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# BMJ Open

## A value-based care pathway for IBD: protocol for the multicentre longitudinal pre-post IBD Value study

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3 1 A value-based care pathway for IBD: protocol for the multicentre longitudinal pre-post

4 2 IBD Value study

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## 38 **ABSTRACT**

39 Introduction: Biologics are effective for the treatment of inflammatory bowel disease (IBD). However,  
40 unwarranted variation in both processes and outcomes has been reported in the treatment of IBD  
41 with biologics. A care pathway for the treatment of IBD with biologics has the potential to reduce this  
42 practice variation and improve outcomes. The aim of this study is to assess the impact of a uniform  
43 care pathway for the treatment of IBD with biologics on health outcomes.

44 Methods and analysis: IBD Value is a multicentre longitudinal pre-post study with non-equivalent  
45 control group. The study takes place in eight centres in the southwest region of the Netherlands. It  
46 compares a care pathway for the treatment of IBD patients with biologics to the current situation.  
47 The primary outcome is the effect of the care pathway on disease control as measured with the IBD-  
48 Control questionnaire. Secondary outcomes are the effect of the care pathway on the other  
49 outcomes of the International Consortium of Health Outcomes Measurement (ICHOM) IBD standard  
50 set, health-related generic quality of life, patient experiences, and degree of variation; cost-  
51 effectiveness of the care pathway; and the variation between hospitals in the aforementioned  
52 outcomes in the baseline period. The study has started on December 1<sup>st</sup> 2020 and at least 200  
53 patients will be included.

54 Ethics and dissemination: The study was deemed not to be subject to Dutch law (WMO; Medical  
55 Research Involving Human Subjects Act) by the Medical Ethics Committee Erasmus MC, the  
56 Netherlands (registration number MEC-2020-075) and a waiver was provided. Results will be  
57 disseminated through peer-reviewed journals and presented at (inter)national conferences.

58 Registration details: This study was registered in the Netherlands Trial Register (NL8276) on 09-01-  
59 2020.

## 61 **STRENGTH AND LIMITATIONS OF THIS STUDY**

- 62 • This prospective study aims to elucidate the important problem of treatment variation in  
63 IBD.
- 64 • It is to our knowledge the first prospective multicentre study assessing the effect of a care  
65 pathway for the treatment of IBD on health outcomes.
- 66 • The Dutch Crohn's and colitis patient organisation was involved in the study design and will  
67 participate in the development of the care pathway.
- 68 • This is the first large multicentre study to implement the International Consortium of Health  
69 Outcomes Measurement (ICHOM) standard set for IBD.
- 70 • The study is a non-randomised trial.

## 73 INTRODUCTION

74 Crohn's disease and ulcerative colitis, subtypes of inflammatory bowel disease (IBD), are chronic  
75 inflammatory diseases of the gastrointestinal tract.[1, 2] Symptoms of IBD are abdominal pain,  
76 diarrhoea, and rectal bleeding. IBD can also affect extraintestinal organs, such as the liver, skin, eyes,  
77 and joints.[3-5] Further, IBD can have a major impact on quality of life because of fatigue and its  
78 psychological impact.[6, 7] To control these symptoms, patients are often dependent on medication  
79 and are sometimes hospitalized or need surgery when drugs fail. The high disease burden leads to  
80 reduced quality of life, high healthcare costs (between €15,000 and €30,000 per patient per year)  
81 and reduced work productivity.[7-9] Biologics and small molecules (which from here on are jointly  
82 referred to as biologics) are proven efficacious treatments for IBD and have shown to induce and  
83 maintain remission, avert hospitalisation and surgery, and reduce productivity loss in randomised  
84 controlled trials.[10-13]

85  
86 Considerable variation exists between healthcare providers in the treatment of IBD with  
87 biologics.[14-18] Treatment variation consists among other things of differences in provided care and  
88 follow-up such as type of medication prescribed, dosing frequency, and interpretation of therapeutic  
89 drug monitoring. Treatment variation can lead to differences in outcomes, such as the proportion of  
90 patients in remission.[19] While variation can be a natural consequence of differences between  
91 patient populations, part of the variation in processes and outcomes was explained by experience  
92 and expertise of healthcare providers, with better process adherence and outcomes for dedicated  
93 IBD or academic physicians.[18, 19]

94  
95 Treatment variation might also lead to reduced effectiveness of biologics in daily practice.  
96 Observational population-based studies showed no association between the use of biologics and  
97 long-term disease progression, nor on hospitalisation or surgery, contradicting the findings of  
98 randomised controlled trials.[20-22] These observational studies hypothesize, while acknowledging  
99 the differences between patient populations, that variation in treatment, mainly under- and misuse  
100 of biologics, may partly explain this gap between the efficaciousness of biologics in randomised trials  
101 and their effectiveness in the real world. Reduction of this variation might thus be a potential avenue  
102 for improving outcomes of IBD patients treated with a biologic.

103  
104 Value-based healthcare (VBHC) is an approach that aims, among other things, at improving technical  
105 value (health outcomes achieved divided by resources spent) for the patient by tackling unwarranted  
106 variation and optimising the care delivery process.[23, 24] Important parts of VBHC are  
107 systematically measuring both patient-reported outcomes and the costs of achieving these  
108 outcomes.[25, 26] These data can consequently be used to evaluate and adjust the care delivery  
109 process and improve (cost-)effectiveness of achieving optimal patient-centred outcomes.

110  
111 Implementing a care pathway in clinical practice seems promising for improving value, which was  
112 illustrated by a retrospective pilot study that evaluated a care pathway for IBD in a VBHC program.  
113 This care pathway showed a favourable effect on flares (-26%) and costs (-16%).[27] Other studies  
114 supported the effect of a care pathway for IBD on costs and also showed an improvement of care  
115 processes.[28, 29]. In other diseases the implementation of a care pathway was also accompanied by  
116 reduced variation.[30] Although these studies showed a promising effect on outcomes and  
117 processes, they suffered from low sample sizes, retrospective study designs and lacked patient-  
118 centred outcome measures. With the prospective multicentre IBD Value study we aim to assess the  
119 impact of a care pathway for the treatment of IBD with biologics on patient-centred outcomes.

## METHODS AND ANALYSIS

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines were followed and the checklist is included with the protocol (online supplementary file 1).[31] The most recent study protocol version 2.0.0 (July 2020) is presented in this manuscript. Changes to the protocol will be submitted to the Medical Ethics Committee Erasmus MC (Rotterdam, the Netherlands) and the institutional review boards of the participating centres. Changes will also be noted in the trial register and communicated to local investigators. The start date of the study was 1 December 2020.

### Study Aim

The main objective of the study is to evaluate the added value of a uniform care pathway on the health outcomes of IBD patients treated with a biologic agent in one of the participating hospitals.

Secondary objectives are to:

- Assess the degree of regional variation in outcomes and costs of the treatment of IBD with biologics;
- Uncover areas of improvement in the care of IBD patients;
- Develop and implement a regional care pathway for the treatment of IBD with biologics based on scientific evidence, current guidelines, and adapted to the local context;
- Evaluate the cost-effectiveness of the care pathway;
- Evaluate the effect of the care pathway on variation in outcomes and costs.

### Study Design

This is a longitudinal pre-post intervention study with a non-equivalent control group (Figure 1). In the first 12 months, before the introduction of the new care pathway, the current situation in IBD care for patients on biologics will be assessed in all participating hospitals to establish baseline measures. These data will primarily be used as comparison with the 2<sup>nd</sup> study period after implementation of the care pathway. The data will also be used to determine areas of improvement, as benchmarking, and aid the design of the care pathway. Subsequently the care pathway will be implemented in six of the participating hospitals during a three-month implementation period.

The participating hospitals are: Franciscus Gasthuis & Vlietland, Rotterdam & Schiedam; Erasmus MC, Rotterdam; Albert Schweitzer Hospital, Dordrecht, Zwijndrecht & Sliedrecht; Maasstad Hospital, Rotterdam; Ikazia Hospital, Rotterdam; IJsselland Hospital, Capelle aan den IJssel; Reinier de Graaf Gasthuis, Delft; Amphia Hospital, Breda. These are hospitals that have collaborated in IBD BeterKeten in the southwest of the Netherlands since 2016 to improve quality of care of IBD patients in the region.[32] The care pathway will not be implemented in Reinier de Graaf Gasthuis and Amphia Hospital; these hospitals will participate as a non-equivalent control group. The content of the care pathway will only be revealed to and implemented in the six hospitals in the intervention group at the start of the implementation period. The development of the care pathway will be completed by the working group in the last period of the baseline measurement phase. After implementation, outcomes will be evaluated during the 12-month follow-up period in all participating hospitals.

### Population

The study population comprises all IBD patients being treated with a biologic agent in the eight participating hospitals. Approximately 3,200 patients are treated with a biologic agent in these hospitals in total.

All participants will meet the following criteria:

- 18 years of age or older
- Have given informed consent for data collection
- Being treated for IBD in one of the participating hospitals

- 1  
2  
3 173 • Have an IBD diagnosis of at least three months  
4 174 • Treated with one of the currently registered biologics or small molecules for IBD treatment  
5 175 or new treatments registered during the study period, including: infliximab, adalimumab,  
6 176 golimumab, vedolizumab, ustekinumab, or tofacitinib.  
7 177

8  
9 178 A potential subject may be excluded from study participation if they have insufficient knowledge of  
10 179 the Dutch language to complete the questionnaires and/or have no access to the internet to  
11 180 complete the questionnaires.  
12 181

### 13 182 **Intervention**

14 183 The intervention is a uniform care pathway for the treatment of IBD patients with biologic agents. It  
15 184 contains uniform guidelines for prescribing, the work-up, and switching of biologic therapy, and for  
16 185 the frequency and type of follow-up. The care pathway will be developed by an IBD BeterKeten  
17 186 working group of gastroenterologists and IBD nurses with multidisciplinary input of a surgeon and a  
18 187 dietician. Moreover, the Dutch IBD patient federation (Crohn & Colitis NL) will participate in the  
19 188 design of the care pathway. The care pathway will be based on national and international  
20 189 guidelines.[33-35] Data from the baseline measurement collected during the first project phase will  
21 190 be used to adjust and improve the care pathway.  
22 191

23 192 To prevent contamination of the control period, the development of the care pathway will be  
24 193 finalised shortly before implementation. The care pathway will address the following issues.

- 25  
26 194 1. Actions that do not depend on current treatment but apply to all patients: examples are  
27 195 periodical colorectal cancer and micronutrient screening.  
28 196 2. Evaluation of a possible flare: when a patient presents with symptoms or when abnormal  
29 197 test results are found, differential diagnoses have to be excluded. Moreover, disease activity  
30 198 has to be measured using objective markers.  
31 199 3. Therapy sequence in case of a flare: it will indicate advice on the next treatment step for a  
32 200 patient with a flare based on their disease and treatment history. This could be either  
33 201 treatment intensification or switching.  
34 202 4. Frequency, type and timing of follow-up for the induction and remission phases of the  
35 203 different therapies: examples are the timing of outpatient clinic visits, laboratory  
36 204 assessments and additional examinations.  
37 205

38 206 The care pathway is a decision-making tool for care providers and patients, and presents treatment  
39 207 guidelines in a simple and interpretable format. It sets out the most appropriate steps in patient  
40 208 management at each therapy stage. Decision trees will be designed to give visual support to the care  
41 209 pathway. Because the treatment of IBD is rapidly changing and studies regularly provide new  
42 210 insights, the care pathway will be updated in IBD BeterKeten meetings after study closure. IBD  
43 211 specialists from IBD BeterKeten will safeguard implementation of the care pathway in their  
44 212 respective centres. They will be supported by a presentation of the working group to the care  
45 213 providers, educational tools and implementation and automatization of the care pathway in the  
46 214 electronic health records.  
47 215

### 48 216 **Comparison**

49 217 The care pathway will be compared to current care by ways of the baseline measurement and  
50 218 adjustment for changes in the control group. All care providers continue their current practice  
51 219 according to their knowledge and local guidelines and treatment plans for the duration of the  
52 220 baseline measurement. The data collected in this period will give more insight into the current  
53 221 variation in practice, and can also be used to inform the design of the care pathway.  
54 222

### 55 223 **Outcome**

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224 To measure outcomes that matter to the patient, the standard set of patient-centred outcomes for  
 225 IBD as defined by the International Consortium of Health Outcomes Measurement (ICHOM) will be  
 226 used as the outcome measure of this study. ICHOM is an organization that creates standard sets to  
 227 measure the outcomes that matter most to patients.[25] Patient-reported disease control as  
 228 measured by the IBD-Control-8 score was chosen to serve as the primary outcome measure. This is a  
 229 questionnaire that validly and reliably measures disease control from the patient perspective on a  
 230 16-point scale, and can distinguish between active disease and remission.[36, 37]

231

232 The other outcomes from the standard set are secondary outcomes:

- 233 • IBD-attributable mortality;
- 234 • Remission, both clinician-reported (biochemical, radiological, endoscopic, histologic) and  
 235 patient-reported (Manitoba IBD Index; MIBDI);[38]
- 236 • Incidence of colorectal cancer;
- 237 • Presence of anaemia;
- 238 • Number of A&E visits;
- 239 • Number and cumulative length of hospital admissions;
- 240 • Number of complications of any intervention for IBD;
- 241 • Long-term (>3 months) steroid use;
- 242 • Presence of fistulae symptoms;
- 243 • BMI as a proxy for nutritional status;

244

245 The MIBDI is a valid and patient-reported outcome measure which can be used to classify disease  
 246 activity on a dichotomous scale. The other outcomes from the standard set will be retrieved from the  
 247 electronic health record. Other secondary outcomes are generic quality of life measured with the  
 248 validated PROMIS-10 Global Health (PROMIS-10) questionnaire, cost-effectiveness and patient  
 249 experience of care, using the Dutch Picker questionnaire.[39, 40]

250

251 The cost-utility analysis (CUA) will be performed alongside the clinical study. In line with the  
 252 recommendations of the National Health Care Institute and the broad societal impact of IBD the CUA  
 253 will take a societal perspective.[8, 41] Utility will be measured with the EQ-5D-5L (Dutch tariffs).[42]  
 254 The IBD-Control-8 score, which is more responsive to health state changes in IBD, will be used for an  
 255 alternative cost-effectiveness analysis.[36] Societal costs will be measured according to the  
 256 guidelines of the National Health Care Institute.[41-43]. Three types of societal costs are  
 257 distinguished: healthcare costs; patient costs; and other non-healthcare costs. For healthcare costs,  
 258 primary care costs (primary care, home care, other out of hospital care) are distinguished from in-  
 259 hospital costs. Use of primary care will be measured using the shortened version of the Medical  
 260 Consumption Questionnaire (iMCQ) of the Institute of Medical Technology Assessment (iMTA).[44]  
 261 For healthcare use in secondary care, data will be collected from the electronic healthcare records.  
 262 Productivity losses will be determined with the iMTA Productivity Cost Questionnaire (iPCQ).  
 263 Measured productivity losses will be extrapolated from one to three months. Absenteeism,  
 264 presenteeism, and lost unpaid work will be determined. Patient costs will be measured using a  
 265 questionnaire on the following: travel costs; type, weeks and hours of informal care; insurance  
 266 deductible; over the counter drug use; other IBD related costs.

267

### 268 **Case mix**

269 To control for case mix differences between hospitals, we will collect the case mix variables defined  
 270 in the ICHOM sets for risk adjustment for IBD care.[25] Data will be collected on the following  
 271 variables:

- 272 • Year of birth
- 273 • Sex at birth
- 274 • Education level as defined by UNESCO[45]
- 275 • Smoking status



- 276 • Diagnosis (Crohn's disease, ulcerative colitis, indeterminate)
- 277 • Year of diagnosis
- 278 • Disease phenotype according to the Montreal classification[46]
- 279 • Presence of extra-intestinal manifestations
- 280 • Medication use for IBD
- 281 • IBD related surgery
- 282 • Comorbidities as defined by the self-administered comorbidity questionnaire (SCQ) with
- 283 inclusion of some extra questions as defined by ICHOM [47]
- 284 • Current or prior infection with tuberculosis, hepatitis B or human immunodeficiency virus
- 285 • Concomitant presence of primary sclerosing cholangitis
- 286 • Treating hospital

### 288 Timing

289 Patients can be included between ethical approval and the end of the study. Outcomes will be  
 290 measured at the following time points as defined by ICHOM (see also Table 1 and 2). The IBD-  
 291 Control, MIBDI, EQ-5D-5L and the PROMIS-10 will be administered when a participant is included in  
 292 the study and at six monthly intervals from the start of the study. Cost questionnaires will be sent to  
 293 patients at three monthly intervals from the start of the study. Demographics and comorbidity  
 294 questionnaires will be sent at inclusion, at the start of the intervention period (t=15) and at the end  
 295 of the study (t=27). Patient experience questionnaires will be distributed once a year after an  
 296 outpatient clinic visit. To reduce questionnaire burden, some questionnaires at inclusion will not be  
 297 sent if a patient is included two months (quality of life) or three months (case mix) before the  
 298 respective questionnaires would be sent again.

300 *Table 1: Timing of questionnaires for patient included at or before T=0*

|                  | Demographics | IBD-Control | MIBDI | SCQ | EQ-5D-5L/<br>PROMIS-10 | iPCQ | iMCQ | Patient costs |
|------------------|--------------|-------------|-------|-----|------------------------|------|------|---------------|
| 0m (study start) | X            | X           | X     | X   | X                      |      |      |               |
| 3m               |              |             |       |     |                        | X    | X    | X             |
| 6m               |              | X           | X     |     | X                      | X    | X    | X             |
| 9m               |              |             |       |     |                        | X    | X    | X             |
| 12m              |              | X           | X     |     | X                      | X    | X    | X             |
| 15m              | X            |             |       | X   |                        | X    | X    | X             |
| 18m              |              |             |       |     |                        | X    | X    | X             |
| 21m              |              | X           | X     |     | X                      | X    | X    | X             |
| 24m              |              |             |       |     |                        | X    | X    | X             |
| 27m              | X            | X           | X     | X   | X                      | X    | X    | X             |

301 *Table 2: Timing of questionnaires for a patient included at T=10m*

|                  | Demographics | IBD-Control | MIBDI | SCQ | EQ-5D-5L/<br>PROMIS-10 | iPCQ | iMCQ | Patient costs |
|------------------|--------------|-------------|-------|-----|------------------------|------|------|---------------|
| 0m (study start) |              |             |       |     |                        |      |      |               |
| 3m               |              |             |       |     |                        |      |      |               |
| 6m               |              |             |       |     |                        |      |      |               |
| 9m               |              |             |       |     |                        |      |      |               |
| 10m (inclusion)  | X            |             |       |     |                        |      |      |               |
| 12m              |              | X           | X     |     | X                      | X    | X    | X             |
| 15m              | X            |             |       | X   |                        | X    | X    | X             |
| 18m              |              |             |       |     |                        | X    | X    | X             |
| 21m              |              | X           | X     |     | X                      | X    | X    | X             |
| 24m              |              |             |       |     |                        | X    | X    | X             |
| 27m              | X            | X           | X     | X   | X                      | X    | X    | X             |

302 Other outcomes will be retrieved from the electronic health records retrospectively, biannually and  
 303 annually as recommended by ICHOM. A subset of the data (e.g. age, gender, hospital healthcare use,  
 304 anaemia, mortality, medication use) can be retrieved from the electronic health records  
 305

1  
2  
3 306 anonymously. This data will be retrieved for the entire source population, as informed consent is not  
4 307 necessary for the use of anonymized data according to Dutch law. This can be used to study possible  
5 308 selection bias.

