to explore our  
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3  
4 302 ability to predict clinical response across specific CID conditions (Y=primary endpoint) and  
5  
6 303 to explore whether diets high in fibre AND low in red and processed meat (X=assessed at  
7  
8  
9 304 baseline) are an informative prognostic factor. Per default, the statistical models will  
10  
11 305 include the specific CID condition and the clinical centre as fixed effects. Specific details  
12  
13  
14 306 will be part of the final statistical analysis plan (SAP). In terms of transparency, when  
15  
16  
17 307 reporting the multivariable models the study will adhere to guidelines from the  
18  
19  
20 308 *'Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis'*  
21  
22 309 (TRIPOD).

23  
24  
25 310 *Sample size considerations:* Deciding sample size is a well-known difficulty with  
26  
27 311 exploratory prognostic factor research studies. To obtain an adequate number of outcome  
28  
29 312 events we apply "the rule of thumb" whereby 10 outcomes are needed for each  
30  
31  
32 313 independent variable. We plan to enrol 320 patients in total and we anticipate that 50% of  
33  
34  
35 314 these will experience a clinical response during the 14-16 week period after TNFi initiation<sup>1</sup>.  
36  
37  
38 315 With this in mind, and anticipating that we will see at least 160 events (i.e. clinical response  
39  
40  
41 316 among the 320 patients), the study is sufficiently power to explore the impact of as many as  
42  
43  
44 317 16 independent variables including condition and clinical centre. Since using the "rule of  
45  
46 318 thumb" method to justify sample size is a debated practice, we went one step further and  
47  
48  
49 319 estimated the statistical power to detect differences between two dietary groups. For the  
50  
51  
52 320 contrast between groups and for a comparison of two independent binomial proportions  
53  
54 321 (those with high fibre AND low meat intake vs other) using Pearson's Chi-square statistic,  
55  
56  
57 322 with a Chi-square approximation, with a two-sided significance level of 0.05 ( $P < 0.05$ ), a  
58  
59 323 total sample size of 318 - assuming an "allocation ratio" of 1 to 2 (one third) - has an  
60

1  
2  
3  
4 324 approximate power of 0.924 (i.e. >90% statistical power) if the anticipated proportions  
5  
6  
7 325 responding are 60% and 40% respectively.  
8

9 326 Statistical programming will be done using the software SAS, STATA or R, with  
10  
11 327 transparent reporting of the source code used to analyse the data. Computational details  
12  
13 328 will be available in the pre-specified SAP. These will be finalised before data collection is  
14  
15 329 complete. Our primary analysis set will be based on observations available at the time of  
16  
17 330 study closure. In other words, we will consider 'Data as observed' to be our primary  
18  
19 331 resource for statistical inference. However, for the purpose of sensitivity, multiple  
20  
21 332 sensitivity analyses will be performed to assess the robustness of the primary analyses,  
22  
23 333 including analyses based on the "Non-responder-imputation" and multiple-imputation  
24  
25 334 analyses, which are based on model-based approaches for missing data (these details will  
26  
27 335 be available in the final SAP). A simplistic "null responder imputation" would represent a  
28  
29 336 conservative base case and is likely valid even if data is "missing not at random"<sup>58</sup>, as it  
30  
31 337 assumes, and implies that patients have not improved or have worsened after entering the  
32  
33 338 study.  
34  
35  
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43 339 No interim analyses will be performed. All reported P values will be two-sided and by  
44  
45 340 default these will not be adjusted for multiple comparisons. However, due to potential  
46  
47 341 issues of multiplicity, as multiple statistical tests will be performed in the study, we will  
48  
49 342 interpret "statistically significant" findings in the context of whether the 95% confidence  
50  
51 343 interval (95%CI) excludes outcomes that could be perceived as clinically important. We will  
52  
53 344 use the following consistent language to describe effects that might appear as chance  
54  
55 345 findings: "*The prognostic factor appears to have little or no effect on the clinical outcome if the point*  
56  
57  
58  
59  
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3  
4 346 *estimate or the boundaries of the 95% CI lies between 0.80 and 1.25*". Thus, despite an apparently  
5  
6 347 statistically significant finding ( $P<0.05$ ), a relative point estimate within the range of 0.80  
7  
8  
9 348 and 1.25 will not be considered a clinically meaningful effect.  
10