6 309  
7  
8 310 **Statistical considerations**

9 311 **Power**

10 312 As our data are clustered longitudinally and per hospital, analytic sample size calculation is not  
11 313 appropriate. Thus, we used simulations to estimate power for different cluster sizes. The calculations  
12 314 were based on the following assumptions:

- 13 315 • a baseline IBD-Control score of 8 with a standard deviation (SD) of 4;[48, 49]
- 14 316 • because of the clustering of data at two levels (within patients over time and patients  
15 317 clustered within hospitals), the degree of clustering has to be accounted for. As this is not  
16 318 reported in the literature, we estimated random effects for patients and hospitals with  
17 319 standard deviations between 0 and 4 (corresponding to intraclass correlation coefficients  
18 320 between 0 and 0.25);
- 20 321 • a change in IBD score of 1 as clinically meaningful. Research has shown minimal  
21 322 important differences of 0.5 SD for health-related quality of life instruments. However, as  
22 323 amelioration of a single symptom changes the score of the IBD Control by 0.25 SD, we  
23 324 powered our study on this effect size.[50]

24 325

25 326 The sample size calculation is further based on:

- 26 327 • simulating data based on the assumptions listed above;
- 27 328 • 8 hospitals of between 1 and 50 patients each, in steps of 5;
- 28 329 • 10,000 iterations per cluster size;
- 29 330 • dropout of 10%;
- 30 331 • type-1 error rate ( $\alpha$ ) of 0.05 two-sided;
- 31 332 • power of at least 80%;
- 32 333 • fitting a linear mixed effect model with random intercepts for patient and hospital and a  
33 334 fixed effect for intervention.

34 335

35 336 Power was defined as the number of iterations that found a statistically significant effect as a  
36 337 proportion of the total number of iterations. To account for our clustered data, 25 patients per  
37 338 hospital (a total of 200 patients) before the six month mark of the study would be required to have  
38 339 sufficient power (>80%) to identify a change of 1 point of the IBD-Control score. We are striving to  
39 340 include all eligible patients to achieve a representative sample of the source population and to  
40 341 prevent selection bias.

41 342

42 343 Business Intelligence (BI) departments in each of the participating hospitals will support patient  
43 344 screening and help reduce the logistic burden. The BI departments will use an algorithm to identify  
44 345 patients who meet the study inclusion criteria. These patients will receive a letter or e-mail from  
45 346 their hospital, asking for their consent to participate in the study. The algorithm will also identify the  
46 347 patient's care provider and next hospital visit. The care providers will be provided with this  
47 348 information to approach the patient for inclusion during the outpatient clinic visit. Patient  
48 349 recruitment should not be a time consuming process as the burden on the patient is low, the study is  
49 350 easy to explain and no randomisation or experimental treatment is used. Because all patients will  
50 351 receive an invitation letter to participate and care providers will remind them during their hospitals  
51 352 visit, we think that the minimum inclusion goal of 25 patients per hospital is feasible. Currently, 588  
52 353 patients have been included.

53 354

54 355 **Data analysis plan**

55 356 All missing data will be assessed whether these data are likely to be missing (completely) at random.  
56 357 If so, Multivariate Imputation by Chained Equations (MICE) will be used to impute missing data for

variables used for adjustment. The primary outcome, IBD-Control-8 score, will be analysed on patient level using a linear mixed effects model of the form:

$$Y_{ijt} = \beta_0 + \eta_j + \theta_{ij} + \beta_1\iota + \beta_t v_t + \beta_c v_c + \varepsilon_{ijt}$$

Where  $Y$  is the IBD-Control-8 score (0-16) of person  $i$  in cluster  $j$  at time  $t$  (0-6 months, 6-12 months, 15-21 months, 21-27 months);  $\beta_0$  the intercept;  $\eta_j$  the cluster level random effect for cluster  $j$ ;  $\theta_{ij}$  the patient level random effect for patient  $i$  in cluster  $j$ ;  $\beta_1$  the estimated difference between standard care ( $\iota = 0$ ) and the care pathway ( $\iota = 1$ );  $\beta_t$  a vector with coefficients for calendar time at the different time points  $t$ , captured as the vector  $v_t$  with dummy variables for the different periods of follow-up;  $\beta_c$  a vector containing the coefficients for the case mix variables in the vector  $v_c$ ; and  $\varepsilon_{ijt}$  is the residual error.

To adjust for case mix we will use the variables from the ICHOM IBD set. These are: age in years (continuous), sex at birth (dichotomous), education level (categorical: low, middle, high), smoking status (categorical: never, ex-smoker, current), comorbidities (self-administered comorbidity questionnaire, continuous), current or prior infection with tuberculosis (dichotomous), hepatitis B (dichotomous), and/or HIV (dichotomous), diagnosis (categorical: Crohn's disease, ulcerative colitis, unknown/indeterminate), disease duration in years (continuous), phenotype according to the Montreal classification (for Crohn's disease: age of onset, localisation, behaviour and for ulcerative colitis and IBD-U: extension, all categorical), presence of extra-intestinal manifestations (categorical: none, skin, joint, hepatobiliary, eye, other), and concomitant presence of primary sclerosing cholangitis (categorical). The secondary outcomes from the ICHOM Standard Set will be analysed on patient level with a (generalized) linear mixed model of the same form as described above.

#### Cost-effectiveness

As the standard of care and the new care pathway will be analysed for a one-year period, this is also the time horizon for the CUA. No discounting of costs and effects will be applied to the one-year period. Costs will be determined by multiplying measured healthcare use and productivity loss with reference prices or cost estimates in line with recommendations of the National Health Care Institute.[51, 52] All costs will be transformed to the same year, adjusted for inflation using the consumer price index (CPI) if necessary. The friction cost method will be used to estimate productivity costs. A sensitivity analysis using the human capital approach will also be performed.

To assess the cost-effectiveness of the care pathway compared to usual care, crude and adjusted differences in costs and quality of life in the before and after groups from the regression models will be used to estimate the incremental cost-effectiveness ratio (ICER). Robustness of results will be evaluated using probabilistic sensitivity analysis (PSA) using Monte Carlo simulation. For the PSA, non-parametric bootstrapping with 2,000 iterations will be used to determine uncertainty around the ICER. To support decision making, calculation of the net monetary/health benefits at the relevant willingness to pay levels, acceptability curves and Value of Information Analysis will be added.

#### Variation

To assess the variation in outcomes and costs between hospitals the intraclass correlation coefficient (ICC) will be used. The ICC is defined as:

$$ICC (Cluster) = \frac{\sigma_{\eta}^2}{\sigma_{\eta}^2 + \sigma_{\theta}^2 + \sigma_{\varepsilon}^2}$$

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3 406 which can be interpreted as the variance explained by the hospital as a proportion of the total  
4 407 variance. For the baseline period, data will be analysed using the aforementioned mixed effects  
5 408 models omitting the coefficient for the care pathway.  
6 409

7  
8 410 To assess the effect of the care pathway on variation, data from the six hospitals that implemented  
9 411 the care pathway will be analysed for the two periods using the aforementioned mixed effects  
10 412 model, without the coefficient for the care pathway. This model will be compared with a model that  
11 413 estimates a random effect per hospital for the baseline period and the care pathway period  
12 414 separately. The effect of the care pathway on variation will then be formally tested using a  
13 415 likelihood-ratio test comparing the two models.  
14 416

#### 15 417 **Patient and public involvement**

16 418 Crohn & Colitis NL (Dutch Crohn's and Colitis Patient Organisation) collaborated in the design of this  
17 419 study. They critically revised the study design and helped in piloting the questionnaires. They will be  
18 420 involved in the working group that is responsible for the development of the care pathway.  
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3 423 **ETHICS AND DISSEMINATION**

4 424 The study was deemed to not be subject to the Wet medisch-wetenschappelijk onderzoek met  
5 425 mensen (WMO; Medical Research Involving Human Subjects Act) by the Medical Ethics Committee  
6 426 Erasmus MC, the Netherlands (registration number MEC-2020-075). Informed consent for  
7 427 questionnaires and chart review will be obtained by local investigators (online supplementary file 2).  
8 428 Data of all participating centres will be collected using electronic CRFs and entered in Castor EDC, an  
9 429 electronic database that is ISO27001 certified.[53] Data will be coded and handled based on the  
10 430 General Data Protection Regulation (GDPR). A data monitoring committee is not necessary as the  
11 431 intervention under study is a change in the standard of care.  
12 432

13 433 The principal investigators and study coordinator will have access to the final dataset. The dataset  
14 434 will be available on reasonable request. The study team is responsible for data analysis and  
15 435 reporting. Results will be fed back to participating centres and disseminated through peer-reviewed  
16 436 journals and presented at (inter)national conferences. The study team will make the decision to  
17 437 publish, and the funder and sponsor had and will have no influence on the research question, study  
18 438 design, data collection or analysis, or decision to publish.  
19 439

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5 442

6 443 **COMPETING INTERESTS STATEMENT**

7 444 Drs. van Linschoten has nothing to disclose.

8 445 Dr. van Leeuwen has nothing to disclose.

9 446 Drs. Nieboer has nothing to disclose.

10 447 Dr. Birnie has nothing to disclose

11 448 Drs. Scherpenzeel, MPM has nothing to disclose

12 449 Dr. de Jonge has nothing to disclose

13 450 Drs. Verweij has nothing to disclose

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21 458

22 459 **LEGEND**

23 460 Figure 1: Study Timeline  
24 461

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33 470 expertise, DN provided statistical expertise and EB provided expertise in economic evaluation during  
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35 472 and RCAvL participated in the design of the intervention. RCAvL drafted the manuscript and all  
36 473 authors read, critically revised and approved the final manuscript. Principal investigators are DvN and  
37 474 RLW. RCAvL ensures daily study management as study coordinator. DvN and RLW share last  
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39 476

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45 482 **KEYWORDS**

46 483 Clinical trial; gastroenterology; inflammatory bowel disease; health economics; value-based  
47 484 healthcare; health services research; care pathway;  
48 485

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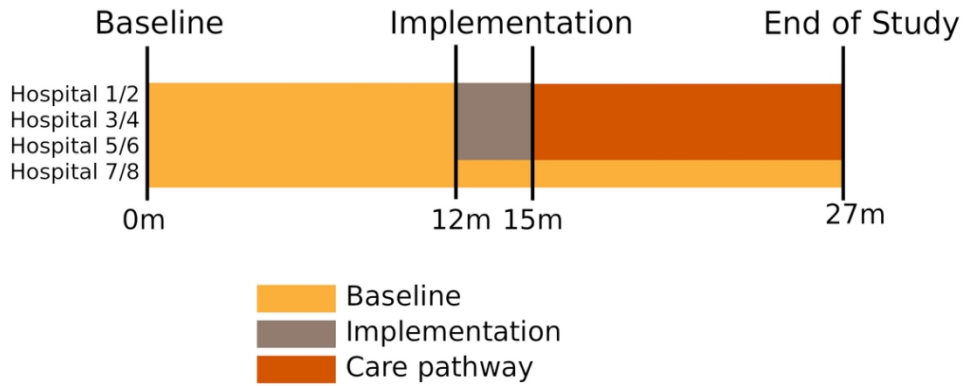


Figure 1: Study Timeline

50x21mm (600 x 600 DPI)

|    | Reporting Item  | Page Number  |         |
|----|---|--|---------|
| 1  |   |  |         |
| 2  |   |  |         |
| 3  |   |  |         |
| 4  | <b>Administrative</b>                                   |  |         |
| 5  | <b>information</b>                                      |  |         |
| 6  |   |  |         |
| 7  | Title   | <a href="#">#1</a> Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym  | 1       |
| 8  |   |  |         |
| 9  |   |  |         |
| 10 |   |  |         |
| 11 |   |  |         |
| 12 | Trial registration                                      | <a href="#">#2a</a> Trial identifier and registry name. If not yet registered, name of intended registry   | 2       |
| 13 |   |  |         |
| 14 |   |  |         |
| 15 |   |  |         |
| 16 | Trial registration: data set                            | <a href="#">#2b</a> All items from the World Health Organization Trial Registration Data Set   | 1 - 13  |
| 17 |   |  |         |
| 18 |   |  |         |
| 19 |   |  |         |
| 20 | Protocol version  | <a href="#">#3</a> Date and version identifier   | 4       |
| 21 |   |  |         |
| 22 | Funding   | <a href="#">#4</a> Sources and types of financial, material, and other support   | 12      |
| 23 |   |  |         |
| 24 |   |  |         |
| 25 |   |  |         |
| 26 | Roles and responsibilities: contributorship             | <a href="#">#5a</a> Names, affiliations, and roles of protocol contributors  | 12      |
| 27 |   |  |         |
| 28 |   |  |         |
| 29 |   |  |         |
| 30 |   |  |         |
| 31 | Roles and responsibilities: sponsor contact information | <a href="#">#5b</a> Name and contact information for the trial sponsor   | 12      |
| 32 |   |  |         |
| 33 |   |  |         |
| 34 |   |  |         |
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| 36 |   |  |         |
| 37 |   |  |         |
| 38 | Roles and responsibilities: sponsor and funder          | <a href="#">#5c</a> 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 | 11      |
| 39 |   |  |         |
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| 48 | Roles and responsibilities: committees                  | <a href="#">#5d</a> 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)                         | 12 - 13 |
| 49 |   |  |         |
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| 57 |   |  |         |
| 58 | <b>Introduction</b>                                     |  |         |
| 59 |   |  |         |
| 60 |   |  |         |

|    |                           |                      |  |       |
|----|---------------------------|----------------------|--|-------|
| 1  | Background and            | <a href="#">#6a</a>  | Description of research question and justification for   | 3     |
| 2  | rationale                 |                      | undertaking the trial, including summary of relevant     |       |
| 3  |                           |                      | studies (published and unpublished) examining            |       |
| 4  |                           |                      | benefits and harms for each intervention                 |       |
| 5  |                           |                      |  |       |
| 6  |                           |                      |  |       |
| 7  |                           |                      |  |       |
| 8  | Background and            | <a href="#">#6b</a>  | Explanation for choice of comparators                    | 5     |
| 9  | rationale: choice of      |                      |  |       |
| 10 | comparators               |                      |  |       |
| 11 |                           |                      |  |       |
| 12 |                           |                      |  |       |
| 13 | Objectives                | <a href="#">#7</a>   | Specific objectives or hypotheses                        | 4     |
| 14 |                           |                      |  |       |
| 15 | Trial design              | <a href="#">#8</a>   | Description of trial design including type of trial (eg, | 4     |
| 16 |                           |                      | parallel group, crossover, factorial, single group),     |       |
| 17 |                           |                      | allocation ratio, and framework (eg, superiority,        |       |
| 18 |                           |                      | equivalence, non-inferiority, exploratory)               |       |
| 19 |                           |                      |  |       |
| 20 |                           |                      |  |       |
| 21 |                           |                      |  |       |
| 22 | <b>Methods:</b>           |                      |  |       |
| 23 | <b>Participants,</b>      |                      |  |       |
| 24 | <b>interventions, and</b> |                      |  |       |
| 25 | <b>outcomes</b>           |                      |  |       |
| 26 |                           |                      |  |       |
| 27 |                           |                      |  |       |
| 28 |                           |                      |  |       |
| 29 | Study setting             | <a href="#">#9</a>   | Description of study settings (eg, community clinic,     | 4     |
| 30 |                           |                      | academic hospital) and list of countries where data      |       |
| 31 |                           |                      | will be collected. Reference to where list of study      |       |
| 32 |                           |                      | sites can be obtained                                    |       |
| 33 |                           |                      |  |       |
| 34 |                           |                      |  |       |
| 35 |                           |                      |  |       |
| 36 | Eligibility criteria      | <a href="#">#10</a>  | Inclusion and exclusion criteria for participants. If    | 4 - 5 |
| 37 |                           |                      | applicable, eligibility criteria for study centres and   |       |
| 38 |                           |                      | individuals who will perform the interventions (eg,      |       |
| 39 |                           |                      | surgeons, psychotherapists)                              |       |
| 40 |                           |                      |  |       |
| 41 |                           |                      |  |       |
| 42 |                           |                      |  |       |
| 43 | Interventions:            | <a href="#">#11a</a> | Interventions for each group with sufficient detail to   | 5     |
| 44 | description               |                      | allow replication, including how and when they will      |       |
| 45 |                           |                      | be administered  |       |
| 46 |                           |                      |  |       |
| 47 |                           |                      |  |       |
| 48 | Interventions:            | <a href="#">#11b</a> | Criteria for discontinuing or modifying allocated        | NA    |
| 49 | modifications             |                      | interventions for a given trial participant (eg, drug    |       |
| 50 |                           |                      | dose change in response to harms, participant            |       |
| 51 |                           |                      | request, or improving / worsening disease)               |       |
| 52 |                           |                      |  |       |
| 53 |                           |                      |  |       |
| 54 |                           |                      |  |       |
| 55 | Interventions:            | <a href="#">#11c</a> | Strategies to improve adherence to intervention          | 5     |
| 56 | adherence                 |                      | protocols, and any procedures for monitoring             |       |
| 57 |                           |                      | adherence (eg, drug tablet return; laboratory tests)     |       |
| 58 |                           |                      |  |       |
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|----|---------------------------|----------------------|--|----|
| 1  | Interventions:            | <a href="#">#11d</a> | Relevant concomitant care and interventions that         | NA |
| 2  | concomitant care          |                      | are permitted or prohibited during the trial             |    |
| 3  |                           |                      |  |    |
| 4  | Outcomes                  | <a href="#">#12</a>  | Primary, secondary, and other outcomes, including        | 6  |
| 5  |                           |                      | the specific measurement variable (eg, systolic          |    |
| 6  |                           |                      | blood pressure), analysis metric (eg, change from        |    |
| 7  |                           |                      | baseline, final value, time to event), method of         |    |
| 8  |                           |                      | aggregation (eg, median, proportion), and time point     |    |
| 9  |                           |                      | for each outcome. Explanation of the clinical            |    |
| 10 |                           |                      | relevance of chosen efficacy and harm outcomes is        |    |
| 11 |                           |                      | strongly recommended                                     |    |
| 12 |                           |                      |  |    |
| 13 | Participant timeline      | <a href="#">#13</a>  | Time schedule of enrolment, interventions (including     | 7  |
| 14 |                           |                      | any run-ins and washouts), assessments, and visits       |    |
| 15 |                           |                      | for participants. A schematic diagram is highly          |    |
| 16 |                           |                      | recommended (see Figure)                                 |    |
| 17 |                           |                      |  |    |
| 18 | Sample size               | <a href="#">#14</a>  | Estimated number of participants needed to achieve       | 8  |
| 19 |                           |                      | study objectives and how it was determined,              |    |
| 20 |                           |                      | including clinical and statistical assumptions           |    |
| 21 |                           |                      | supporting any sample size calculations                  |    |
| 22 |                           |                      |  |    |
| 23 |                           |                      |  |    |
| 24 | Recruitment               | <a href="#">#15</a>  | Strategies for achieving adequate participant            | 8  |
| 25 |                           |                      | enrolment to reach target sample size                    |    |
| 26 |                           |                      |  |    |
| 27 |                           |                      |  |    |
| 28 |                           |                      |  |    |
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| 30 |                           |                      |  |    |
| 31 | <b>Methods:</b>           |                      |  |    |
| 32 | <b>Assignment of</b>      |                      |  |    |
| 33 | <b>interventions (for</b> |                      |  |    |
| 34 | <b>controlled trials)</b> |                      |  |    |
| 35 |                           |                      |  |    |
| 36 | Allocation: sequence      | <a href="#">#16a</a> | Method of generating the allocation sequence (eg,        | 4  |
| 37 | generation                |                      | computer-generated random numbers), and list of          |    |
| 38 |                           |                      | any factors for stratification. To reduce predictability |    |
| 39 |                           |                      | of a random sequence, details of any planned             |    |
| 40 |                           |                      | restriction (eg, blocking) should be provided in a       |    |
| 41 |                           |                      | separate document that is unavailable to those who       |    |
| 42 |                           |                      | enrol participants or assign interventions               |    |
| 43 |                           |                      |  |    |
| 44 |                           |                      |  |    |
| 45 | Allocation                | <a href="#">#16b</a> | Mechanism of implementing the allocation sequence        | NA |
| 46 | concealment               |                      | (eg, central telephone; sequentially numbered,           |    |
| 47 | mechanism                 |                      | opaque, sealed envelopes), describing any steps to       |    |
| 48 |                           |                      | conceal the sequence until interventions are             |    |
| 49 |                           |                      |  |    |
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assigned