11 349

### 14 350 **Strengths and limitations of the study**

16  
17 351 The food frequency questionnaire (FFQ) we use in the present study has been widely used  
18  
19 352 in prospective cohort studies, including in European prospective investigations in the fields  
20  
21 353 of oncology and chronic diseases<sup>59 60</sup>. It has been extensively used and evaluated in the  
22  
23 354 Danish population, and results from different methods demonstrate consistency<sup>61 62</sup>.  
24  
25

26  
27 355 However, the FFQ is not without limits, in particular with respect to the lack of information  
28  
29 356 on portion sizes<sup>63 64</sup>. We, therefore, modified the FFQ to capture information on portion  
30  
31 357 size<sup>63</sup>. A second potential limitation relates to comprehensive questionnaire completion.  
32  
33

34  
35 358 However, in a pilot study of 10 hospital patients (50-70 years of age) the FFQ was  
36  
37 359 completed within 40-50 minutes and no complaints were reported. The imprecision of the  
38  
39

40 360 FFQ will lead to large confidence intervals. The result will most likely lead to null results  
41  
42

43 361 (rather than type 2 errors). The disease groups are expected to vary in several aspects such  
44  
45 362 as age, gender and body mass index (BMI). We will, however, be unable to determine the  
46  
47

48 363 potential effect of selective diet reporting on responders and non-responders<sup>65</sup>. On the  
49  
50

51 364 other hand, studies have suggested that dietary patterns are relatively stable among adults  
52  
53

54 365 in the Danish population<sup>66</sup>. Due to study design and the limited number of participants,  
55  
56

57 366 this study may not capture every lifestyle difference between responders and  
58  
59

60 367 non-responders. Similarly, this study has only limited power to detect gene-environment

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2  
3  
4 368 interactions. In order to avoid potential type 2 errors, it is important that the results are  
5  
6 369 replicated in other well-characterized patient populations using prospectively sampled  
7  
8  
9 370 dietary information. To further evaluate the robustness of the results, study results would  
10  
11  
12 371 preferably be replicated in cohorts from other countries.  
13

14 372

15 373

#### 16 17 18 19 20 21 374 **Project organisation**

22  
23  
24 375 The study team is organised into three significant groups: a Clinical Research Group  
25  
26  
27 376 (CRG), an Analytical Research Group (ARG) (Figure 2) and a Steering Committee (SC). The  
28  
29  
30 377 CRG includes specialists from gastroenterology, rheumatology, dermatology and  
31  
32 378 ophthalmology who will be implicated in the clinical care and assessment of study  
33  
34  
35 379 participants. The ARG will be responsible for performing laboratory analyses on the  
36  
37 380 collected biological material. Finally, the SC -- whose members include Professor Uffe  
38  
39  
40 381 Holmskov, Professor Jens Kjeldsen, Professor Torkell Ellingsen, and Professor Vibeke  
41  
42  
43 382 Andersen -- are responsible for planning and organizing the study within the appropriate  
44  
45  
46 383 legal framework, facilitating meetings for the three study groups and for scientific  
47  
48 384 follow-up. The group as a whole, including clinicians and analysts, is responsible for the  
49  
50  
51 385 scientific results and budget.

52  
53 386 Collaboration between patients and health professionals on research projects is a  
54  
55  
56 387 relatively new phenomenon<sup>67-69</sup>. The involvement of patients in research (patient research  
57  
58  
59 388 partners [PRPs]) will ideally will give a stronger voice to patients' views on research,  
60

1  
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3  
4 389 specifically with respect to research priorities. Furthermore, individual patients and patient  
5  
6  
7 390 organisations can contribute to research study design, preparing educational material,  
8  
9 391 discussing results, disseminating results, and recruiting study participants.  
10  
11 392 Recommendations on incorporating PRPs into research study processes suggest that they  
12  
13  
14 393 should be provided with relevant support and education. With this initiative, we were keen  
15  
16  
17 394 to gain experience with PRPs. Thus, this project was built with input from the Danish  
18  
19 395 Colitis-Crohn's Association, represented by its director Charlotte Lindgaard Nielsen, the  
20  
21  
22 396 Danish Psoriasis Association, represented by its director Lars Werner, and three individual  
23  
24  
25 397 RA patients from one of the participating clinical departments.

26  
27 398 The SC will hold telephone conferences every 2-4 week, but more often when  
28  
29  
30 399 necessary, and face-to-face meetings 3-4 times per year. Among participants, the SC will  
31  
32  
33 400 organise telephone conferences every 2-4 weeks, again more often when necessary, and  
34  
35  
36 401 face-to-face meetings at the time of enrolment and every year thereafter until the  
37  
38 402 conclusion of the study.

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41 403

#### 42 43 44 404 **Perspectives**

45  
46  
47 405 The use of prognosis research evidence at multiple stages is central to the process of  
48  
49  
50 406 translational research, with the ultimate goal of improving patient outcomes. Prognosis  
51  
52  
53 407 research includes various aspects of importance to healthcare professionals, enabling them  
54  
55  
56 408 to guide individual patients in terms of shared decision making via overall prognosis,  
57  
58 409 knowledge on important prognostic factors or models and subsequently (from randomised  
59  
60



1  
2  
3 410 trial evidence) stratified medicine<sup>56 70-72</sup>. We anticipate that the BELIEVE study will reveal  
4  
5 411 prognostic factors of importance, including whether the diet of the patient is likely to  
6  
7 412 interfere with the outcome of being prescribed a TNFi treatment. Hopefully, by combining  
8  
9 413 various phenotype and genotype aspects into the prognostic models, the BELIEVE study  
10  
11 414 will add value to the long-term goal of achieving “personalised medicine”.

12  
13  
14  
15  
16 415 We will seek to replicate findings that are identified as having prognostic value in  
17  
18 416 other prospective cohorts, including from a planned study of CID cases from the Danish  
19  
20 417 “Diet, Health and Cancer” cohort and potentially from other cohorts with lifestyle data<sup>73 74</sup>.

#### 21 22 23 24 418 **Dissemination of results to the public and scientifically**

25  
26  
27 419 The target journal for the primary outcome will be a general medical journal directed at  
28  
29 420 family physicians. Family physicians see CID patients across the entire spectrum of disease.  
30  
31 421 Moreover, lifestyle recommendations are an important element of general practice. Hence,  
32  
33 422 although family physicians are not necessarily the primary decision-makers with respect to  
34  
35 423 treatment of CID patients, a role more ably assumed by specialists, they have considerable  
36  
37 424 influence on lifestyle decisions for CID patients. Subsequently, other hypotheses will be  
38  
39 425 analysed and manuscripts prepared (independent of findings), with the intention of  
40  
41 426 submitting additional articles to specialized journals in the areas of nutrition, immunology,  
42  
43 427 gastroenterology, rheumatology, dermatology and ophthalmology.

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51 428 Authorship confers credit and has important academic, social and financial implications,  
52  
53 429 and therefore any authorship on manuscripts coming from the BELIEVE study is  
54  
55  
56 430 associated with responsibility and accountability for the published work. Thus we intend  
57  
58  
59 431 to follow the recommendations of the International Committee of Medical Journal Editors  
60