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|----|------------------------|----------------------|---|
| 1  |                        |                      |   |
| 2  |                        |                      |   |
| 3  | Allocation:            | <a href="#">#16c</a> | Who will generate the allocation sequence, who will       |
| 4  | implementation         |                      | enrol participants, and who will assign participants to   |
| 5  |                        |                      | interventions   |
| 6  |                        |                      |   |
| 7  |                        |                      |   |
| 8  | Blinding (masking)     | <a href="#">#17a</a> | Who will be blinded after assignment to interventions     |
| 9  |                        |                      | (eg, trial participants, care providers, outcome          |
| 10 |                        |                      | assessors, data analysts), and how                        |
| 11 |                        |                      |   |
| 12 |                        |                      |   |
| 13 | Blinding (masking):    | <a href="#">#17b</a> | If blinded, circumstances under which unblinding is       |
| 14 | emergency              |                      | permissible, and procedure for revealing a                |
| 15 | unblinding             |                      | participant's allocated intervention during the trial     |
| 16 |                        |                      |   |
| 17 |                        |                      |   |
| 18 | <b>Methods: Data</b>   |                      |   |
| 19 | <b>collection,</b>     |                      |   |
| 20 | <b>management, and</b> |                      |   |
| 21 | <b>analysis</b>        |                      |   |
| 22 |                        |                      |   |
| 23 |                        |                      |   |
| 24 |                        |                      |   |
| 25 | Data collection plan   | <a href="#">#18a</a> | Plans for assessment and collection of outcome,           |
| 26 |                        |                      | baseline, and other trial data, including any related     |
| 27 |                        |                      | processes to promote data quality (eg, duplicate          |
| 28 |                        |                      | measurements, training of assessors) and a                |
| 29 |                        |                      | description of study instruments (eg, questionnaires,     |
| 30 |                        |                      | laboratory tests) along with their reliability and        |
| 31 |                        |                      | validity, if known. Reference to where data collection    |
| 32 |                        |                      | forms can be found, if not in the protocol                |
| 33 |                        |                      |   |
| 34 |                        |                      |   |
| 35 |                        |                      |   |
| 36 |                        |                      |   |
| 37 |                        |                      |   |
| 38 | Data collection plan:  | <a href="#">#18b</a> | Plans to promote participant retention and complete       |
| 39 | retention              |                      | follow-up, including list of any outcome data to be       |
| 40 |                        |                      | collected for participants who discontinue or deviate     |
| 41 |                        |                      | from intervention protocols                               |
| 42 |                        |                      |   |
| 43 |                        |                      |   |
| 44 |                        |                      |   |
| 45 | Data management        | <a href="#">#19</a>  | Plans for data entry, coding, security, and storage,      |
| 46 |                        |                      | including any related processes to promote data           |
| 47 |                        |                      | quality (eg, double data entry; range checks for data     |
| 48 |                        |                      | values). Reference to where details of data               |
| 49 |                        |                      | management procedures can be found, if not in the         |
| 50 |                        |                      | protocol  |
| 51 |                        |                      |   |
| 52 |                        |                      |   |
| 53 |                        |                      |   |
| 54 |                        |                      |   |
| 55 | Statistics: outcomes   | <a href="#">#20a</a> | Statistical methods for analysing primary and             |
| 56 |                        |                      | secondary outcomes. Reference to where other              |
| 57 |                        |                      | details of the statistical analysis plan can be found, if |
| 58 |                        |                      |   |
| 59 |                        |                      |   |
| 60 |                        |                      |   |

not in the protocol

|    |                        |  |       |
|----|------------------------|--|-------|
| 1  |                        |  |       |
| 2  |                        |  |       |
| 3  | Statistics: additional | <a href="#">#20b</a>                                     | 8 - 9 |
| 4  | analyses               | Methods for any additional analyses (eg, subgroup        |       |
| 5  |                        | and adjusted analyses)                                   |       |
| 6  | Statistics: analysis   | <a href="#">#20c</a>                                     | 8 - 9 |
| 7  | population and         | Definition of analysis population relating to protocol   |       |
| 8  | missing data           | non-adherence (eg, as randomised analysis), and          |       |
| 9  |                        | any statistical methods to handle missing data (eg,      |       |
| 10 |                        | multiple imputation)                                     |       |
| 11 |                        |  |       |
| 12 |                        |  |       |
| 13 | <b>Methods:</b>        |  |       |
| 14 | <b>Monitoring</b>      |  |       |
| 15 |                        |  |       |
| 16 |                        |  |       |
| 17 | Data monitoring:       | <a href="#">#21a</a>                                     | 11    |
| 18 | formal committee       | Composition of data monitoring committee (DMC);          |       |
| 19 |                        | summary of its role and reporting structure;             |       |
| 20 |                        | statement of whether it is independent from the          |       |
| 21 |                        | sponsor and competing interests; and reference to        |       |
| 22 |                        | where further details about its charter can be found,    |       |
| 23 |                        | if not in the protocol. Alternatively, an explanation of |       |
| 24 |                        | why a DMC is not needed                                  |       |
| 25 |                        |  |       |
| 26 |                        |  |       |
| 27 |                        |  |       |
| 28 | Data monitoring:       | <a href="#">#21b</a>                                     | NA    |
| 29 | interim analysis       | Description of any interim analyses and stopping         |       |
| 30 |                        | guidelines, including who will have access to these      |       |
| 31 |                        | interim results and make the final decision to           |       |
| 32 |                        | terminate the trial                                      |       |
| 33 |                        |  |       |
| 34 |                        |  |       |
| 35 | Harms                  | <a href="#">#22</a>                                      | NA    |
| 36 |                        | Plans for collecting, assessing, reporting, and          |       |
| 37 |                        | managing solicited and spontaneously reported            |       |
| 38 |                        | adverse events and other unintended effects of trial     |       |
| 39 |                        | interventions or trial conduct                           |       |
| 40 |                        |  |       |
| 41 |                        |  |       |
| 42 | Auditing               | <a href="#">#23</a>                                      | NA    |
| 43 |                        | Frequency and procedures for auditing trial conduct,     |       |
| 44 |                        | if any, and whether the process will be independent      |       |
| 45 |                        | from investigators and the sponsor                       |       |
| 46 |                        |  |       |
| 47 | <b>Ethics and</b>      |  |       |
| 48 | <b>dissemination</b>   |  |       |
| 49 |                        |  |       |
| 50 |                        |  |       |
| 51 | Research ethics        | <a href="#">#24</a>                                      | 11    |
| 52 | approval               | Plans for seeking research ethics committee /            |       |
| 53 |                        | institutional review board (REC / IRB) approval          |       |
| 54 |                        |  |       |
| 55 | Protocol               | <a href="#">#25</a>                                      | 4, 11 |
| 56 | amendments             | Plans for communicating important protocol               |       |
| 57 |                        | modifications (eg, changes to eligibility criteria,      |       |
| 58 |                        | outcomes, analyses) to relevant parties (eg,             |       |
| 59 |                        |  |       |
| 60 |                        |  |       |



investigators, REC / IRBs, trial participants, trial registries, journals, regulators)

|    |   |                      |   |
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| 1  |   |                      |   |
| 2  |   |                      |   |
| 3  |   |                      |   |
| 4  | Consent or assent                           | <a href="#">#26a</a> | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)  |
| 5  |   |                      | 8   |
| 6  |   |                      |   |
| 7  |   |                      |   |
| 8  |   |                      |   |
| 9  | Consent or assent: ancillary studies        | <a href="#">#26b</a> | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable   |
| 10 |   |                      | NA  |
| 11 |   |                      |   |
| 12 |   |                      |   |
| 13 |   |                      |   |
| 14 | Confidentiality                             | <a href="#">#27</a>  | 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  |
| 15 |   |                      | 8, 11   |
| 16 |   |                      |   |
| 17 |   |                      |   |
| 18 |   |                      |   |
| 19 |   |                      |   |
| 20 |   |                      |   |
| 21 | Declaration of interests                    | <a href="#">#28</a>  | Financial and other competing interests for principal investigators for the overall trial and each study site   |
| 22 |   |                      | 12  |
| 23 |   |                      |   |
| 24 |   |                      |   |
| 25 | Data access                                 | <a href="#">#29</a>  | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators   |
| 26 |   |                      | 11  |
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| 29 |   |                      |   |
| 30 | Ancillary and post trial care               | <a href="#">#30</a>  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation   |
| 31 |   |                      | NA  |
| 32 |   |                      |   |
| 33 |   |                      |   |
| 34 |   |                      |   |
| 35 |   |                      |   |
| 36 | Dissemination policy: trial results         | <a href="#">#31a</a> | 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 |
| 37 |   |                      | 11  |
| 38 |   |                      |   |
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| 46 | Dissemination policy: authorship            | <a href="#">#31b</a> | Authorship eligibility guidelines and any intended use of professional writers  |
| 47 |   |                      | NA  |
| 48 |   |                      |   |
| 49 | Dissemination policy: reproducible research | <a href="#">#31c</a> | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code   |
| 50 |   |                      | 11  |
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| 52 |   |                      |   |
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## Appendices

|    |                            |                     |   |
|----|----------------------------|---------------------|---|
| 54 |                            |                     |   |
| 55 |                            |                     |   |
| 56 |                            |                     |   |
| 57 | Informed consent materials | <a href="#">#32</a> | Model consent form and other related documentation given to participants and authorised |
| 58 |                            |                     | Supplementary file 2  |
| 59 |                            |                     |   |

surrogates

1  
2  
3 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and  
4 storage of biological specimens for genetic or  
5 molecular analysis in the current trial and for future  
6 use in ancillary studies, if applicable  
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NA

For peer review only

# Informatie voor deelname aan medisch-wetenschappelijk onderzoek

## Verbeteren van de zorg voor mensen met een chronische darmontsteking

*Officiële titel: Waardegedreven zorg voor inflammatoire darmziekten: het verbeteren van (kosten-)effectiviteit*

### Inleiding

Geachte heer/mevrouw,

U ontvangt deze brief omdat u een chronische darmontsteking (ziekte van Crohn of colitis ulcerosa) heeft en gaat starten met een behandeling met krachtige ontstekingsremmers (biological) of deze al gebruikt. Wij vragen u om mee te doen aan een medisch-wetenschappelijk onderzoek. Dit onderzoek gaat over de verbetering van de zorg voor mensen met een chronische darmontsteking. Meedoen is vrijwillig. Om mee te doen, hebben wij wel uw schriftelijke toestemming nodig.

Voordat u beslist of u wilt meedoen aan dit onderzoek, krijgt u uitleg over wat het onderzoek inhoudt. Lees deze informatie rustig door en vraag de onderzoeker om uitleg als u vragen heeft. U kunt ook de onafhankelijk deskundige, die aan het eind van deze brief genoemd wordt, om aanvullende informatie vragen. U kunt er ook over praten met uw partner, vrienden of familie.

### 1. Achtergrond van het onderzoek

Mensen met een chronische darmontsteking kunnen veel klachten hebben en moeten soms dure ontstekingsremmende medicijnen gebruiken. Er wordt steeds meer onderzoek gedaan naar chronische darmontsteking. Ook komen er steeds meer medicijnen om chronische darmontsteking te behandelen. Door de nieuwe informatie en behandelingen wordt de zorg voor chronische darmontsteking ingewikkelder. Daarom werken MDL-artsen in het Zuidwesten van Nederland samen om de zorg te verbeteren. Er wordt een zorgpad ontwikkeld, zodat iedereen op een vergelijkbare manier wordt behandeld in de regio. Een zorgpad is een stappenplan, met daarin praktische adviezen over keuzes tijdens de behandeling van chronische darmontsteking.

### 2. Doel van het onderzoek

Het doel van het onderzoek is om de zorg te verbeteren voor mensen met een chronische darmontsteking die sterke ontstekingsremmers krijgen. Door gegevens te verzamelen over de uitkomsten van uw behandeling kunnen wij kijken wat er goed gaat, en wat er beter kan.

Daarnaast kijken wij ook naar de kosten van de behandeling, en de kosten die u zelf maakt. Wij hopen met dit onderzoek de kwaliteit van zorg te verbeteren en de kosten te reduceren.

### 3. Wat meedoen inhoudt

Meedoen houdt in dat u tot maart 2023 vragenlijsten invult over de zorg die u krijgt. U krijgt dezelfde behandeling als normaal. De ziekenhuizen zijn ingedeeld in twee groepen, een groep ziekenhuizen die volgens het nieuwe zorgpad werkt en een groep ziekenhuizen die dit niet doet. Door deze twee groepen te vergelijken kunnen we kijken of het zorgpad ook echt beter is dan de huidige situatie.

Door de COVID-19 pandemie kan het gebeuren dat de start van deze studie moet worden uitgesteld. Als de start wordt uitgesteld begint u later met het invullen van vragenlijsten. In dat geval loopt de studie langer door en vragen wij u ook om door te gaan met het invullen van de vragenlijsten. Mocht dit het geval zijn, dan laten wij u dat weten.

#### Anders dan bij gebruikelijke zorg

Als u meedoet met het onderzoek wordt u niet anders behandeld dan normaal. Eerst willen wij de zorg die u nu krijgt evalueren. Daarom vragen wij u om vragenlijsten in te vullen. In december 2021 zal het zorgpad geïntroduceerd worden. Dit is voor alle patiënten, dus ook als u niet meedoet aan het onderzoek. Dit kan bijvoorbeeld betekenen dat de MDL-artsen afspreken dat u vaker, of minder vaak op de polikliniek moet komen. Wij willen dan kijken of deze verandering beter is.

#### Vragenlijsten

Voor dit onderzoek willen wij u vragen om enkele vragenlijsten in te vullen.

- Aan het begin van het onderzoek, en elk jaar krijgt u een vragenlijst opgestuurd via de e-mail om te kijken naar uw persoonlijke omstandigheden, de aanwezigheid van andere ziekten en uw leefstijl. Het invullen kost u ongeveer 5 minuten.
- U krijgt elke drie maanden een vragenlijst toegestuurd via de e-mail. Deze vragen gaan over hoe de ziekte uw werk beïnvloedt, en de (zorg)kosten die u maakt door uw ziekte. Het invullen kost u ongeveer 5 minuten.
- Daarnaast krijgt u elke 6 maanden een vragenlijst toegestuurd via de mail om de invloed van de ziekte op uw leven en uw kwaliteit van leven te meten. Het invullen kost u ongeveer 10 minuten.

Daarnaast zullen wij ook aan uw behandelend specialist gegevens vragen over de uitkomsten van uw behandeling. Dit gaat bijvoorbeeld over het verloop van uw ziekte, en welke medicijnen u gebruikt.

### 4. Afspraken

Om het onderzoek goed te laten verlopen, is het belangrijk dat u de vragenlijsten invult volgens de uitleg.

Het is belangrijk dat u contact opneemt met de onderzoeker:

- als u niet meer wilt meedoen aan het onderzoek.
- als uw contactgegevens wijzigen.

## 5. Mogelijke voor- en nadelen

Het is belangrijk dat u de mogelijke voor- en nadelen goed afweegt voordat u besluit mee te doen. Als u meedoet aan dit onderzoek betekent het niet dat u minder last krijgt van uw ziekte. Maar u draagt wel bij aan meer kennis over de behandeling van chronische darmziekten, en aan de verbetering hiervan. Een nadeel van het meedoen aan het onderzoek kan zijn dat het invullen van de vragenlijsten u tijd kost.

## 6. Als u niet wilt meedoen of wilt stoppen met het onderzoek

U beslist zelf of u meedoet aan het onderzoek. Deelname is vrijwillig. Als u niet wilt meedoen, wordt u op de gebruikelijke manier behandeld voor uw chronische darmziekte. Dit is niet anders dan als u wel mee zou doen met het onderzoek.

Als u wel meedoet, kunt u zich altijd bedenken en toch stoppen, ook tijdens het onderzoek. U wordt dan op dezelfde manier behandeld voor uw chronische darmziekte. U hoeft niet te zeggen waarom u stopt. Wel moet u dit direct melden aan de onderzoeker. De gegevens die tot dat moment zijn verzameld, worden gebruikt voor het onderzoek.

Als er nieuwe informatie over het onderzoek is die belangrijk voor u is, laat de onderzoeker dit aan u weten. U wordt dan gevraagd of u blijft meedoen.

## 7. Algemene informatie

Dit onderzoek is opgezet door het Franciscus Gasthuis & Vlietland en wordt gedaan door artsen in verschillende ziekenhuizen in de regio Rotterdam. Voor dit onderzoek worden alle patiënten benaderd die in de regio Rotterdam behandeld worden met een sterke ontstekingsremmer voor een chronische darmontsteking.

De studie is aangemeld bij de medisch-ethische toetsingscommissie (METC) Erasmus MC die heeft bepaald dat deze studie niet valt onder de wet medische wetenschappelijk onderzoek met mensen. Dat betekent dat deze studie niet door de METC goedgekeurd hoeft te worden.

## 8. Einde van het onderzoek

Uw deelname aan het onderzoek stopt als

- alle vragenlijsten ingevuld zijn
- u zelf kiest om te stoppen
- de onderzoeker het beter voor u vindt om te stoppen
- het Franciscus Gasthuis & Vlietland of de overheid besluit om het onderzoek te stoppen.

1  
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5 Het hele onderzoek is afgelopen als alle deelnemers klaar zijn. Na het verwerken van alle  
6 gegevens informeert de onderzoeker u over de belangrijkste uitkomsten van het onderzoek.  
7 Dit gebeurt ongeveer 6 maanden na uw deelname. Als u dit niet wilt, dan kunt u dit tegen de  
8 onderzoeker zeggen. Hij mag het u dan niet vertellen.  
9

## 10 11 12 **9. Gebruik en bewaren van uw gegevens**

13 Voor dit onderzoek worden uw persoonsgegevens verzameld, gebruikt en bewaard. Het gaat  
14 om gegevens zoals uw naam, geboortjaar en om gegevens over uw gezondheid. Het  
15 verzamelen, gebruiken en bewaren van uw gegevens is nodig om de vragen die in dit  
16 onderzoek worden gesteld te kunnen beantwoorden en de resultaten te kunnen publiceren.  
17 Wij vragen voor het gebruik van uw gegevens uw toestemming.  
18  
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### 20 21 **Vertrouwelijkheid van uw gegevens**

22 Om uw privacy te beschermen krijgen uw gegevens een code. Uw naam en andere  
23 gegevens die u direct kunnen identificeren worden daarbij weggelaten. Alleen met de sleutel  
24 van de code zijn gegevens tot u te herleiden. De sleutel van de code blijft veilig opgeborgen  
25 in de lokale onderzoeksinstelling. De gegevens die naar de opdrachtgever worden gestuurd,  
26 bevatten alleen de code en uw e-mailadres om de vragenlijsten te versturen, maar niet uw  
27 naam of andere gegevens waarmee u kunt worden geïdentificeerd. Ook in rapporten en  
28 publicaties over het onderzoek zijn de gegevens niet tot u te herleiden.  
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### 32 33 **Toegang tot uw gegevens voor controle**

34 Sommige personen kunnen op de onderzoekslocatie toegang krijgen tot al uw gegevens.  
35 Ook tot de gegevens zonder code. Dit is nodig om te kunnen controleren of het onderzoek  
36 goed en betrouwbaar is uitgevoerd. Personen die ter controle inzage krijgen in uw gegevens  
37 zijn: onderzoekers en studenten die hen hierbij assisteren, een monitor die voor de  
38 opdrachtgever van het onderzoek werkt, en nationale en internationale toezichthoudende  
39 autoriteiten, bijvoorbeeld, de Inspectie Gezondheidszorg en Jeugd. Zij houden uw gegevens  
40 geheim. Wij vragen u voor deze inzage toestemming te geven.  
41  
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### 45 46 **Bewaren en gebruik van gegevens**

47 Uw gegevens moeten 15 jaar worden bewaard op de onderzoekslocatie en 15 jaar bij de  
48 opdrachtgever. Uw gegevens kunnen na afloop van dit onderzoek ook nog van belang zijn  
49 voor ander wetenschappelijk onderzoek op het gebied van chronische darmontsteking. U  
50 kunt op het toestemmingsformulier aangeven of u hier wel of niet mee instemt. Indien u hier  
51 niet mee instemt, kunt u gewoon deelnemen aan het huidige onderzoek. Uw bewaarde  
52 gegevens zullen dan niet gebruikt worden voor ander wetenschappelijk onderzoek.  
53  
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### 56 57 **Intrekken toestemming**