1  
2  
3  
4 432 (ICMJE) to ensure that contributors who have made substantive intellectual contributions  
5  
6  
7 433 to a paper are given credit as authors, but also that contributors credited as authors  
8  
9 434 understand their role in taking responsibility and being accountable for the published  
10  
11  
12 435 work.  
13  
14  
15 436 The ICMJE criteria for authorship was designed to distinguish authors from other  
16  
17  
18 437 contributors based on the following 4 criteria: (i) substantial contributions to the conception  
19  
20  
21 438 or design of the work; or the acquisition, analysis or interpretation of data for the work;  
22  
23 439 AND (ii) drafting the work or revising it critically for important intellectual content; AND  
24  
25  
26 440 (iii) final approval of the version to be published; AND (iv) agreement to be accountable for  
27  
28  
29 441 all aspects of the work in ensuring that questions related to the accuracy or integrity of any  
30  
31 442 part of the work are appropriately investigated and resolved.  
32  
33

34 443 In addition to the scientific reporting of results, major findings with translational  
35  
36 444 implications will be communicated to health professionals, patient organisations, public  
37  
38  
39 445 health policy-makers and to the general public through various media and news activities.  
40  
41  
42  
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44

#### 447 **Ethics**

448 Written informed consent will be obtained from participants before participation in the  
49  
50  
51 449 study. The project has been approved by The Regional Scientific Ethical Committee  
52  
53 450 (S-20160124) and the Danish Data Protection Agency (2008-58-035). The procedures  
54  
55  
56 451 followed are in accordance with the ethical standards of the responsible committee on  
57  
58 452 human experimentation (institutional and national) and with the Helsinki  
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4 453 Declaration of 1975 with later amendments.  
5  
6

7 454  
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9

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13  
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22  
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39 467 OHN, SBS, MJ, AB, LH, JG, JW, HG, UF, JAV, SGK, JF, SAGRM, TK, JB, JF, JFD, ABB, GLS,  
40  
41 468 ST, NJF, IB, TBB, AS, EBS, AF, DE, PR, JR, MB, LW, CLN, HLM, ABN, TK, JK, UH,  
42  
43 469 contributed to the conception and design of the study. All authors accepted the final  
44  
45 470 submitted version.  
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48

49 471  
50

51  
52 472 **Conflicts of Interest:**

53  
54  
55 473 All authors declare no conflict of interest. However, the following authors declare: B.  
56  
57 474 Heitmann has received funding from "MatPrat", the information office for Norwegian egg  
58  
59  
60

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2  
3 475 and meat; L. Hvid is on the advisory board for Abbvie A/S; J. Fallingborg is on the advisory  
4  
5 476 boards for AbbVie A/S, MSD Denmark, Takeda Pharma A/S, and Ferring Pharmaceuticals  
6  
7  
8 477 A/S; V. Andersen receives compensation for consultancy and for being a member of the  
9  
10 478 advisory board for MSD Denmark (Merck) and Janssen A/S. The funding sponsors had no  
11  
12 479 role in the design of the study; in the collection, analysis, or interpretation of data; in the  
13  
14 480 writing of the manuscript, or in the decision to publish the results.  
15  
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23 483

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

**variables**

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

1			
2			
3			
4	Non-dietary lifestyle factors <sup>3</sup> (predefined choices)	X	X
5			
6			
7			
8			
9	<i>Investigations:</i>		
10			
11	Height (cm)	X	
12			
13	Weight (kg)	X	X
14			
15	Body mass index (kg/cm <sup>2</sup> )	X	X
16			
17	Routine blood analyses <sup>4</sup>	X	X
18			
19	Endoscopy <sup>5</sup>	X	X
20			
21			
22			
23			
24			
25			
26			
27			
28	<i>Biological samples<sup>6</sup>:</i>		
29			
30	Fasting blood samples	X	X
31			
32	Faeces samples	X	X
33			
34	Urine samples	X	X
35			
36	Biopsies <sup>5</sup>	X	X
37			
38			
39			
40			
41			
42			
43			
44	<i>Crohn's disease (CD)</i>		
45			
46	Disease location (predefined choices)	X	
47			
48	Prior operations (y/n, description)	X	
49			
50	Disease behaviour (fistulising, luminal)	X	
51			
52	Perianal involvement (y/n)	X	
53			
54	STRIDE – (y/n)	n.a.	X
55			
56			
57			
58			
59			
60			

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) <sup>7</sup>	X	X
HBI index (score)	X	X
<b>*HBI of 4 or less (y/n)</b>	<b>X</b>	<b>X</b>
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 <sup>8</sup> (y/n)		X
Concomitant medication (y/n, predefined choices)	X	X
Number of draining fistulas (fistulising CD)	X	X
<b><i>Ulcerative colitis (UC)</i></b>		
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 <sup>9</sup> (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 <sup>8</sup> (y/n)		X
Concomitant medication (y/n, predefined choices)	X	X
<b><i>Rheumatoid arthritis (RA)</i></b>		
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
<b>*ACR20 (y/n)</b>	<b>n.a.</b>	<b>X</b>
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
<i>Axial spondyloarthritis (axSpA)</i>		
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
<b>*ASAS20 (y/n)</b>	<b>n.a.</b>	<b>X</b>
ASAS40 (y/n)	n.a.	X
ASAS partial response (y/n)	n.a.	X
ASAS5/6 response (y/n)	n.a.	X

<i>Psoriatic arthritis (PsA)</i>		
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
<b>*ACR20</b>	<b>n.a.</b>	<b>X</b>
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
<i>Psoriasis (PsO)</i>		
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
<i>Hidradenitis Suppurativa (HS)</i>		
<b>*HiSCR response</b>	<b>n.a.</b>	<b>X</b>
Hurley stage <sup>10</sup> (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

<i>Non-infectious uveitis (NiU)</i>		
SUN (score)	X	X
<b>*Uveitis treatment failure (y/n)</b>	<b>n.a.</b>	<b>X</b>
New active, inflammatory chorioretinal or retinal vascular lesions relative to baseline (y/n)	X	X
Inability to achieve $\leq 0.5+$ 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 $\geq 15$ letters relative to best state achieved (y/n)	X	X
<i>Health-related quality of life<sup>11</sup></i>	<b>X</b>	<b>X</b>
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
<i>Adverse events</i>		

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
<i>Laboratory</i> <sup>4</sup>		
CRP (mg/l) <sup>12</sup>	X	X

**\*Primary endpoint for the individual diseases**

<sup>1</sup>Data will be collected using a questionnaire as well as local and national registries.

<sup>2</sup>Registry data will be retrieved from the Danish registries using the Danish individual civil registration number (CPR) including BIO-IBD<sup>75</sup>, DANBIO<sup>76</sup>, DERMBIO<sup>77</sup> (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).

<sup>3</sup>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,

1  
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4 physical activity, alcohol consumption, and use of over-the-counter medicine [use of  
5  
6 probiotics, prebiotics, painkillers, laxative, and anti-diarrhoea agents]) as well as  
7  
8 educational level and year of menopause (female) are included<sup>63</sup>. The follow-up  
9  
10 questionnaire is identical to the initial questionnaire apart from the questions on food items  
11  
12 that only contain questions on changes of diet since the last questionnaire.  
13  
14

15  
16  
17 <sup>4</sup>Routine blood analyses include C-reactive protein (CRP), haemoglobin, erythrocyte  
18  
19 count, haematocrit, erythrocyte mean cell volume (MCV), mean cell haemoglobin (MCH)  
20  
21 and mean cell haemoglobin concentration (MCHC), leucocyte count, differential count,  
22  
23 thrombocytes, albumin, K<sup>+</sup> potassium, Na<sup>+</sup> sodium, creatinine, coagulation factor II+VII+X,  
24  
25 alanine aminotransferase (ALAT), alkaline phosphatase, gamma-glutamyl transferase  
26  
27 (GGT), haemoglobin glycation (Hb1Ac), lipids (cholesterol, high density, low density  
28  
29 cholesterol), and transglutaminase.  
30  
31  
32  
33

34  
35 <sup>5</sup>Only IBD patients  
36  
37

38  
39 <sup>6</sup>From all participants, blood, urine, and faeces are sampled. In addition, from IBD patients,  
40  
41 intestinal biopsies are sampled. In selected cases, the additional biological material on  
42  
43 participants from this study may be retrieved from the Patobank and the Danish Biobank.  
44  
45 The samples will be collected adhering to the Sample PRE-analytical Code (SPREC) and  
46  
47 Biospecimen Reporting for Improved Study Quality (BRISQ) guidelines, using standard  
48  
49 operational procedures (SOPs) describing and logging primary container, centrifugation  
50  
51 conditions, centrifugation parameters, and storage conditions<sup>78 79</sup>. The biological material  
52  
53 will be stored in OPEN (biological material from OUH) or at SHS (biological material from  
54  
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the other hospitals).