58 U kunt uw toestemming voor gebruik van uw persoonsgegevens altijd weer intrekken. Dit  
59 geldt voor dit onderzoek en ook voor het bewaren en het gebruik voor het toekomstige  
60

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4 onderzoek. De onderzoeksgegevens die zijn verzameld tot het moment dat u uw  
5 toestemming intrekt, worden nog wel gebruikt in het onderzoek.  
6  
7

### 8 **Meer informatie over uw rechten bij verwerking van gegevens**

9 Voor algemene informatie over uw rechten bij verwerking van uw persoonsgegevens kunt u  
10 de website van de Autoriteit Persoonsgegevens raadplegen. Bij vragen over uw rechten kunt  
11 u contact opnemen met de verantwoordelijke voor de verwerking van uw persoonsgegevens.  
12 Voor dit onderzoek is dat: het Franciscus Gasthuis & Vlietland. Zie bijlage A voor  
13 contactgegevens en website.  
14  
15  
16

17 Bij vragen of klachten over de verwerking van uw persoonsgegevens raden we u aan eerst  
18 contact op te nemen met de onderzoekslocatie. U kunt ook contact opnemen met de  
19 Functionaris voor de Gegevensbescherming van de instelling (zie bijlage A) of de Autoriteit  
20 Persoonsgegevens.  
21  
22

### 23 **Registratie van het onderzoek**

24 Informatie over dit onderzoek is ook opgenomen in een overzicht van medisch-  
25 wetenschappelijke onderzoeken namelijk (<https://www.trialregister.nl/trial/8276>). Daarin zijn  
26 geen gegevens opgenomen die naar u herleidbaar zijn. Na het onderzoek kan de website  
27 een samenvatting van de resultaten van dit onderzoek tonen.  
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## 32 **10. Geen vergoeding voor meedoen**

33 Het meedoen aan het onderzoek kost u niets. U wordt niet betaald voor het meedoen aan dit  
34 onderzoek.  
35  
36  
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## 38 **11. Heeft u vragen?**

39 Bij vragen kunt u contact opnemen met de onderzoeker. Voor onafhankelijk advies over  
40 meedoen aan dit onderzoek kunt u terecht bij de onafhankelijke arts. Hij weet veel over het  
41 onderzoek, maar heeft niets te maken met dit onderzoek.  
42  
43  
44

45 Indien u klachten heeft over het onderzoek, kunt u dit bespreken met de onderzoeker of uw  
46 behandelend arts. Wilt u dit liever niet, dan kunt u zich wenden tot de klachtenfunctionaris of  
47 klachtencommissie van het Franciscus Gasthuis & Vlietland. Alle gegevens vindt u in bijlage  
48 A: Contactgegevens.  
49  
50  
51

## 52 **12. Ondertekening toestemmingsformulier**

53 Indien u besluit mee te doen met dit onderzoek, vragen wij u dit op de bijbehorende  
54 toestemmingsverklaring schriftelijk te bevestigen. Door uw schriftelijke toestemming geeft u  
55 aan dat u de informatie heeft begrepen en instemt met deelname aan het onderzoek. Zowel  
56 uzelf als de onderzoeker ontvangen een getekende versie van deze toestemmingsverklaring.  
57  
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Dank voor uw aandacht.

### 13. Bijlagen bij deze informatie

- A. Contactgegevens
- B. Toestemmingsformulier(en)

For peer review only



## Bijlage A: contactgegevens voor Franciscus Gasthuis & Vlietland

Als u nog vragen heeft over dit onderzoek, neem dan contact op met de onderzoeksarts of zijn of haar onderzoeksmedewerkers:

- de hoofdonderzoekers: dr. D. Leemreis-van Noord en dr. R.L. West, 010-4616161
- de coördinerend onderzoeker: drs. R.C.A. van Linschoten, 010-4617838
- de onafhankelijk arts: Dr. G.J. Braunstahl, 010-4616161
- Buiten kantooruren kunt u met het algemene nummer van het ziekenhuis bellen:
  - Franciscus Gasthuis: 010-461 61 61
  - Franciscus Vlietland: 010-893 93 93

en vragen naar de dienstdoend arts van de Maag-, Darm-, en Leverziekten.

### Cliëntvertrouwenspersoon:

Deze studie wordt uitgevoerd met toestemming van de Raad van Bestuur van dit ziekenhuis. Het *Franciscus Gasthuis & Vlietland* vindt het belangrijk dat patiënten, proefpersonen en bezoekers tevreden zijn. Toch kan het gebeuren dat u niet tevreden bent en een klacht wilt indienen. In dat geval kunt u het beste eerst praten met de onderzoeksarts of uw behandelend arts. Als u dat liever niet doet, kunt u ook contact opnemen met de cliëntvertrouwenspersoon van het ziekenhuis. Dit kan zowel telefonisch als door het invullen van het online klachtenformulier.

Contact met de cliëntvertrouwenspersoon voor compliment, suggestie of klacht:

### **Franciscus Gasthuis en Franciscus Berkel**

Telefoonnummer: 010 – 461 6701

### **Franciscus Vlietland, Franciscus Haven, Franciscus Hoogvliet en Franciscus Maassluis**

Telefoonnummer: 010 – 893 4125

Digitaal via [www.franciscus.nl/klacht](http://www.franciscus.nl/klacht) (voor alle locaties)

### **Functionaris Gegevensbescherming (alle locaties):**

Mw. L. Pollinger

E-mail: [fg@franciscus.nl](mailto:fg@franciscus.nl)

Telefoonnummer: 010-4616898

## Bijlage B: toestemmingsformulier deelnemer

### Waardegedreven zorg voor inflammatoire darmziekten: IBD Value

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn voldoende beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen of te stoppen met het onderzoek. Daarvoor hoef ik geen reden te geven.
- Ik geef toestemming om, in het geval ik tijdens de looptijd van het onderzoek zou komen te overlijden, mijn officiële doodsoorzaakgegevens op te vragen bij het Centraal Bureau voor de Statistiek.
- Ik geef toestemming voor het opvragen van informatie bij mijn specialist(en) die mij behandelt over de uitkomsten van de behandeling van mijn chronische darmontsteking.
- Ik geef toestemming voor het verzamelen en gebruiken van mijn gegevens voor de beantwoording van de onderzoeksvraag in dit onderzoek.
- Ik weet dat voor de controle van het onderzoek sommige mensen toegang tot al mijn gegevens kunnen krijgen. Die mensen staan vermeld in deze informatiebrief. Ik geef toestemming voor die inzage door deze personen.
- Ik geef toestemming om mijn e-mailadres aan het onderzoeksteam door te geven, zodat de vragenlijsten naar mij verstuurd kunnen worden.
- Ik geef  **wel**  **geen**  
toestemming om mijn persoonsgegevens langer te bewaren en te gebruiken voor toekomstig onderzoek op het gebied van chronische darmontsteking.
- Ik geef  **wel**  **geen**  
toestemming om mij na dit onderzoek opnieuw te benaderen voor een vervolgonderzoek.
- Ik wil  **wel**  **niet**  
geïnformeerd worden over de uitkomsten van dit onderzoek.
- Ik wil meedoen aan dit onderzoek.

Naam deelnemer:

E-mailadres:

Handtekening:

Datum : \_\_ / \_\_ / \_\_

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*De deelnemer krijgt een volledige informatiebrief mee.*

# BMJ Open

## A value-based care pathway for inflammatory bowel disease: protocol for the multicentre longitudinal non-randomised parallel cluster IBD Value study with baseline period

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1 A value-based care pathway for inflammatory bowel disease: protocol for the  
2 multicentre longitudinal non-randomised parallel cluster IBD Value study with baseline  
3 period

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34  
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37

## 38 **ABSTRACT**

39 Introduction: Biologics are effective for the treatment of inflammatory bowel disease (IBD). However,  
40 unwarranted variation in processes and outcomes has been reported in the treatment of IBD. A care  
41 pathway for the treatment of IBD has the potential to reduce practice variation and improve  
42 outcomes. This study aims to compare the effect of a uniform care pathway for the treatment of IBD  
43 patients with biologics to the current situation.

44 Methods and analysis: IBD Value is a longitudinal multicentre non-randomised parallel cluster trial  
45 with a baseline period. The study takes place in eight centres in the Netherlands. The baseline period  
46 will run for 12 months, after which the care pathway will be implemented in six of the eight  
47 participating hospitals during the implementation phase of 3 months. Hereafter the effect of the care  
48 pathway will be assessed for 12 months. Total study period is 27 months. The primary outcome is the  
49 effect of the care pathway on disease control (IBD-Control questionnaire). Secondary outcomes are  
50 the effect of the care pathway on the other outcomes of the International Consortium of Health  
51 Outcomes Measurement IBD standard set, health-related generic quality of life, patient experiences,  
52 and degree of variation; cost-effectiveness of the care pathway; and the variation between hospitals  
53 in the aforementioned outcomes in the baseline period. Outcomes will be measured every six  
54 months. The study started on December 1<sup>st</sup> 2020 and a minimum of 200 patients will be included.

55 Ethics and dissemination: The study was deemed not to be subject to Dutch law (WMO; Medical  
56 Research Involving Human Subjects Act) by the Medical Ethics Committee Erasmus MC, the  
57 Netherlands (registration number MEC-2020-075) and a waiver was provided. Results will be  
58 disseminated through peer-reviewed journals and presented at (inter)national conferences.

59 Registration details: This study was registered in the Netherlands Trial Register (NL8276) on 09-01-  
60 2020.

## 62 **STRENGTH AND LIMITATIONS OF THIS STUDY**

- 63 • This prospective study aims to elucidate the important problem of treatment variation in  
64 IBD.
- 65 • It is to our knowledge the first prospective multicentre study assessing the effect of a care  
66 pathway for the treatment of IBD on health outcomes.
- 67 • The Dutch Crohn's and colitis patient organisation was involved in the study design and will  
68 participate in the development of the care pathway.
- 69 • This is the first large multicentre study to implement the International Consortium of Health  
70 Outcomes Measurement (ICHOM) standard set for IBD.
- 71 • The study is a non-randomised trial.

## 74 INTRODUCTION

75 Crohn's disease and ulcerative colitis, subtypes of inflammatory bowel disease (IBD), are chronic  
76 inflammatory diseases of the gastrointestinal tract.[1, 2] Signs and symptoms of IBD are abdominal  
77 pain, diarrhoea, and rectal bleeding. IBD can also affect extraintestinal organs, such as the liver, skin,  
78 eyes, and joints.[3-5] Further, IBD can have a major impact on quality of life because of fatigue and  
79 its psychological impact.[6, 7] To control these symptoms, patients are often dependent on  
80 medication and are sometimes hospitalized or need surgery when drugs fail. The high disease burden  
81 leads to reduced quality of life, high healthcare costs (between €15,000 and €30,000 per patient per  
82 year) and reduced work productivity.[7, 8] Biologics and new small molecules (i.e. tofacitinib) are  
83 proven efficacious treatments for IBD and have shown to induce and maintain remission, avert  
84 hospitalisation and surgery, and reduce productivity loss in randomised controlled trials.[9-12]

85  
86 Considerable variation exists between healthcare providers in the treatment of IBD with  
87 biologics.[13-18] Treatment variation consists among other things of differences in provided care and  
88 follow-up such as type of medication prescribed, dosing frequency, and interpretation of therapeutic  
89 drug monitoring. Treatment variation can lead to differences in outcomes, such as the proportion of  
90 patients in remission, side effects, and treatment costs.[19] While variation can be a natural  
91 consequence of differences between patient populations, part of the variation in processes and  
92 outcomes was explained by experience and expertise of healthcare providers, with better process  
93 adherence and outcomes for dedicated IBD or academic physicians.[17, 19]

94  
95 Treatment variation might also lead to reduced effectiveness of biologics in daily practice.  
96 Observational population-based studies showed no association between the use of biologics and  
97 long-term disease progression, nor on hospitalisation or surgery, contradicting the findings of  
98 randomised controlled trials.[20-22] Taking into account the differences in patient populations and  
99 study designs, these observational studies hypothesize that variation in treatment, mainly under- and  
100 misuse of biologics, may partly explain the gap between the efficaciousness of biologics in  
101 randomised trials and their effectiveness in the real world. Reduction of this variation might thus be  
102 a potential avenue for improving outcomes of IBD patients treated with a biologic.

103  
104 Value-based healthcare (VBHC) is an approach that aims, among other things, at improving technical  
105 value (health outcomes achieved divided by resources spent) for the patient by tackling unwarranted  
106 variation and optimising the care delivery process.[23, 24] Important parts of VBHC are  
107 systematically measuring both patient-reported outcomes and the costs of achieving these  
108 outcomes.[25, 26] These data can consequently be used to evaluate and adjust the care delivery  
109 process and improve (cost-)effectiveness of achieving optimal patient-centred outcomes.

110  
111 Implementing a care pathway in clinical practice seems promising for improving value, which was  
112 illustrated by a retrospective pilot study that evaluated a care pathway for IBD in a VBHC program.  
113 This care pathway showed a favourable effect on flares (-26%) and costs (-16%).[27] Other studies  
114 supported the effect of a care pathway for IBD on costs and also showed an improvement of care  
115 processes.[28, 29]. In inguinal hernia repair, chronic heart failure and total hip replacement the  
116 implementation of a care pathway was also accompanied by reduced variation in processes and  
117 outcomes.[30] Although these studies showed a promising effect on outcomes and processes, they  
118 suffered from low sample sizes, retrospective study designs and lacked patient-centred outcome  
119 measures. With the prospective multicentre IBD Value study we aim to assess the impact of a care  
120 pathway for the treatment of IBD with biologics and new small molecules on patient-centred  
121 outcomes.

## METHODS AND ANALYSIS

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines were followed and the checklist is included with the protocol (online supplementary file 1).[31] The most recent study protocol version 2.0.0 (July 2020) is presented in this manuscript. Changes to the protocol will be submitted to the Medical Ethics Committee Erasmus MC (Rotterdam, the Netherlands). Changes will also be noted in the trial register and communicated to local investigators. The start date of the study was 1 December 2020.

### Study Aim

The main objective of the study is to evaluate the added value of a uniform care pathway on the health outcomes of IBD patients treated with a biologic or new small molecule in one of the participating hospitals. Secondary objectives are to:

- Assess the degree of regional variation in outcomes and costs of the treatment of IBD with biologics and new small molecules;
- Uncover areas of improvement in the care of IBD patients;
- Develop and implement a regional care pathway for the treatment of IBD with biologics and new small molecules based on scientific evidence, current guidelines, and adapted to the local context;
- Evaluate the cost-effectiveness of the care pathway;
- Evaluate the effect of the care pathway on variation in outcomes and costs.

### Study Design

This is a longitudinal multicentre non-randomised parallel cluster trial with a baseline period (Figure 1). This design was chosen because the care pathway is an intervention on hospital level making a patient level study infeasible. A randomised cluster trial was logistically not possible as the care pathway will be developed by the six intervention hospitals and they can therefore not be blinded to the intervention. A randomised stepped wedge cluster trial would run into problems with contamination of the control period as the care pathway would need to be developed before the first clusters moved to the intervention group. This would lead to providers from the control cluster not being blinded to the intervention as they would be in the working group.

In the first 12 months of the study, before the introduction of the new care pathway, the current situation in IBD care for patients on biologics or new small molecules will be assessed in all participating hospitals to establish baseline measures. These data will primarily be used as comparison with the 2<sup>nd</sup> study period after implementation of the care pathway. The data will also be used to determine areas of improvement, as benchmarking, and aid the design of the care pathway. Subsequently the care pathway will be implemented in six of the participating hospitals during a three-month implementation period.

The participating hospitals are: Franciscus Gasthuis & Vlietland, Rotterdam & Schiedam; Erasmus MC, Rotterdam; Albert Schweitzer Hospital, Dordrecht, Zwijndrecht & Sliedrecht; Maasstad Hospital, Rotterdam; Ikazia Hospital, Rotterdam; IJsselland Hospital, Capelle aan den IJssel; Reinier de Graaf Gasthuis, Delft; Amphia Hospital, Breda. These are hospitals that have collaborated in IBD BeterKeten in the southwest of the Netherlands since 2016 to improve quality of care of IBD patients in the region.[32] The care pathway will not be implemented in Reinier de Graaf Gasthuis and Amphia Hospital; these hospitals will participate as the control group. The content of the care pathway will only be revealed to and implemented in the six hospitals in the intervention group at the start of the implementation period. The development of the care pathway will be completed by the working group in the last period of the baseline measurement phase. After implementation, outcomes will be evaluated during the 12-month follow-up period in all participating hospitals.

## 175 **Population**

176 The study population comprises all IBD patients being treated with a biologic agent or new small  
177 molecule in the eight participating hospitals. The care pathway also covers patients treated with new  
178 small molecules, as these belong to the same group as patients treated with a biologic: complex  
179 disease and a high cost of treatment. Approximately 3,200 patients are treated with the  
180 aforementioned medication in these hospitals in total.

181  
182 All participants will meet the following criteria:

- 183 • 18 years of age or older
- 184 • Have given informed consent for data collection
- 185 • Being treated for IBD in one of the participating hospitals
- 186 • Have an IBD diagnosis of at least three months
- 187 • Treated with one of the currently registered biologics or new small molecules for IBD  
188 treatment or new treatments registered during the study period, including: infliximab,  
189 adalimumab, golimumab, vedolizumab, ustekinumab, or tofacitinib.

190  
191 A potential subject may be excluded from study participation if they have insufficient knowledge of  
192 the Dutch language to complete the questionnaires and/or have no access to the internet to  
193 complete the questionnaires.

## 194 **Intervention**

### 195 **Design**

196 The intervention is a uniform care pathway for the treatment of IBD patients with biologic agents. It  
197 contains uniform guidelines for prescribing, the work-up, and switching of biologic therapy and new  
198 small molecules, and for the frequency and type of follow-up. As IBD is a heterogeneous disease, the  
199 care pathway will not be able to cover all possible treatment decisions, but aims to guarantee the  
200 same level of care for IBD patients in all participating hospitals, while taking into account patient  
201 preference and uncertainty in the evidence concerning IBD treatment.

202  
203 To prevent contamination of the control period, the development of the care pathway will be  
204 finalised shortly before implementation. The care pathway will be developed by an IBD BeterKeten  
205 working group of gastroenterologists and IBD nurses with multidisciplinary input of a surgeon and a  
206 dietician. Moreover, the Dutch IBD patient federation (Crohn & Colitis NL) will participate in the  
207 design of the care pathway. The care pathway will be based on national and international guidelines  
208 and will be designed according to the following steps.[33-35]

209  
210  
211 First, the main topics of what the care pathway should cover will be drafted by the project manager.  
212 These topics will then be discussed until consensus is reached by the working group. Hereafter the  
213 project manager will draft care pathways for each topic (see below) on the basis of (inter)national  
214 guidelines. These drafts will then be discussed in the working group until consensus is reached on  
215 exact content and timing of the care pathway. Literature searches will be performed to inform the  
216 working group in cases of uncertainty around best practices. When the evidence around treatment  
217 decisions is uncertain or scarce, this will be clearly reflected in the care pathway.

218  
219 Outcomes from the baseline measurement collected during the first project phase will be used to  
220 adjust and improve the care pathway. These will be analysed according to their pre-specified  
221 definitions (see Outcomes below) and stratified per institute to assess areas of improvement in IBD  
222 care. Results of these analyses and consequences for improvement will be discussed in a working  
223 group meeting and implemented in the care pathway. The final draft of the care pathway will be  
224 presented for approval of the IBD specialists of all participating intervention centres.

225  
226 **Content**



1  
2  
3 227 The care pathway will address the following issues.

- 4 228 1. Actions that do not depend on current treatment but apply to all patients: examples are  
5 229 periodical colorectal cancer and micronutrient screening.  
6 230 2. Evaluation of a possible flare: when a patient presents with symptoms or when abnormal  
7 231 test results are found, differential diagnoses have to be excluded. Moreover, disease activity  
8 232 has to be measured using objective markers.  
9 233 3. Therapy sequence in case of a flare: it will indicate advice on the next treatment step for a  
10 234 patient with a flare based on their disease and treatment history. This could be either  
11 235 treatment intensification or switching.  
12 236 4. Frequency, type and timing of follow-up for the induction and remission phases of the  
13 237 different therapies: examples are the timing of outpatient clinic visits, laboratory  
14 238 assessments and additional examinations.  
15 239

16 239  
17 240 The care pathway is a decision-making tool for care providers and patients, and presents treatment  
18 241 guidelines in a simple and interpretable format. It sets out the most appropriate steps in patient  
19 242 management at each therapy stage. Decision trees will be designed to give visual support to the care  
20 243 pathway. Because the treatment of IBD is rapidly changing and studies regularly provide new  
21 244 insights, the care pathway will be updated in IBD BeterKeten meetings after study closure.  
22 245

#### 23 245 24 246 Implementation & Adherence

25 247 IBD specialists from IBD BeterKeten will safeguard implementation of the care pathway in their  
26 248 respective centres. They will be supported by a presentation of the working group to the care  
27 249 providers. To facilitate working according to the care pathway, we will implement the care pathway  
28 250 in electronic health records. Care providers will be able to schedule follow-up or diagnostics  
29 251 according to the care pathway with a single action. We will assess adherence to the care pathway by  
30 252 randomly sampling patients and comparing treatment decisions made for these patients with the  
31 253 treatment algorithms set out in the care pathway.  
32 254

#### 33 254 34 255 Comparison

35 256 The care pathway will be compared to current care by ways of the baseline measurement and  
36 257 adjustment for changes in the control group. All care providers continue their current practice  
37 258 according to their knowledge and local guidelines and treatment plans for the duration of the  
38 259 baseline measurement. The data collected in this period will give more insight into the current  
39 260 variation in practice, and can also be used to inform the design of the care pathway.  
40 261

#### 41 261 42 262 Outcome

43 263 To measure outcomes that matter to the patient, the standard set of patient-centred outcomes for  
44 264 IBD as defined by the International Consortium of Health Outcomes Measurement (ICHOM) will be  
45 265 used as the outcome measure of this study. ICHOM is an organization that creates standard sets to  
46 266 measure the outcomes that matter most to patients.[25] Patient-reported disease control as  
47 267 measured by the IBD-Control-8 score was chosen to serve as the primary outcome measure. This is a  
48 268 questionnaire that validly and reliably measures disease control from the patient perspective on a  
49 269 16-point scale, and can distinguish between active disease and remission.[36, 37]  
50 270

51 270  
52 271 The other outcomes from the standard set are secondary outcomes:

- 53 272 • IBD-attributable mortality;  
54 273 • Remission, both clinician-reported (biochemical, radiological, endoscopic, histologic) and  
55 274 patient-reported (Manitoba IBD Index; MIBDI);[38]  
56 275 • Incidence of colorectal cancer;  
57 276 • Presence of anaemia;  
58 277 • Number of A&E visits;  
59 278 • Number and cumulative length of hospital admissions;

- 1  
2  
3 279 • Number of complications of any intervention for IBD;  
4 280 • Long-term (>3 months) steroid use;  
5 281 • Presence of fistulae symptoms;  
6 282 • BMI as a proxy for nutritional status;  
7 283

8 284 The MIBDI is a valid and patient-reported outcome measure which can be used to classify disease  
9 285 activity on a dichotomous scale. The other outcomes from the standard set will be retrieved from the  
10 286 electronic health record. Other secondary outcomes are generic quality of life measured with the  
11 287 validated PROMIS-10 Global Health (PROMIS-10) questionnaire, cost-effectiveness and patient  
12 288 experience of care, using the Dutch Picker questionnaire.[39, 40]  
13 289

14 290 The cost-utility analysis (CUA) will be performed alongside the clinical study. In line with the  
15 291 recommendations of the National Health Care Institute and the broad societal impact of IBD the CUA  
16 292 will take a societal perspective.[41, 42] Utility will be measured with the EQ-5D-5L (Dutch tariffs).[43]  
17 293 The IBD-Control-8 score, which is more responsive to health state changes in IBD, will be used for an  
18 294 alternative cost-effectiveness analysis.[36] Societal costs will be measured according to the  
19 295 guidelines of the National Health Care Institute.[42-44]. Three types of societal costs are  
20 296 distinguished: healthcare costs; patient costs; and other non-healthcare costs. For healthcare costs,  
21 297 primary care costs (primary care, home care, other out of hospital care) are distinguished from in-  
22 298 hospital costs (e.g. number of admissions, MRIs, and blood tests). Use of primary care will be  
23 299 measured using the shortened version of the Medical Consumption Questionnaire (iMCQ) of the  
24 300 Institute of Medical Technology Assessment (iMTA).[45] For healthcare use in secondary care, data  
25 301 will be collected from the electronic healthcare records. Productivity losses will be determined with  
26 302 the iMTA Productivity Cost Questionnaire (iPCQ). Measured productivity losses will be extrapolated  
27 303 from one to three months. Absenteeism, presenteeism, and lost unpaid work will be determined.  
28 304 Patient costs will be measured using a questionnaire on the following: travel costs; type, weeks and  
29 305 hours of informal care; insurance deductible; over the counter drug use; other IBD related costs. For  
30 306 all outcomes and their respective source, see Table 1.  
31 307

| Outcome                          | Source                                      |
|----------------------------------|---|
| <u>Primary</u>                   |   |
| Patient-reported disease control | Patient-reported (IBD-Control)[36, 37]      |
|                                  |   |
| <u>Secondary</u>                 |   |
| IBD-attributable mortality       | Chart review                                |
| Clinical remission               | Chart review                                |
| Endoscopic/radiologic remission  | Chart review                                |
| Colorectal cancer                | Chart review                                |
| Complications of IBD treatment   | Chart review                                |
| Biochemical remission            | Medical record                              |
| Anaemia                          | Medical record                              |
| A&E visits                       | Medical record                              |
| Hospital admissions              | Medical record                              |
| Long-term steroid use            | Medical record                              |
| Hospital costs                   | Medical record & Dutch reference prices[46] |
| Fistulae symptoms                | Patient-reported                            |
| BMI                              | Patient-reported                            |
| Patient-reported remission       | Patient-reported (MIBDI)[38]                |
| Generic quality of life          | Patient-reported (PROMIS-10)[39]            |
| Patient experience               | Patient-reported (Picker)[40]               |
| Utility                          | Patient-reported (EQ-5D-5L)[43, 44]         |

|                    |  |
|--------------------|--|
| Primary care costs | Patient-reported (iMCQ)[45] & Dutch reference prices[46] |
| Productivity costs | Patient-reported (iPCQ)[47] & Dutch reference prices[46] |
| Patient costs      | Patient-reported   |

Table 1: Outcomes and their respective source. IBD: Inflammatory bowel disease; MIBDI: Manitoba IBD Index; PROMIS-10: PROMIS-10 Global Health questionnaire; iMTA: Institute of Medical Technology Assessment; IPCQ: iMTA Productivity Cost Questionnaire; iMCQ: iMTA Medical Consumption Questionnaire

**Case mix**

To control for case mix differences between hospitals, we will collect the case mix variables defined in the ICHOM sets for risk adjustment for IBD care.[25] Data will be collected on the following variables:

- Year of birth
- Sex at birth
- Education level as defined by UNESCO[48]
- Smoking status
- Diagnosis (Crohn’s disease, ulcerative colitis, indeterminate colitis)
- Year of diagnosis
- Disease phenotype according to the Montreal classification[49]
- Presence of extra-intestinal manifestations
- Medication use for IBD
- IBD related surgery
- Comorbidities as defined by the self-administered comorbidity questionnaire (SCQ) with inclusion of some extra questions as defined by ICHOM [50]
- Current or prior infection with tuberculosis, hepatitis B or human immunodeficiency virus
- Concomitant presence of primary sclerosing cholangitis
- Treating hospital

**Timing**

Patients can be included between ethical approval and the end of the study. Outcomes will be measured at the following time points as defined by ICHOM (see also Tables 2 and 3). The IBD-Control, MIBDI, EQ-5D-5L and the PROMIS-10 will be administered when a participant is included in the study and at six monthly intervals from the start of the study. Cost questionnaires will be sent to patients at three monthly intervals from the start of the study. Demographics and comorbidity questionnaires will be sent at inclusion, at the start of the intervention period (t=15) and at the end of the study (t=27). Patient experience questionnaires will be distributed once a year after an outpatient clinic visit. To reduce questionnaire burden, some questionnaires at inclusion will not be sent if a patient is included two months (quality of life) or three months (case mix) before the respective questionnaires would be sent again.

Table 2: Timing of questionnaires for patient included at or before T=0

|                  | Demographics | IBD-Control | MIBDI | SCQ | EQ-5D-5L/<br>PROMIS-10 | iPCQ | iMCQ | Patient costs |
|------------------|--------------|-------------|-------|-----|------------------------|------|------|---------------|
| 0m (study start) | X            | X           | X     | X   | X                      |      |      |               |
| 3m               |              |             |       |     |                        | X    | X    | X             |
| 6m               |              | X           | X     |     | X                      | X    | X    | X             |
| 9m               |              |             |       |     |                        | X    | X    | X             |
| 12m              |              | X           | X     |     | X                      | X    | X    | X             |
| 15m              | X            |             |       | X   |                        | X    | X    | X             |
| 18m              |              |             |       |     |                        | X    | X    | X             |
| 21m              |              | X           | X     |     | X                      | X    | X    | X             |
| 24m              |              |             |       |     |                        | X    | X    | X             |
| 27m              | X            | X           | X     | X   | X                      | X    | X    | X             |

IBD: Inflammatory bowel disease; MIBDI: Manitoba IBD Index; SCQ: self-administered comorbidity questionnaire; PROMIS-10: PROMIS-10 Global Health questionnaire; iMTA: Institute of Medical Technology Assessment; iPCQ: iMTA Productivity Cost Questionnaire; iMCQ: iMTA Medical Consumption Questionnaire

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Table 3: Timing of questionnaires for a patient included at T=10m

|                  | Demographics | IBD-Control | MIBDI | SCQ | EQ-5D-5L/<br>PROMIS-10 | iPCQ | iMCQ | Patient costs |
|------------------|--------------|-------------|-------|-----|------------------------|------|------|---------------|
| 0m (study start) |              |             |       |     |                        |      |      |               |
| 3m               |              |             |       |     |                        |      |      |               |
| 6m               |              |             |       |     |                        |      |      |               |
| 9m               |              |             |       |     |                        |      |      |               |
| 10m (inclusion)  | X            |             |       |     |                        |      |      |               |
| 12m              |              | X           | X     |     | X                      | X    | X    | X             |
| 15m              | X            |             |       | X   |                        | X    | X    | X             |
| 18m              |              |             |       |     |                        | X    | X    | X             |
| 21m              |              | X           | X     |     | X                      | X    | X    | X             |
| 24m              |              |             |       |     |                        | X    | X    | X             |
| 27m              | X            | X           | X     | X   | X                      | X    | X    | X             |

IBD: Inflammatory bowel disease; MIBDI: Manitoba IBD Index; SCQ: self-administered comorbidity questionnaire; PROMIS-10: PROMIS-10 Global Health questionnaire; iMTA: Institute of Medical Technology Assessment; iPCQ: iMTA Productivity Cost Questionnaire; iMCQ: iMTA Medical Consumption Questionnaire

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Other outcomes will be retrieved from the electronic health records retrospectively, biannually and annually as recommended by ICHOM. A subset of the data (e.g. age, gender, hospital healthcare use, anaemia, mortality, medication use) can be retrieved from the electronic health records anonymously. This data will be retrieved for the entire source population, as informed consent is not necessary for the use of anonymized data according to Dutch law. This can be used to study possible selection bias.

### Statistical considerations

#### Power

As our data are clustered longitudinally and per hospital, analytic sample size calculation is not appropriate. Thus, we used simulations to estimate power for different cluster sizes. The calculations were based on the following assumptions:

- a baseline IBD-Control score of 8 with a standard deviation (SD) of 4;[51, 52]
- because of the clustering of data at two levels (within patients over time and patients clustered within hospitals), the degree of clustering has to be accounted for. As this is not reported in the literature, we estimated random effects for patients and hospitals with standard deviations between 0 and 4 (corresponding to intraclass correlation coefficients between 0 and 0.25);
- a change in IBD-Control score of 1 as clinically meaningful. Research has shown minimal important differences of 0.5 SD for health-related quality of life instruments. However, as amelioration of a single symptom changes the score of the IBD Control by 0.25 SD, we powered our study on this effect size.[53]

The sample size calculation is further based on:

- simulating data based on the assumptions listed above;
- 8 hospitals of between 1 and 50 patients each, in steps of 5;
- 10,000 iterations per cluster size;
- dropout of 10%;
- type-1 error rate ( $\alpha$ ) of 0.05 two-sided;
- power of at least 80%;
- fitting a linear mixed effect model with random intercepts for patient and hospital and a fixed effect for intervention.

376  
 377 Power was defined as the number of iterations that found a statistically significant effect as a  
 378 proportion of the total number of iterations. To account for our clustered data, 25 patients per  
 379 hospital (a total of 200 patients) before the six month mark of the study would be required to have  
 380 sufficient power (>80%) to identify a change of 1 point of the IBD-Control score. We are striving to  
 381 include all eligible patients to achieve a representative sample of the source population and to  
 382 prevent selection bias.

383  
 384 Business Intelligence (BI) departments in each of the participating hospitals will support patient  
 385 screening and help reduce the logistic burden. The BI departments will use an algorithm to identify  
 386 patients who meet the study inclusion criteria. These patients will receive a letter or e-mail from  
 387 their hospital, asking for their consent to participate in the study. The algorithm will also identify the  
 388 patient's care provider and next hospital visit. The care providers will be provided with this  
 389 information to approach the patient for inclusion during the outpatient clinic visit. Patient  
 390 recruitment should not be a time consuming process as the burden on the patient is low, the study is  
 391 easy to explain and no randomisation or experimental treatment is used. Because all patients will  
 392 receive an invitation letter to participate and care providers will remind them during their hospitals  
 393 visit, we think that the minimum inclusion goal of 25 patients per hospital is feasible. Currently, 1001  
 394 patients have been included.

#### 395 Data analysis plan

396 All missing data will be assessed whether these data are likely to be missing (completely) at random.  
 397 If so, Multivariate Imputation by Chained Equations (MICE) will be used to impute missing data for  
 398 variables used for adjustment. The primary outcome, IBD-Control-8 score, will be analysed on patient  
 399 level using a linear mixed effects model of the form:

$$400 \quad Y_{ijt} = \beta_0 + \eta_j + \theta_{ij} + \beta_1 \iota + \beta_t v_t + \beta_c v_c + \varepsilon_{ijt}$$

401  
 402  
 403  
 404 Where  $Y$  is the IBD-Control-8 score (0-16) of person  $i$  in cluster  $j$  at time  $t$  (0-6 months, 6-12 months,  
 405 15-21 months, 21-27 months);  $\beta_0$  the intercept;  $\eta_j$  the cluster level random effect for cluster  $j$ ;  $\theta_{ij}$  the  
 406 patient level random effect for patient  $i$  in cluster  $j$ ;  $\beta_1$  the estimated difference between standard  
 407 care ( $\iota = 0$ ) and the care pathway ( $\iota = 1$ );  $\beta_t$  a vector with coefficients for calendar time at the  
 408 different time points  $t$ , captured as the vector  $v_t$  with dummy variables for the different periods of  
 409 follow-up;  $\beta_c$  a vector containing the coefficients for the case mix variables in the vector  $v_c$ ; and  $\varepsilon_{ijt}$  is  
 410 the residual error.

411  
 412 To adjust for case mix we will use the variables from the ICHOM IBD set. These are: age in years  
 413 (continuous), sex at birth (dichotomous), education level (categorical: low, middle, high), smoking  
 414 status (categorical: never, ex-smoker, current), comorbidities (self-administered comorbidity  
 415 questionnaire, continuous), current or prior infection with tuberculosis (dichotomous), hepatitis B  
 416 (dichotomous), and/or HIV (dichotomous), diagnosis (categorical: Crohn's disease, ulcerative colitis,  
 417 unknown/indeterminate), disease duration in years (continuous), phenotype according to the  
 418 Montreal classification (for Crohn's disease: age of onset, localisation, behaviour and for ulcerative  
 419 colitis and IBD-U: extension, all categorical), presence of extra-intestinal manifestations (categorical:  
 420 none, skin, joint, hepatobiliary, eye, other), and concomitant presence of primary sclerosing  
 421 cholangitis (categorical). The secondary outcomes from the ICHOM Standard Set will be analysed on  
 422 patient level with a (generalized) linear mixed model of the same form as described above.

#### 423 Cost-effectiveness

424  
 425 As the standard of care and the new care pathway will be analysed for a one-year period, this is also  
 426 the time horizon for the CUA. No discounting of costs and effects will be applied to the one-year

1  
2  
3 427 period. Costs will be determined by multiplying measured healthcare use and productivity loss with  
4 428 reference prices or cost estimates in line with recommendations of the National Health Care  
5 429 Institute.[46, 54] All costs will be transformed to the same year, adjusted for inflation using the  
6 430 consumer price index (CPI) if necessary. The friction cost method will be used to estimate  
7 431 productivity costs. A sensitivity analysis using the human capital approach will also be performed.  
8 432

9 433 To assess the cost-effectiveness of the care pathway compared to usual care, crude and adjusted  
10 434 differences in costs and quality of life in the before and after groups from the regression models will  
11 435 be used to estimate the incremental cost-effectiveness ratio (ICER). Robustness of results will be  
12 436 evaluated using probabilistic sensitivity analysis (PSA) using Monte Carlo simulation. For the PSA,  
13 437 non-parametric bootstrapping with 2,000 iterations will be used to determine uncertainty around the  
14 438 ICER. To support decision making, calculation of the net monetary/health benefits at the relevant  
15 439 willingness to pay levels, acceptability curves and Value of Information Analysis will be added.  
16 440

#### 17 441 Variation

18 442 To assess the variation in outcomes and costs between hospitals the intraclass correlation coefficient  
19 443 (ICC) will be used. The ICC is defined as:  
20 444

$$21 \quad ICC (Cluster) = \frac{\sigma_{\eta}^2}{\sigma_{\eta}^2 + \sigma_{\theta}^2 + \sigma_{\varepsilon}^2}$$

22 445  
23 446  
24 447 which can be interpreted as the variance explained by the hospital as a proportion of the total  
25 448 variance. For the baseline period, data will be analysed using the aforementioned mixed effects  
26 449 models omitting the coefficient for the care pathway.  
27 450

28 451 To assess the effect of the care pathway on variation, data from the six hospitals that implemented  
29 452 the care pathway will be analysed for the two periods using the aforementioned mixed effects  
30 453 model, without the coefficient for the care pathway. This model will be compared with a model that  
31 454 estimates a random effect per hospital for the baseline period and the care pathway period  
32 455 separately. The effect of the care pathway on variation will then be formally tested using a  
33 456 likelihood-ratio test comparing the two models.  
34 457

#### 35 458 Patient and public involvement

36 459 Crohn & Colitis NL (Dutch Crohn's and Colitis Patient Organisation) collaborated in the design of this  
37 460 study. They critically revised the study design and helped in piloting the questionnaires. They will be  
38 461 involved in the working group that is responsible for the development of the care pathway.  
39 462  
40 463

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2  
3 464 **ETHICS AND DISSEMINATION**

4 465 The study was deemed to not be subject to the Wet medisch-wetenschappelijk onderzoek met  
5 466 mensen (WMO; Medical Research Involving Human Subjects Act) by the Medical Ethics Committee  
6 467 Erasmus MC, the Netherlands (registration number MEC-2020-075). The study is not subject to the  
7 468 Medical Research Involving Human Subjects Act as the implementation of the care pathway is a  
8 469 change in the local standard of care, patients aren't randomised to different treatment groups, and  
9 470 patients do not undergo invasive procedures for the study. Informed consent for questionnaires and  
10 471 chart review will be obtained by local investigators (online supplementary file 2). Data of all  
11 472 participating centres will be collected using electronic CRFs and entered in Castor EDC, an electronic  
12 473 database that is ISO27001 certified.[55] Data will be coded and handled based on the General Data  
13 474 Protection Regulation (GDPR). A data monitoring committee is not necessary as the intervention  
14 475 under study is a change in the standard of care.  
15  
16 476

17  
18 477 The principal investigators and study coordinator will have access to the final dataset. The dataset  
19 478 will be available on reasonable request. The study team is responsible for data analysis and  
20 479 reporting. Results will be fed back to participating centres and disseminated through peer-reviewed  
21 480 journals and presented at (inter)national conferences. The study team will make the decision to  
22 481 publish, and the funder and sponsor had and will have no influence on the research question, study  
23 482 design, data collection or analysis, or decision to publish.  
24 483

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2  
3 484 **ACKNOWLEDGEMENTS:**

4 485 Conny Nuis and Daniëlle van der Horst for their assistance in design the care pathway.  
5 486

6 487 **COMPETING INTERESTS STATEMENT**

7 488 Drs. van Linschoten has nothing to disclose.