<sup>7</sup>Only CD patients when endoscopy cannot adequately evaluate inflammation.

<sup>8</sup>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.

<sup>9</sup>A reduction in complete Mayo score of  $\geq 3$  points and  $\geq 30\%$  from baseline (or a partial Mayo score of  $\geq 2$  points and  $\geq 25\%$  from baseline, if the complete Mayo score was not performed at the visit) with an accompanying decrease in rectal bleeding sub-score of  $\geq 1$  point or absolute rectal bleeding sub-score of  $\leq 1$  point

<sup>10</sup>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.

<sup>11</sup>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.

<sup>12</sup>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)<sup>80</sup>.

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

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4 Activity Index; BASFI (Bath Ankylosing Spondylitis Functional Index; BASMI, Bath  
5  
6 Ankylosing Spondylitis Metrology Index; CRP, C-reactive protein; DAS28, Disease activity  
7  
8 score; DLQI<sup>81,82</sup>, Dermatology Life Quality Index; FFQ, Food frequency questionnaire; HBI,  
9  
10 Harvey-Bradshaw Index; HiSCR<sup>51</sup>, Hidradenitis Suppurativa Clinical Response; HAQ,  
11  
12 Health Assessment Questionnaire; NYHA, New York Heart Association; PASI, Psoriasis  
13  
14 Area and Severity Index; SCCAI, Simple Clinical Colitis Activity Index; SES-CD, Simple  
15  
16 Endoscopic Score for Crohn's Disease; SF12, Short Form Health Survey; SHS<sup>83,84</sup>, Short  
17  
18 Health Scale; SUN, Standardization of Uveitis Nomenclature for Reporting Clinical Data;  
19  
20 STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease <sup>53</sup>  
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485 **FIGURE LEGENDS**486 **Figure 1. Hypothesis for effects of diet in relation to treatment effect**