8 489 Dr. van Leeuwen has nothing to disclose.

9 490 Drs. Nieboer has nothing to disclose.

10 491 Dr. Birnie has nothing to disclose

11 492 Drs. Scherpenzeel, MPM has nothing to disclose

12 493 Dr. de Jonge has nothing to disclose

13 494 Drs. Verweij has nothing to disclose

14 495 Prof. Dr. Hazelzet has nothing to disclose.

15 496 Prof. Dr. van der Woude reports grants from Pfizer and Janssen and personal fees from AbbVie and  
16 497 Celltrion outside the submitted work.

17 498 Dr. van Noord reports personal fees from Janssen and Takeda outside the submitted work.

18 499 Dr. West reports personal fees from AbbVie, Janssen and Pfizer outside the submitted work.  
19 500

20 501 **LEGEND**

21 502 Figure 1: Study Timeline  
22 503

23 504 **AUTHORSHIP STATEMENT**

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32 513 the trial design. MS, CJvdW and JAH critically reviewed the study design. CJvdW, RLW, KEV, VdJ and  
33 514 RCAvL participated in the design of the intervention. RCAvL drafted the manuscript and all authors  
34 515 read, critically revised and approved the final manuscript. Principal investigators are DvN and RLW.  
35 516 RCAvL ensures daily study management as study coordinator. DvN and RLW share last authorship.  
36 517

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43 524 **KEYWORDS**

44 525 Clinical trial; gastroenterology; inflammatory bowel disease; health economics; value-based  
45 526 healthcare; health services research; care pathway;  
46 527

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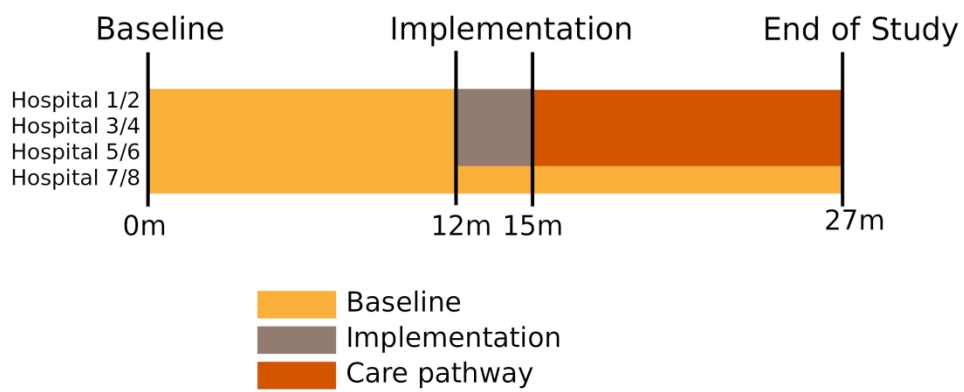


Figure 1: Study Timeline

50x21mm (1200 x 1200 DPI)

|    | Reporting Item  | Page Number  |         |
|----|---|--|---------|
| 1  |   |  |         |
| 2  |   |  |         |
| 3  | <b>Administrative</b>                                   |  |         |
| 4  | <b>information</b>                                      |  |         |
| 5  |   |  |         |
| 6  |   |  |         |
| 7  | Title   | <a href="#">#1</a> Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym  | 1       |
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| 10 |   |  |         |
| 11 |   |  |         |
| 12 | Trial registration                                      | <a href="#">#2a</a> Trial identifier and registry name. If not yet registered, name of intended registry   | 2       |
| 13 |   |  |         |
| 14 |   |  |         |
| 15 |   |  |         |
| 16 | Trial registration: data set                            | <a href="#">#2b</a> All items from the World Health Organization Trial Registration Data Set   | 1 - 13  |
| 17 |   |  |         |
| 18 |   |  |         |
| 19 |   |  |         |
| 20 | Protocol version  | <a href="#">#3</a> Date and version identifier   | 4       |
| 21 |   |  |         |
| 22 | Funding   | <a href="#">#4</a> Sources and types of financial, material, and other support   | 13      |
| 23 |   |  |         |
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| 26 | Roles and responsibilities: contributorship             | <a href="#">#5a</a> Names, affiliations, and roles of protocol contributors  | 13      |
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| 31 | Roles and responsibilities: sponsor contact information | <a href="#">#5b</a> Name and contact information for the trial sponsor   | 13      |
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| 38 | Roles and responsibilities: sponsor and funder          | <a href="#">#5c</a> 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 | 12      |
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| 48 | Roles and responsibilities: committees                  | <a href="#">#5d</a> 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)                         | 13 - 14 |
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| 58 | <b>Introduction</b>                                     |  |         |
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|    |                           |                      |  |       |
|----|---------------------------|----------------------|--|-------|
| 1  | Background and            | <a href="#">#6a</a>  | Description of research question and justification for   | 3     |
| 2  | rationale                 |                      | undertaking the trial, including summary of relevant     |       |
| 3  |                           |                      | studies (published and unpublished) examining            |       |
| 4  |                           |                      | benefits and harms for each intervention                 |       |
| 5  |                           |                      |  |       |
| 6  |                           |                      |  |       |
| 7  | Background and            | <a href="#">#6b</a>  | Explanation for choice of comparators                    | 6     |
| 8  | rationale: choice of      |                      |  |       |
| 9  | comparators               |                      |  |       |
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| 12 |                           |                      |  |       |
| 13 | Objectives                | <a href="#">#7</a>   | Specific objectives or hypotheses                        | 4     |
| 14 |                           |                      |  |       |
| 15 | Trial design              | <a href="#">#8</a>   | Description of trial design including type of trial (eg, | 4     |
| 16 |                           |                      | parallel group, crossover, factorial, single group),     |       |
| 17 |                           |                      | allocation ratio, and framework (eg, superiority,        |       |
| 18 |                           |                      | equivalence, non-inferiority, exploratory)               |       |
| 19 |                           |                      |  |       |
| 20 |                           |                      |  |       |
| 21 |                           |                      |  |       |
| 22 | <b>Methods:</b>           |                      |  |       |
| 23 | <b>Participants,</b>      |                      |  |       |
| 24 | <b>interventions, and</b> |                      |  |       |
| 25 | <b>outcomes</b>           |                      |  |       |
| 26 |                           |                      |  |       |
| 27 |                           |                      |  |       |
| 28 |                           |                      |  |       |
| 29 | Study setting             | <a href="#">#9</a>   | Description of study settings (eg, community clinic,     | 4     |
| 30 |                           |                      | academic hospital) and list of countries where data      |       |
| 31 |                           |                      | will be collected. Reference to where list of study      |       |
| 32 |                           |                      | sites can be obtained                                    |       |
| 33 |                           |                      |  |       |
| 34 |                           |                      |  |       |
| 35 |                           |                      |  |       |
| 36 | Eligibility criteria      | <a href="#">#10</a>  | Inclusion and exclusion criteria for participants. If    | 5     |
| 37 |                           |                      | applicable, eligibility criteria for study centres and   |       |
| 38 |                           |                      | individuals who will perform the interventions (eg,      |       |
| 39 |                           |                      | surgeons, psychotherapists)                              |       |
| 40 |                           |                      |  |       |
| 41 |                           |                      |  |       |
| 42 |                           |                      |  |       |
| 43 | Interventions:            | <a href="#">#11a</a> | Interventions for each group with sufficient detail to   | 5 - 6 |
| 44 | description               |                      | allow replication, including how and when they will      |       |
| 45 |                           |                      | be administered  |       |
| 46 |                           |                      |  |       |
| 47 |                           |                      |  |       |
| 48 | Interventions:            | <a href="#">#11b</a> | Criteria for discontinuing or modifying allocated        | NA    |
| 49 | modifications             |                      | interventions for a given trial participant (eg, drug    |       |
| 50 |                           |                      | dose change in response to harms, participant            |       |
| 51 |                           |                      | request, or improving / worsening disease)               |       |
| 52 |                           |                      |  |       |
| 53 |                           |                      |  |       |
| 54 |                           |                      |  |       |
| 55 | Interventions:            | <a href="#">#11c</a> | Strategies to improve adherence to intervention          | 6     |
| 56 | adherence                 |                      | protocols, and any procedures for monitoring             |       |
| 57 |                           |                      | adherence (eg, drug tablet return; laboratory tests)     |       |
| 58 |                           |                      |  |       |
| 59 |                           |                      |  |       |
| 60 |                           |                      |  |       |

|    |                           |                      |  |        |
|----|---------------------------|----------------------|--|--------|
| 1  | Interventions:            | <a href="#">#11d</a> | Relevant concomitant care and interventions that         | NA     |
| 2  | concomitant care          |                      | are permitted or prohibited during the trial             |        |
| 3  |                           |                      |  |        |
| 4  | Outcomes                  | <a href="#">#12</a>  | Primary, secondary, and other outcomes, including        | 6 - 8  |
| 5  |                           |                      | the specific measurement variable (eg, systolic          |        |
| 6  |                           |                      | blood pressure), analysis metric (eg, change from        |        |
| 7  |                           |                      | baseline, final value, time to event), method of         |        |
| 8  |                           |                      | aggregation (eg, median, proportion), and time point     |        |
| 9  |                           |                      | for each outcome. Explanation of the clinical            |        |
| 10 |                           |                      | relevance of chosen efficacy and harm outcomes is        |        |
| 11 |                           |                      | strongly recommended                                     |        |
| 12 |                           |                      |  |        |
| 13 | Participant timeline      | <a href="#">#13</a>  | Time schedule of enrolment, interventions (including     | 8 - 9  |
| 14 |                           |                      | any run-ins and washouts), assessments, and visits       |        |
| 15 |                           |                      | for participants. A schematic diagram is highly          |        |
| 16 |                           |                      | recommended (see Figure)                                 |        |
| 17 |                           |                      |  |        |
| 18 | Sample size               | <a href="#">#14</a>  | Estimated number of participants needed to achieve       | 9 - 10 |
| 19 |                           |                      | study objectives and how it was determined,              |        |
| 20 |                           |                      | including clinical and statistical assumptions           |        |
| 21 |                           |                      | supporting any sample size calculations                  |        |
| 22 |                           |                      |  |        |
| 23 |                           |                      |  |        |
| 24 | Recruitment               | <a href="#">#15</a>  | Strategies for achieving adequate participant            | 10     |
| 25 |                           |                      | enrolment to reach target sample size                    |        |
| 26 |                           |                      |  |        |
| 27 |                           |                      |  |        |
| 28 |                           |                      |  |        |
| 29 |                           |                      |  |        |
| 30 |                           |                      |  |        |
| 31 | <b>Methods:</b>           |                      |  |        |
| 32 | <b>Assignment of</b>      |                      |  |        |
| 33 | <b>interventions (for</b> |                      |  |        |
| 34 | <b>controlled trials)</b> |                      |  |        |
| 35 |                           |                      |  |        |
| 36 | Allocation: sequence      | <a href="#">#16a</a> | Method of generating the allocation sequence (eg,        | 4      |
| 37 | generation                |                      | computer-generated random numbers), and list of          |        |
| 38 |                           |                      | any factors for stratification. To reduce predictability |        |
| 39 |                           |                      | of a random sequence, details of any planned             |        |
| 40 |                           |                      | restriction (eg, blocking) should be provided in a       |        |
| 41 |                           |                      | separate document that is unavailable to those who       |        |
| 42 |                           |                      | enrol participants or assign interventions               |        |
| 43 |                           |                      |  |        |
| 44 |                           |                      |  |        |
| 45 | Allocation                | <a href="#">#16b</a> | Mechanism of implementing the allocation sequence        | NA     |
| 46 | concealment               |                      | (eg, central telephone; sequentially numbered,           |        |
| 47 | mechanism                 |                      | opaque, sealed envelopes), describing any steps to       |        |
| 48 |                           |                      | conceal the sequence until interventions are             |        |
| 49 |                           |                      |  |        |
| 50 |                           |                      |  |        |
| 51 |                           |                      |  |        |
| 52 |                           |                      |  |        |
| 53 |                           |                      |  |        |
| 54 |                           |                      |  |        |
| 55 |                           |                      |  |        |
| 56 |                           |                      |  |        |
| 57 |                           |                      |  |        |
| 58 |                           |                      |  |        |
| 59 |                           |                      |  |        |
| 60 |                           |                      |  |        |



assigned

|    |                        |                      |   |
|----|------------------------|----------------------|---|
| 1  |                        |                      |   |
| 2  |                        |                      |   |
| 3  | Allocation:            | <a href="#">#16c</a> | Who will generate the allocation sequence, who will       |
| 4  | implementation         |                      | enrol participants, and who will assign participants to   |
| 5  |                        |                      | interventions   |
| 6  |                        |                      |   |
| 7  |                        |                      |   |
| 8  | Blinding (masking)     | <a href="#">#17a</a> | Who will be blinded after assignment to interventions     |
| 9  |                        |                      | (eg, trial participants, care providers, outcome          |
| 10 |                        |                      | assessors, data analysts), and how                        |
| 11 |                        |                      |   |
| 12 |                        |                      |   |
| 13 | Blinding (masking):    | <a href="#">#17b</a> | If blinded, circumstances under which unblinding is       |
| 14 | emergency              |                      | permissible, and procedure for revealing a                |
| 15 | unblinding             |                      | participant's allocated intervention during the trial     |
| 16 |                        |                      |   |
| 17 |                        |                      |   |
| 18 | <b>Methods: Data</b>   |                      |   |
| 19 | <b>collection,</b>     |                      |   |
| 20 | <b>management, and</b> |                      |   |
| 21 | <b>analysis</b>        |                      |   |
| 22 |                        |                      |   |
| 23 |                        |                      |   |
| 24 |                        |                      |   |
| 25 | Data collection plan   | <a href="#">#18a</a> | Plans for assessment and collection of outcome,           |
| 26 |                        |                      | baseline, and other trial data, including any related     |
| 27 |                        |                      | processes to promote data quality (eg, duplicate          |
| 28 |                        |                      | measurements, training of assessors) and a                |
| 29 |                        |                      | description of study instruments (eg, questionnaires,     |
| 30 |                        |                      | laboratory tests) along with their reliability and        |
| 31 |                        |                      | validity, if known. Reference to where data collection    |
| 32 |                        |                      | forms can be found, if not in the protocol                |
| 33 |                        |                      |   |
| 34 |                        |                      |   |
| 35 |                        |                      |   |
| 36 |                        |                      |   |
| 37 |                        |                      |   |
| 38 | Data collection plan:  | <a href="#">#18b</a> | Plans to promote participant retention and complete       |
| 39 | retention              |                      | follow-up, including list of any outcome data to be       |
| 40 |                        |                      | collected for participants who discontinue or deviate     |
| 41 |                        |                      | from intervention protocols                               |
| 42 |                        |                      |   |
| 43 |                        |                      |   |
| 44 |                        |                      |   |
| 45 | Data management        | <a href="#">#19</a>  | Plans for data entry, coding, security, and storage,      |
| 46 |                        |                      | including any related processes to promote data           |
| 47 |                        |                      | quality (eg, double data entry; range checks for data     |
| 48 |                        |                      | values). Reference to where details of data               |
| 49 |                        |                      | management procedures can be found, if not in the         |
| 50 |                        |                      | protocol  |
| 51 |                        |                      |   |
| 52 |                        |                      |   |
| 53 |                        |                      |   |
| 54 |                        |                      |   |
| 55 | Statistics: outcomes   | <a href="#">#20a</a> | Statistical methods for analysing primary and             |
| 56 |                        |                      | secondary outcomes. Reference to where other              |
| 57 |                        |                      | details of the statistical analysis plan can be found, if |
| 58 |                        |                      |   |
| 59 |                        |                      |   |
| 60 |                        |                      |   |

not in the protocol

1  
2  
3 Statistics: additional [#20b](#) Methods for any additional analyses (eg, subgroup 10 - 11  
4 analyses and adjusted analyses)  
5

6 Statistics: analysis [#20c](#) Definition of analysis population relating to protocol 10 - 11  
7 population and non-adherence (eg, as randomised analysis), and  
8 missing data any statistical methods to handle missing data (eg,  
9 multiple imputation)  
10  
11

12  
13 **Methods:**  
14 **Monitoring**  
15

16  
17 Data monitoring: [#21a](#) Composition of data monitoring committee (DMC); 12  
18 formal committee summary of its role and reporting structure;  
19 statement of whether it is independent from the  
20 sponsor and competing interests; and reference to  
21 where further details about its charter can be found,  
22 if not in the protocol. Alternatively, an explanation of  
23 why a DMC is not needed  
24  
25  
26  
27

28 Data monitoring: [#21b](#) Description of any interim analyses and stopping NA  
29 interim analysis guidelines, including who will have access to these  
30 interim results and make the final decision to  
31 terminate the trial  
32  
33  
34

35 Harms [#22](#) Plans for collecting, assessing, reporting, and NA  
36 managing solicited and spontaneously reported  
37 adverse events and other unintended effects of trial  
38 interventions or trial conduct  
39  
40  
41

42 Auditing [#23](#) Frequency and procedures for auditing trial conduct, NA  
43 if any, and whether the process will be independent  
44 from investigators and the sponsor  
45  
46

47 **Ethics and**  
48 **dissemination**  
49

50  
51 Research ethics [#24](#) Plans for seeking research ethics committee / 12  
52 approval institutional review board (REC / IRB) approval  
53  
54

55 Protocol [#25](#) Plans for communicating important protocol 4, 12  
56 amendments modifications (eg, changes to eligibility criteria,  
57 outcomes, analyses) to relevant parties (eg,  
58  
59  
60

|    |                       |  |               |
|----|-----------------------|--|---------------|
| 1  |                       | investigators, REC / IRBs, trial participants, trial                       |               |
| 2  |                       | registries, journals, regulators)  |               |
| 3  |                       |  |               |
| 4  | Consent or assent     | <a href="#">#26a</a> Who will obtain informed consent or assent from       | 10            |
| 5  |                       | potential trial participants or authorised surrogates,                     |               |
| 6  |                       | and how (see Item 32)  |               |
| 7  |                       |  |               |
| 8  |                       |  |               |
| 9  | Consent or assent:    | <a href="#">#26b</a> Additional consent provisions for collection and use  | NA            |
| 10 | ancillary studies     | of participant data and biological specimens in                            |               |
| 11 |                       | ancillary studies, if applicable   |               |
| 12 |                       |  |               |
| 13 |                       |  |               |
| 14 | Confidentiality       | <a href="#">#27</a> How personal information about potential and           | 10, 12        |
| 15 |                       | enrolled participants will be collected, shared, and                       |               |
| 16 |                       | maintained in order to protect confidentiality before,                     |               |
| 17 |                       | during, and after the trial  |               |
| 18 |                       |  |               |
| 19 |                       |  |               |
| 20 |                       |  |               |
| 21 | Declaration of        | <a href="#">#28</a> Financial and other competing interests for principal  | 13            |
| 22 | interests             | investigators for the overall trial and each study site                    |               |
| 23 |                       |  |               |
| 24 |                       |  |               |
| 25 | Data access           | <a href="#">#29</a> Statement of who will have access to the final trial   | 12            |
| 26 |                       | dataset, and disclosure of contractual agreements                          |               |
| 27 |                       | that limit such access for investigators                                   |               |
| 28 |                       |  |               |
| 29 |                       |  |               |
| 30 | Ancillary and post    | <a href="#">#30</a> Provisions, if any, for ancillary and post-trial care, | NA            |
| 31 | trial care            | and for compensation to those who suffer harm from                         |               |
| 32 |                       | trial participation  |               |
| 33 |                       |  |               |
| 34 |                       |  |               |
| 35 |                       |  |               |
| 36 | Dissemination policy: | <a href="#">#31a</a> Plans for investigators and sponsor to communicate    | 12            |
| 37 | trial results         | trial results to participants, healthcare professionals,                   |               |
| 38 |                       | the public, and other relevant groups (eg, via                             |               |
| 39 |                       | publication, reporting in results databases, or other                      |               |
| 40 |                       | data sharing arrangements), including any                                  |               |
| 41 |                       | publication restrictions   |               |
| 42 |                       |  |               |
| 43 |                       |  |               |
| 44 |                       |  |               |
| 45 | Dissemination policy: | <a href="#">#31b</a> Authorship eligibility guidelines and any intended    | NA            |
| 46 | authorship            | use of professional writers  |               |
| 47 |                       |  |               |
| 48 |                       |  |               |
| 49 | Dissemination policy: | <a href="#">#31c</a> Plans, if any, for granting public access to the full | 12            |
| 50 | reproducible          | protocol, participant-level dataset, and statistical                       |               |
| 51 | research              | code   |               |
| 52 |                       |  |               |
| 53 |                       |  |               |
| 54 |                       |  |               |
| 55 | <b>Appendices</b>     |  |               |
| 56 |                       |  |               |
| 57 | Informed consent      | <a href="#">#32</a> Model consent form and other related                   | Supplementary |
| 58 | materials             | documentation given to participants and authorised                         | file 2        |
| 59 |                       |  |               |
| 60 |                       |  |               |

surrogates

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

NA

For peer review only

# Informatie voor deelname aan medisch-wetenschappelijk onderzoek

## Verbeteren van de zorg voor mensen met een chronische darmontsteking

*Officiële titel: Waardegedreven zorg voor inflammatoire darmziekten: het verbeteren van (kosten-)effectiviteit*

### Inleiding

Geachte heer/mevrouw,

U ontvangt deze brief omdat u een chronische darmontsteking (ziekte van Crohn of colitis ulcerosa) heeft en gaat starten met een behandeling met krachtige ontstekingsremmers (biological) of deze al gebruikt. Wij vragen u om mee te doen aan een medisch-wetenschappelijk onderzoek. Dit onderzoek gaat over de verbetering van de zorg voor mensen met een chronische darmontsteking. Meedoen is vrijwillig. Om mee te doen, hebben wij wel uw schriftelijke toestemming nodig.

Voordat u beslist of u wilt meedoen aan dit onderzoek, krijgt u uitleg over wat het onderzoek inhoudt. Lees deze informatie rustig door en vraag de onderzoeker om uitleg als u vragen heeft. U kunt ook de onafhankelijk deskundige, die aan het eind van deze brief genoemd wordt, om aanvullende informatie vragen. U kunt er ook over praten met uw partner, vrienden of familie.

### 1. Achtergrond van het onderzoek

Mensen met een chronische darmontsteking kunnen veel klachten hebben en moeten soms dure ontstekingsremmende medicijnen gebruiken. Er wordt steeds meer onderzoek gedaan naar chronische darmontsteking. Ook komen er steeds meer medicijnen om chronische darmontsteking te behandelen. Door de nieuwe informatie en behandelingen wordt de zorg voor chronische darmontsteking ingewikkelder. Daarom werken MDL-artsen in het Zuidwesten van Nederland samen om de zorg te verbeteren. Er wordt een zorgpad ontwikkeld, zodat iedereen op een vergelijkbare manier wordt behandeld in de regio. Een zorgpad is een stappenplan, met daarin praktische adviezen over keuzes tijdens de behandeling van chronische darmontsteking.

### 2. Doel van het onderzoek

Het doel van het onderzoek is om de zorg te verbeteren voor mensen met een chronische darmontsteking die sterke ontstekingsremmers krijgen. Door gegevens te verzamelen over de uitkomsten van uw behandeling kunnen wij kijken wat er goed gaat, en wat er beter kan.

Daarnaast kijken wij ook naar de kosten van de behandeling, en de kosten die u zelf maakt. Wij hopen met dit onderzoek de kwaliteit van zorg te verbeteren en de kosten te reduceren.

### 3. Wat meedoen inhoudt

Meedoen houdt in dat u tot maart 2023 vragenlijsten invult over de zorg die u krijgt. U krijgt dezelfde behandeling als normaal. De ziekenhuizen zijn ingedeeld in twee groepen, een groep ziekenhuizen die volgens het nieuwe zorgpad werkt en een groep ziekenhuizen die dit niet doet. Door deze twee groepen te vergelijken kunnen we kijken of het zorgpad ook echt beter is dan de huidige situatie.

Door de COVID-19 pandemie kan het gebeuren dat de start van deze studie moet worden uitgesteld. Als de start wordt uitgesteld begint u later met het invullen van vragenlijsten. In dat geval loopt de studie langer door en vragen wij u ook om door te gaan met het invullen van de vragenlijsten. Mocht dit het geval zijn, dan laten wij u dat weten.

#### Anders dan bij gebruikelijke zorg

Als u meedoet met het onderzoek wordt u niet anders behandeld dan normaal. Eerst willen wij de zorg die u nu krijgt evalueren. Daarom vragen wij u om vragenlijsten in te vullen. In december 2021 zal het zorgpad geïntroduceerd worden. Dit is voor alle patiënten, dus ook als u niet meedoet aan het onderzoek. Dit kan bijvoorbeeld betekenen dat de MDL-artsen afspreken dat u vaker, of minder vaak op de polikliniek moet komen. Wij willen dan kijken of deze verandering beter is.

#### Vragenlijsten

Voor dit onderzoek willen wij u vragen om enkele vragenlijsten in te vullen.

- Aan het begin van het onderzoek, en elk jaar krijgt u een vragenlijst opgestuurd via de e-mail om te kijken naar uw persoonlijke omstandigheden, de aanwezigheid van andere ziekten en uw leefstijl. Het invullen kost u ongeveer 5 minuten.
- U krijgt elke drie maanden een vragenlijst toegestuurd via de e-mail. Deze vragen gaan over hoe de ziekte uw werk beïnvloedt, en de (zorg)kosten die u maakt door uw ziekte. Het invullen kost u ongeveer 5 minuten.
- Daarnaast krijgt u elke 6 maanden een vragenlijst toegestuurd via de mail om de invloed van de ziekte op uw leven en uw kwaliteit van leven te meten. Het invullen kost u ongeveer 10 minuten.

Daarnaast zullen wij ook aan uw behandelend specialist gegevens vragen over de uitkomsten van uw behandeling. Dit gaat bijvoorbeeld over het verloop van uw ziekte, en welke medicijnen u gebruikt.

### 4. Afspraken

Om het onderzoek goed te laten verlopen, is het belangrijk dat u de vragenlijsten invult volgens de uitleg.

Het is belangrijk dat u contact opneemt met de onderzoeker:

- als u niet meer wilt meedoen aan het onderzoek.
- als uw contactgegevens wijzigen.

## 5. Mogelijke voor- en nadelen

Het is belangrijk dat u de mogelijke voor- en nadelen goed afweegt voordat u besluit mee te doen. Als u meedoet aan dit onderzoek betekent het niet dat u minder last krijgt van uw ziekte. Maar u draagt wel bij aan meer kennis over de behandeling van chronische darmziekten, en aan de verbetering hiervan. Een nadeel van het meedoen aan het onderzoek kan zijn dat het invullen van de vragenlijsten u tijd kost.

## 6. Als u niet wilt meedoen of wilt stoppen met het onderzoek

U beslist zelf of u meedoet aan het onderzoek. Deelname is vrijwillig. Als u niet wilt meedoen, wordt u op de gebruikelijke manier behandeld voor uw chronische darmziekte. Dit is niet anders dan als u wel mee zou doen met het onderzoek.

Als u wel meedoet, kunt u zich altijd bedenken en toch stoppen, ook tijdens het onderzoek. U wordt dan op dezelfde manier behandeld voor uw chronische darmziekte. U hoeft niet te zeggen waarom u stopt. Wel moet u dit direct melden aan de onderzoeker. De gegevens die tot dat moment zijn verzameld, worden gebruikt voor het onderzoek.

Als er nieuwe informatie over het onderzoek is die belangrijk voor u is, laat de onderzoeker dit aan u weten. U wordt dan gevraagd of u blijft meedoen.

## 7. Algemene informatie

Dit onderzoek is opgezet door het Franciscus Gasthuis & Vlietland en wordt gedaan door artsen in verschillende ziekenhuizen in de regio Rotterdam. Voor dit onderzoek worden alle patiënten benaderd die in de regio Rotterdam behandeld worden met een sterke ontstekingsremmer voor een chronische darmontsteking.

De studie is aangemeld bij de medisch-ethische toetsingscommissie (METC) Erasmus MC die heeft bepaald dat deze studie niet valt onder de wet medische wetenschappelijk onderzoek met mensen. Dat betekent dat deze studie niet door de METC goedgekeurd hoeft te worden.

## 8. Einde van het onderzoek

Uw deelname aan het onderzoek stopt als

- alle vragenlijsten ingevuld zijn
- u zelf kiest om te stoppen
- de onderzoeker het beter voor u vindt om te stoppen
- het Franciscus Gasthuis & Vlietland of de overheid besluit om het onderzoek te stoppen.

1  
2  
3  
4  
5 Het hele onderzoek is afgelopen als alle deelnemers klaar zijn. Na het verwerken van alle  
6 gegevens informeert de onderzoeker u over de belangrijkste uitkomsten van het onderzoek.  
7 Dit gebeurt ongeveer 6 maanden na uw deelname. Als u dit niet wilt, dan kunt u dit tegen de  
8 onderzoeker zeggen. Hij mag het u dan niet vertellen.  
9

## 10 11 12 **9. Gebruik en bewaren van uw gegevens**

13 Voor dit onderzoek worden uw persoonsgegevens verzameld, gebruikt en bewaard. Het gaat  
14 om gegevens zoals uw naam, geboortjaar en om gegevens over uw gezondheid. Het  
15 verzamelen, gebruiken en bewaren van uw gegevens is nodig om de vragen die in dit  
16 onderzoek worden gesteld te kunnen beantwoorden en de resultaten te kunnen publiceren.  
17 Wij vragen voor het gebruik van uw gegevens uw toestemming.  
18  
19

### 20 21 **Vertrouwelijkheid van uw gegevens**

22 Om uw privacy te beschermen krijgen uw gegevens een code. Uw naam en andere  
23 gegevens die u direct kunnen identificeren worden daarbij weggelaten. Alleen met de sleutel  
24 van de code zijn gegevens tot u te herleiden. De sleutel van de code blijft veilig opgeborgen  
25 in de lokale onderzoeksinstelling. De gegevens die naar de opdrachtgever worden gestuurd,  
26 bevatten alleen de code en uw e-mailadres om de vragenlijsten te versturen, maar niet uw  
27 naam of andere gegevens waarmee u kunt worden geïdentificeerd. Ook in rapporten en  
28 publicaties over het onderzoek zijn de gegevens niet tot u te herleiden.  
29  
30  
31

### 32 33 **Toegang tot uw gegevens voor controle**

34 Sommige personen kunnen op de onderzoekslocatie toegang krijgen tot al uw gegevens.  
35 Ook tot de gegevens zonder code. Dit is nodig om te kunnen controleren of het onderzoek  
36 goed en betrouwbaar is uitgevoerd. Personen die ter controle inzage krijgen in uw gegevens  
37 zijn: onderzoekers en studenten die hen hierbij assisteren, een monitor die voor de  
38 opdrachtgever van het onderzoek werkt, en nationale en internationale toezichthoudende  
39 autoriteiten, bijvoorbeeld, de Inspectie Gezondheidszorg en Jeugd. Zij houden uw gegevens  
40 geheim. Wij vragen u voor deze inzage toestemming te geven.  
41  
42  
43  
44

### 45 46 **Bewaren en gebruik van gegevens**

47 Uw gegevens moeten 15 jaar worden bewaard op de onderzoekslocatie en 15 jaar bij de  
48 opdrachtgever. Uw gegevens kunnen na afloop van dit onderzoek ook nog van belang zijn  
49 voor ander wetenschappelijk onderzoek op het gebied van chronische darmontsteking. U  
50 kunt op het toestemmingsformulier aangeven of u hier wel of niet mee instemt. Indien u hier  
51 niet mee instemt, kunt u gewoon deelnemen aan het huidige onderzoek. Uw bewaarde  
52 gegevens zullen dan niet gebruikt worden voor ander wetenschappelijk onderzoek.  
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### 56 57 **Intrekken toestemming**

58 U kunt uw toestemming voor gebruik van uw persoonsgegevens altijd weer intrekken. Dit  
59 geldt voor dit onderzoek en ook voor het bewaren en het gebruik voor het toekomstige  
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4 onderzoek. De onderzoeksgegevens die zijn verzameld tot het moment dat u uw  
5 toestemming intrekt, worden nog wel gebruikt in het onderzoek.  
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### 8 **Meer informatie over uw rechten bij verwerking van gegevens**

9 Voor algemene informatie over uw rechten bij verwerking van uw persoonsgegevens kunt u  
10 de website van de Autoriteit Persoonsgegevens raadplegen. Bij vragen over uw rechten kunt  
11 u contact opnemen met de verantwoordelijke voor de verwerking van uw persoonsgegevens.  
12 Voor dit onderzoek is dat: het Franciscus Gasthuis & Vlietland. Zie bijlage A voor  
13 contactgegevens en website.  
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17 Bij vragen of klachten over de verwerking van uw persoonsgegevens raden we u aan eerst  
18 contact op te nemen met de onderzoekslocatie. U kunt ook contact opnemen met de  
19 Functionaris voor de Gegevensbescherming van de instelling (zie bijlage A) of de Autoriteit  
20 Persoonsgegevens.  
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### 23 **Registratie van het onderzoek**

24 Informatie over dit onderzoek is ook opgenomen in een overzicht van medisch-  
25 wetenschappelijke onderzoeken namelijk (<https://www.trialregister.nl/trial/8276>). Daarin zijn  
26 geen gegevens opgenomen die naar u herleidbaar zijn. Na het onderzoek kan de website  
27 een samenvatting van de resultaten van dit onderzoek tonen.  
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## 32 **10. Geen vergoeding voor meedoen**

33 Het meedoen aan het onderzoek kost u niets. U wordt niet betaald voor het meedoen aan dit  
34 onderzoek.  
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## 38 **11. Heeft u vragen?**

39 Bij vragen kunt u contact opnemen met de onderzoeker. Voor onafhankelijk advies over  
40 meedoen aan dit onderzoek kunt u terecht bij de onafhankelijke arts. Hij weet veel over het  
41 onderzoek, maar heeft niets te maken met dit onderzoek.  
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45 Indien u klachten heeft over het onderzoek, kunt u dit bespreken met de onderzoeker of uw  
46 behandelend arts. Wilt u dit liever niet, dan kunt u zich wenden tot de klachtenfunctionaris of  
47 klachtencommissie van het Franciscus Gasthuis & Vlietland. Alle gegevens vindt u in bijlage  
48 A: Contactgegevens.  
49  
50  
51

## 52 **12. Ondertekening toestemmingsformulier**

53 Indien u besluit mee te doen met dit onderzoek, vragen wij u dit op de bijbehorende  
54 toestemmingsverklaring schriftelijk te bevestigen. Door uw schriftelijke toestemming geeft u  
55 aan dat u de informatie heeft begrepen en instemt met deelname aan het onderzoek. Zowel  
56 uzelf als de onderzoeker ontvangen een getekende versie van deze toestemmingsverklaring.  
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Dank voor uw aandacht.

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**13. Bijlagen bij deze informatie**

- A. Contactgegevens
- B. Toestemmingsformulier(en)

For peer review only

## Bijlage A: contactgegevens voor Franciscus Gasthuis & Vlietland

Als u nog vragen heeft over dit onderzoek, neem dan contact op met de onderzoeksarts of zijn of haar onderzoeksmedewerkers:

- de hoofdonderzoekers: dr. D. Leemreis-van Noord en dr. R.L. West, 010-4616161
- de coördinerend onderzoeker: drs. R.C.A. van Linschoten, 010-4617838
- de onafhankelijk arts: Dr. G.J. Braunstahl, 010-4616161
- Buiten kantooruren kunt u met het algemene nummer van het ziekenhuis bellen:
  - Franciscus Gasthuis: 010-461 61 61
  - Franciscus Vlietland: 010-893 93 93

en vragen naar de dienstdoend arts van de Maag-, Darm-, en Leverziekten.

### Cliëntvertrouwenspersoon:

Deze studie wordt uitgevoerd met toestemming van de Raad van Bestuur van dit ziekenhuis. Het *Franciscus Gasthuis & Vlietland* vindt het belangrijk dat patiënten, proefpersonen en bezoekers tevreden zijn. Toch kan het gebeuren dat u niet tevreden bent en een klacht wilt indienen. In dat geval kunt u het beste eerst praten met de onderzoeksarts of uw behandelend arts. Als u dat liever niet doet, kunt u ook contact opnemen met de cliëntvertrouwenspersoon van het ziekenhuis. Dit kan zowel telefonisch als door het invullen van het online klachtenformulier.

Contact met de cliëntvertrouwenspersoon voor compliment, suggestie of klacht:

### **Franciscus Gasthuis en Franciscus Berkel**

Telefoonnummer: 010 – 461 6701

### **Franciscus Vlietland, Franciscus Haven, Franciscus Hoogvliet en Franciscus Maassluis**

Telefoonnummer: 010 – 893 4125

Digitaal via [www.franciscus.nl/klacht](http://www.franciscus.nl/klacht) (voor alle locaties)

### **Functionaris Gegevensbescherming (alle locaties):**

Mw. L. Pollinger

E-mail: [fg@franciscus.nl](mailto:fg@franciscus.nl)

Telefoonnummer: 010-4616898

## Bijlage B: toestemmingsformulier deelnemer

### Waardegedreven zorg voor inflammatoire darmziekten: IBD Value

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn voldoende beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen of te stoppen met het onderzoek. Daarvoor hoef ik geen reden te geven.
- Ik geef toestemming om, in het geval ik tijdens de looptijd van het onderzoek zou komen te overlijden, mijn officiële doodsoorzaakgegevens op te vragen bij het Centraal Bureau voor de Statistiek.
- Ik geef toestemming voor het opvragen van informatie bij mijn specialist(en) die mij behandelt over de uitkomsten van de behandeling van mijn chronische darmontsteking.
- Ik geef toestemming voor het verzamelen en gebruiken van mijn gegevens voor de beantwoording van de onderzoeksvraag in dit onderzoek.
- Ik weet dat voor de controle van het onderzoek sommige mensen toegang tot al mijn gegevens kunnen krijgen. Die mensen staan vermeld in deze informatiebrief. Ik geef toestemming voor die inzage door deze personen.
- Ik geef toestemming om mijn e-mailadres aan het onderzoeksteam door te geven, zodat de vragenlijsten naar mij verstuurd kunnen worden.
- Ik geef  **wel**  **geen** toestemming om mijn persoonsgegevens langer te bewaren en te gebruiken voor toekomstig onderzoek op het gebied van chronische darmontsteking.
- Ik geef  **wel**  **geen** toestemming om mij na dit onderzoek opnieuw te benaderen voor een vervolgonderzoek.
- Ik wil  **wel**  **niet** geïnformeerd worden over de uitkomsten van dit onderzoek.
- Ik wil meedoen aan dit onderzoek.