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

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2  
3 511 high consumption of meat, particularly red and processed meat, protein, and alcohol was associated  
4  
5 512 with risk of relapse, and that high sulphur or sulphate intakes may offer an explanation for the  
6  
7 513 observed findings<sup>95</sup>. Additionally, support of the notation that diet may affect systemic immune  
8  
9 514 response is provided by the finding that intake of low-glycemic index diet was found to lower  
10  
11 515 secretion of TNF and IL-6 from stimulated peripheral blood mononuclear cells from obese humans<sup>96</sup>.  
12  
13  
14 516 **(Right)** Intake of high fibre and low meat may promote an effective mucosal barrier and support the  
15  
16 517 effects of outcome after drug targeting the pro-inflammatory molecule TNF (TNF inhibitors [TNFi]).  
17  
18 518 Intake of soluble plant fibre has been found to block bacterial adhesion to gut enterocytes in animal  
19  
20 519 and cell studies<sup>97</sup>. The genetic architecture of the individual may also impact the influence of lifestyle  
21  
22 520 factors<sup>15</sup>. Hence, in order to provide lifestyle recommendations, we need to understand the effects of  
23  
24 521 lifestyle on the immune system, and how lifestyle may improve the therapeutic outcome and reduce  
25  
26 522 the need of medical treatment in the individual person. Information on diet and non-diet lifestyle  
27  
28 523 exposures may be collected by using e.g. questionnaires and lifestyle-associated biomarkers or a  
29  
30 524 combination of these methods<sup>98-100</sup>. Evidence-based biomarkers for lifestyle assessment are scarce  
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32 525 <sup>101-121</sup> and mostly used for studies on healthy individuals<sup>122-125</sup>.  
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37 526 **Figure 2. Organisation and patient research partners**  
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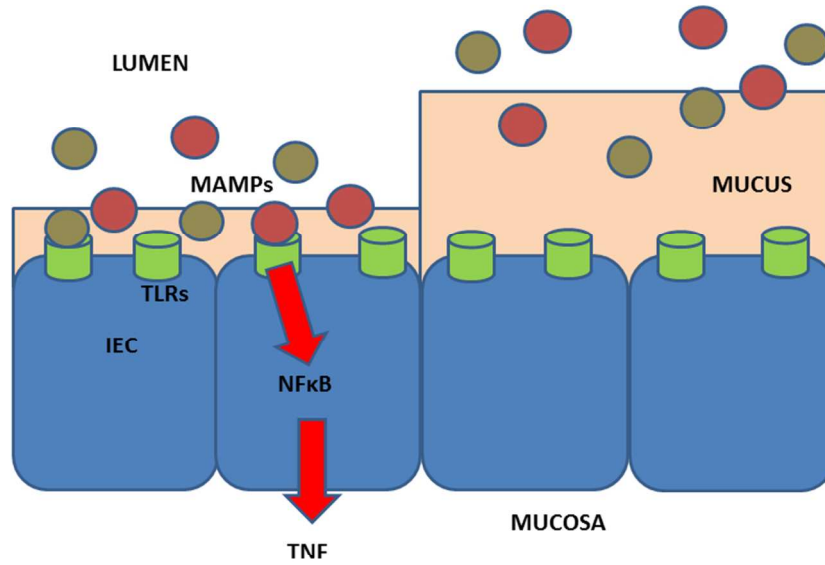


Figure 1. Hypothesis for effects of diet in relation to treatment effect

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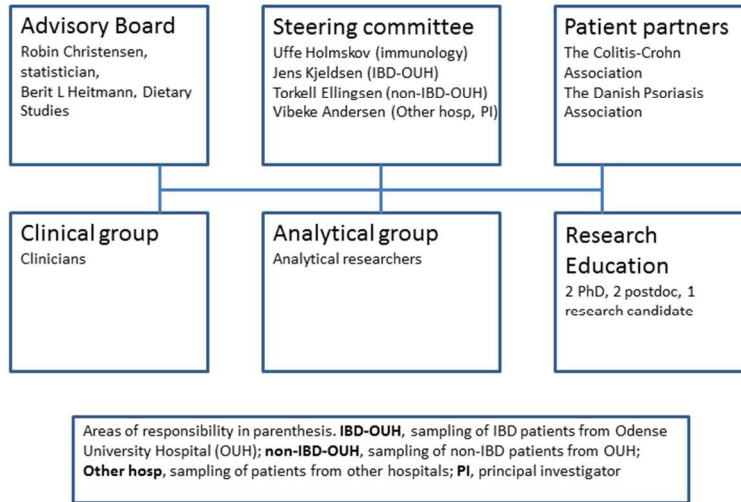


Figure 2. Organisation and patient research partners

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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
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



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3 **Introduction**  
4

5 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__
10 Objectives	7	Specific objectives or hypotheses	__6__
12 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__

15  
16 **Methods: Participants, interventions, and outcomes**  
17

18 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__
21 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__
24 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__
35 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__
41 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__

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__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__

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3	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___
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7	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___
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10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___12___
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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___
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16	<b>Methods: Monitoring</b>			
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18	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___
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23		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___
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26	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___
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29	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___NA___
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33	<b>Ethics and dissemination</b>			
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35	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___14___
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38	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___
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	___7___
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	___NA___
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9	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___
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12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	___14___
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15	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___
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18	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___NA___
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21	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___
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26		31b	Authorship eligibility guidelines and any intended use of professional writers	___NA___
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28		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	___NA___
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30	<b>Appendices</b>			
31				
32	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	__suppl__
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35	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___
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38 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
 39 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
 40 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.  
 41