Naam deelnemer:

E-mailadres:

Handtekening:

Datum : \_\_ / \_\_ / \_\_

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*De deelnemer krijgt een volledige informatiebrief mee.*

# BMJ Open

## A value-based care pathway for inflammatory bowel disease: protocol for the multicentre longitudinal non-randomised parallel cluster IBD Value study with baseline period

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1 A value-based care pathway for inflammatory bowel disease: protocol for the  
2 multicentre longitudinal non-randomised parallel cluster IBD Value study with baseline  
3 period

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34  
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36 4803  
37

## 38 ABSTRACT

39 Introduction: Biologics are effective for the treatment of inflammatory bowel disease (IBD). However,  
40 unwarranted variation in processes and outcomes has been reported in the treatment of IBD. A care  
41 pathway for the treatment of IBD has the potential to reduce practice variation and improve  
42 outcomes. This study aims to compare the effect of a uniform care pathway for the treatment of IBD  
43 patients with biologics to the current situation.

44 Methods and analysis: IBD Value is a longitudinal multicentre non-randomised parallel cluster trial  
45 with a baseline period. The study takes place in eight centres in the Netherlands. The baseline period  
46 will run for 12 months, after which the care pathway will be implemented in six of the eight  
47 participating hospitals during the implementation phase of 3 months. Hereafter the effect of the care  
48 pathway will be assessed for 12 months. Total study period is 27 months. The primary outcome is the  
49 effect of the care pathway on disease control (IBD-Control questionnaire). Secondary outcomes are  
50 the effect of the care pathway on the other outcomes of the International Consortium of Health  
51 Outcomes Measurement IBD standard set, health-related generic quality of life, patient experiences,  
52 and degree of variation; cost-effectiveness of the care pathway; and the variation between hospitals  
53 in the aforementioned outcomes in the baseline period. Outcomes will be measured every six  
54 months. The study started on December 1<sup>st</sup> 2020 and a minimum of 200 patients will be included.

55 Ethics and dissemination: The study was deemed not to be subject to Dutch law (WMO; Medical  
56 Research Involving Human Subjects Act) by the Medical Ethics Committee Erasmus MC, the  
57 Netherlands (registration number MEC-2020-075) and a waiver was provided. Results will be  
58 disseminated through peer-reviewed journals and presented at (inter)national conferences.

59 Registration details: This study was registered in the Netherlands Trial Register (NL8276) on 09-01-  
60 2020.

## 62 STRENGTH AND LIMITATIONS OF THIS STUDY

- 63 • This study is to our knowledge the first prospective multicentre study assessing the effect of  
64 a care pathway for the treatment of IBD on health outcomes.
- 65 • The use of a baseline period and control group allow for controlling for time trends when  
66 analysing the effect of the care pathway.
- 67 • The Dutch Crohn's and colitis patient organisation was involved in the study design and will  
68 participate in the development of the care pathway.
- 69 • This is the first large multicentre study to implement the International Consortium of Health  
70 Outcomes Measurement (ICHOM) standard set for IBD.
- 71 • As the study is a non-randomised trial analyses will have to be adjusted for case-mix to  
72 correct for possible confounding bias.

## 75 INTRODUCTION

76 Crohn's disease and ulcerative colitis, subtypes of inflammatory bowel disease (IBD), are chronic  
77 inflammatory diseases of the gastrointestinal tract.[1, 2] Signs and symptoms of IBD are abdominal  
78 pain, diarrhoea, and rectal bleeding. IBD can also affect extraintestinal organs, such as the liver, skin,  
79 eyes, and joints.[3-5] Further, IBD can have a major impact on quality of life because of fatigue and  
80 its psychological impact.[6, 7] To control these symptoms, patients are often dependent on  
81 medication and are sometimes hospitalized or need surgery when drugs fail. The high disease burden  
82 leads to reduced quality of life, high healthcare costs (between €15,000 and €30,000 per patient per  
83 year) and reduced work productivity.[7, 8] Biologics and new small molecules (i.e. tofacitinib) are  
84 proven efficacious treatments for IBD and have shown to induce and maintain remission, avert  
85 hospitalisation and surgery, and reduce productivity loss in randomised controlled trials.[9-12]

86  
87 Considerable variation exists between healthcare providers in the treatment of IBD with  
88 biologics.[13-18] Treatment variation consists among other things of differences in provided care and  
89 follow-up such as type of medication prescribed, dosing frequency, and interpretation of therapeutic  
90 drug monitoring. Treatment variation can lead to differences in outcomes, such as the proportion of  
91 patients in remission, side effects, and treatment costs.[19] While variation can be a natural  
92 consequence of differences between patient populations, part of the variation in processes and  
93 outcomes was explained by experience and expertise of healthcare providers, with better process  
94 adherence and outcomes for dedicated IBD or academic physicians.[17, 19]

95  
96 Treatment variation might also lead to reduced effectiveness of biologics in daily practice.  
97 Observational population-based studies showed no association between the use of biologics and  
98 long-term disease progression, nor on hospitalisation or surgery, contradicting the findings of  
99 randomised controlled trials.[20-22] Taking into account the differences in patient populations and  
100 study designs, these observational studies hypothesize that variation in treatment, mainly under- and  
101 misuse of biologics, may partly explain the gap between the efficaciousness of biologics in  
102 randomised trials and their effectiveness in the real world. Reduction of this variation might thus be  
103 a potential avenue for improving outcomes of IBD patients treated with a biologic.

104  
105 Value-based healthcare (VBHC) is an approach that aims, among other things, at improving technical  
106 value (health outcomes achieved divided by resources spent) for the patient by tackling unwarranted  
107 variation and optimising the care delivery process.[23, 24] Important parts of VBHC are  
108 systematically measuring both patient-reported outcomes and the costs of achieving these  
109 outcomes.[25, 26] These data can consequently be used to evaluate and adjust the care delivery  
110 process and improve (cost-)effectiveness of achieving optimal patient-centred outcomes.

111  
112 Implementing a care pathway in clinical practice seems promising for improving value, which was  
113 illustrated by a retrospective pilot study that evaluated a care pathway for IBD in a VBHC program.  
114 This care pathway showed a favourable effect on flares (-26%) and costs (-16%).[27] Other studies  
115 supported the effect of a care pathway for IBD on costs and also showed an improvement of care  
116 processes.[28, 29]. In inguinal hernia repair, chronic heart failure and total hip replacement the  
117 implementation of a care pathway was also accompanied by reduced variation in processes and  
118 outcomes.[30] Although these studies showed a promising effect on outcomes and processes, they  
119 suffered from low sample sizes, retrospective study designs and lacked patient-centred outcome  
120 measures. With the prospective multicentre IBD Value study we aim to assess the impact of a care  
121 pathway for the treatment of IBD with biologics and new small molecules on patient-centred  
122 outcomes.



## 125 **METHODS AND ANALYSIS**

126 The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines were  
127 followed and the checklist is included with the protocol (online supplementary file 1).[31] The most  
128 recent study protocol version 2.0.0 (July 2020) is presented in this manuscript. Changes to the  
129 protocol will be submitted to the Medical Ethics Committee Erasmus MC (Rotterdam, the  
130 Netherlands). Changes will also be noted in the trial register and communicated to local  
131 investigators. The start date of the study was 1 December 2020.

### 132 **Study Aim**

133 The main objective of the study is to evaluate the added value of a uniform care pathway on the  
134 health outcomes of IBD patients treated with a biologic or new small molecule in one of the  
135 participating hospitals. Secondary objectives are to:

- 136 • Assess the degree of regional variation in outcomes and costs of the treatment of IBD with  
137 biologics and new small molecules;
- 138 • Uncover areas of improvement in the care of IBD patients;
- 139 • Develop and implement a regional care pathway for the treatment of IBD with biologics and  
140 new small molecules based on scientific evidence, current guidelines, and adapted to the  
141 local context;
- 142 • Evaluate the cost-effectiveness of the care pathway;
- 143 • Evaluate the effect of the care pathway on variation in outcomes and costs.

### 144 **Study Design**

145 This is a longitudinal multicentre non-randomised parallel cluster trial with a baseline period (Figure  
146 1). In the first 12 months of the study, before the introduction of the new care pathway, the current  
147 situation in IBD care for patients on biologics or new small molecules will be assessed in all  
148 participating hospitals to establish baseline measures. These data will primarily be used as  
149 comparison with the 2<sup>nd</sup> study period after implementation of the care pathway. The data will also be  
150 used to determine areas of improvement, as benchmarking, and aid the design of the care pathway.  
151 Subsequently the care pathway will be implemented in six of the participating hospitals during a  
152 three-month implementation period.

153 The participating hospitals are: Franciscus Gasthuis & Vlietland, Rotterdam & Schiedam; Erasmus MC,  
154 Rotterdam; Albert Schweitzer Hospital, Dordrecht, Zwijndrecht & Sliedrecht; Maasstad Hospital,  
155 Rotterdam; Ikazia Hospital, Rotterdam; IJsselland Hospital, Capelle aan den IJssel; Reinier de Graaf  
156 Gasthuis, Delft; Amphia Hospital, Breda. These are hospitals that have collaborated in IBD BeterKeten  
157 in the southwest of the Netherlands since 2016 to improve quality of care of IBD patients in the  
158 region.[32] The care pathway will not be implemented in Reinier de Graaf Gasthuis and Amphia  
159 Hospital; these hospitals will participate as the control group. The content of the care pathway will  
160 only be revealed to and implemented in the six hospitals in the intervention group at the start of the  
161 implementation period. The development of the care pathway will be completed by the working  
162 group in the last period of the baseline measurement phase. After implementation, outcomes will be  
163 evaluated during the 12-month follow-up period in all participating hospitals.

### 164 **Population**

165 The study population comprises all IBD patients being treated with a biologic agent or new small  
166 molecule in the eight participating hospitals. The care pathway also covers patients treated with new  
167 small molecules, as these belong to the same group as patients treated with a biologic: complex  
168 disease and a high cost of treatment. Approximately 3,200 patients are treated with the  
169 aforementioned medication in these hospitals in total.

170 All participants will meet the following criteria:

- 176 • 18 years of age or older
- 177 • Have given informed consent for data collection
- 178 • Being treated for IBD in one of the participating hospitals
- 179 • Have an IBD diagnosis of at least three months
- 180 • Treated with one of the currently registered biologics or new small molecules for IBD
- 181 treatment or new treatments registered during the study period, including: infliximab,
- 182 adalimumab, golimumab, vedolizumab, ustekinumab, or tofacitinib.

183  
184 A potential subject may be excluded from study participation if they have insufficient knowledge of  
185 the Dutch language to complete the questionnaires and/or have no access to the internet to  
186 complete the questionnaires.

## 187 188 **Intervention**

### 189 **Design**

190 The intervention is a uniform care pathway for the treatment of IBD patients with biologic agents. It  
191 contains uniform guidelines for prescribing, the work-up, and switching of biologic therapy and new  
192 small molecules, and for the frequency and type of follow-up. As IBD is a heterogeneous disease, the  
193 care pathway will not be able to cover all possible treatment decisions, but aims to guarantee the  
194 same level of care for IBD patients in all participating hospitals, while taking into account patient  
195 preference and uncertainty in the evidence concerning IBD treatment.

196  
197 To prevent contamination of the control period, the development of the care pathway will be  
198 finalised shortly before implementation. The care pathway will be developed by an IBD BeterKeten  
199 working group of gastroenterologists and IBD nurses with multidisciplinary input of a surgeon and a  
200 dietician. Moreover, the Dutch IBD patient federation (Crohn & Colitis NL) will participate in the  
201 design of the care pathway. The care pathway will be based on national and international guidelines  
202 and will be designed according to the following steps.[33-35]

203  
204 First, the main topics of what the care pathway should cover will be drafted by the project manager.  
205 These topics will then be discussed until consensus is reached by the working group. Hereafter the  
206 project manager will draft care pathways for each topic (see below) on the basis of (inter)national  
207 guidelines. These drafts will then be discussed in the working group until consensus is reached on  
208 exact content and timing of the care pathway. Literature searches will be performed to inform the  
209 working group in cases of uncertainty around best practices. When the evidence around treatment  
210 decisions is uncertain or scarce, this will be clearly reflected in the care pathway.

211  
212 Outcomes from the baseline measurement collected during the first project phase will be used to  
213 adjust and improve the care pathway. These will be analysed according to their pre-specified  
214 definitions (see Outcomes below) and stratified per institute to assess areas of improvement in IBD  
215 care. Results of these analyses and consequences for improvement will be discussed in a working  
216 group meeting and implemented in the care pathway. The final draft of the care pathway will be  
217 presented for approval of the IBD specialists of all participating intervention centres.

### 218 219 **Content**

220 The care pathway will address the following issues.

- 221 1. Actions that do not depend on current treatment but apply to all patients: examples are  
222 periodical colorectal cancer and micronutrient screening.
- 223 2. Evaluation of a possible flare: when a patient presents with symptoms or when abnormal  
224 test results are found, differential diagnoses have to be excluded. Moreover, disease activity  
225 has to be measured using objective markers.

- 1  
2  
3 226 3. Therapy sequence in case of a flare: it will indicate advice on the next treatment step for a  
4 227 patient with a flare based on their disease and treatment history. This could be either  
5 228 treatment intensification or switching.  
6 229 4. Frequency, type and timing of follow-up for the induction and remission phases of the  
7 230 different therapies: examples are the timing of outpatient clinic visits, laboratory  
8 231 assessments and additional examinations.  
9 232

10 233 The care pathway is a decision-making tool for care providers and patients, and presents treatment  
11 234 guidelines in a simple and interpretable format. It sets out the most appropriate steps in patient  
12 235 management at each therapy stage. Decision trees will be designed to give visual support to the care  
13 236 pathway. Because the treatment of IBD is rapidly changing and studies regularly provide new  
14 237 insights, the care pathway will be updated in IBD BeterKeten meetings after study closure.  
15 238

#### 16 239 Implementation & Adherence

17 240 IBD specialists from IBD BeterKeten will safeguard implementation of the care pathway in their  
18 241 respective centres. They will be supported by a presentation of the working group to the care  
19 242 providers. To facilitate working according to the care pathway, we will implement the care pathway  
20 243 in electronic health records. Care providers will be able to schedule follow-up or diagnostics  
21 244 according to the care pathway with a single action. We will assess adherence to the care pathway by  
22 245 randomly sampling patients and comparing treatment decisions made for these patients with the  
23 246 treatment algorithms set out in the care pathway.  
24 247

#### 25 248 Comparison

26 249 The care pathway will be compared to current care by ways of the baseline measurement and  
27 250 adjustment for changes in the control group. All care providers continue their current practice  
28 251 according to their knowledge and local guidelines and treatment plans for the duration of the  
29 252 baseline measurement. The data collected in this period will give more insight into the current  
30 253 variation in practice, and can also be used to inform the design of the care pathway.  
31 254

#### 32 255 Outcome

33 256 To measure outcomes that matter to the patient, the standard set of patient-centred outcomes for  
34 257 IBD as defined by the International Consortium of Health Outcomes Measurement (ICHOM) will be  
35 258 used as the outcome measure of this study. ICHOM is an organization that creates standard sets to  
36 259 measure the outcomes that matter most to patients.[25] Patient-reported disease control as  
37 260 measured by the IBD-Control-8 score was chosen to serve as the primary outcome measure. This is a  
38 261 questionnaire that validly and reliably measures disease control from the patient perspective on a  
39 262 16-point scale, and can distinguish between active disease and remission.[36, 37]  
40 263

41 264 The other outcomes from the standard set are secondary outcomes:

- 42 265 • IBD-attributable mortality;
- 43 266 • Remission, both clinician-reported (biochemical, radiological, endoscopic, histologic) and  
44 267 patient-reported (Manitoba IBD Index; MIBDI);[38]
- 45 268 • Incidence of colorectal cancer;
- 46 269 • Presence of anaemia;
- 47 270 • Number of A&E visits;
- 48 271 • Number and cumulative length of hospital admissions;
- 49 272 • Number of complications of any intervention for IBD;
- 50 273 • Long-term (>3 months) steroid use;
- 51 274 • Presence of fistulae symptoms;
- 52 275 • BMI as a proxy for nutritional status;
- 53 276

277 The MIBDI is a valid and patient-reported outcome measure which can be used to classify disease  
 278 activity on a dichotomous scale. The other outcomes from the standard set will be retrieved from the  
 279 electronic health record. Other secondary outcomes are generic quality of life measured with the  
 280 validated PROMIS-10 Global Health (PROMIS-10) questionnaire, cost-effectiveness and patient  
 281 experience of care, using the Dutch Picker questionnaire.[39, 40]

283 The cost-utility analysis (CUA) will be performed alongside the clinical study. In line with the  
 284 recommendations of the National Health Care Institute and the broad societal impact of IBD the CUA  
 285 will take a societal perspective.[41, 42] Utility will be measured with the EQ-5D-5L (Dutch tariffs).[43]  
 286 The IBD-Control-8 score, which is more responsive to health state changes in IBD, will be used for an  
 287 alternative cost-effectiveness analysis.[36] Societal costs will be measured according to the  
 288 guidelines of the National Health Care Institute.[42-44]. Three types of societal costs are  
 289 distinguished: healthcare costs; patient costs; and other non-healthcare costs. For healthcare costs,  
 290 primary care costs (primary care, home care, other out of hospital care) are distinguished from in-  
 291 hospital costs (e.g. number of admissions, MRIs, and blood tests). Use of primary care will be  
 292 measured using the shortened version of the Medical Consumption Questionnaire (iMCQ) of the  
 293 Institute of Medical Technology Assessment (iMTA).[45] For healthcare use in secondary care, data  
 294 will be collected from the electronic healthcare records. Productivity losses will be determined with  
 295 the iMTA Productivity Cost Questionnaire (iPCQ). Measured productivity losses will be extrapolated  
 296 from one to three months. Absenteeism, presenteeism, and lost unpaid work will be determined.  
 297 Patient costs will be measured using a questionnaire on the following: travel costs; type, weeks and  
 298 hours of informal care; insurance deductible; over the counter drug use; other IBD related costs. For  
 299 all outcomes and their respective source, see Table 1.

| Outcome   | Source   |
|---|--|
| <u>Primary</u>  |  |
| Patient-reported disease control  | Patient-reported (IBD-Control)[36, 37]                   |
| <u>Secondary</u>  |  |
| IBD-attributable mortality  | Chart review   |
| Clinical remission  | Chart review   |
| Endoscopic/radiologic remission   | Chart review   |
| Colorectal cancer   | Chart review   |
| Complications of IBD treatment  | Chart review   |
| Biochemical remission   | Medical record   |
| Anaemia   | Medical record   |
| A&E visits  | Medical record   |
| Hospital admissions   | Medical record   |
| Long-term steroid use   | Medical record   |
| Hospital costs  | Medical record & Dutch reference prices[46]              |
| Fistulae symptoms   | Patient-reported   |
| BMI   | Patient-reported   |
| Patient-reported remission  | Patient-reported (MIBDI)[38]                             |
| Generic quality of life   | Patient-reported (PROMIS-10)[39]                         |
| Patient experience  | Patient-reported (Picker)[40]                            |
| Utility   | Patient-reported (EQ-5D-5L)[43, 44]                      |
| Primary care costs  | Patient-reported (iMCQ)[45] & Dutch reference prices[46] |
| Productivity costs  | Patient-reported (iPCQ)[47] & Dutch reference prices[46] |
| Patient costs   | Patient-reported   |
| Table 1: Outcomes and their respective source. IBD: Inflammatory bowel disease; MIBDI: Manitoba IBD Index; PROMIS-10: PROMIS-10 Global Health questionnaire; iMTA: Institute of Medical |  |

Technology Assessment; iPCQ: iMTA Productivity Cost Questionnaire; iMCQ: iMTA Medical Consumption Questionnaire

301

302 **Case mix**

303 To control for case mix differences between hospitals, we will collect the case mix variables defined  
 304 in the ICHOM sets for risk adjustment for IBD care.[25] Data will be collected on the following  
 305 variables:

- 306 • Year of birth
- 307 • Sex at birth
- 308 • Education level as defined by UNESCO[48]
- 309 • Smoking status
- 310 • Diagnosis (Crohn’s disease, ulcerative colitis, indeterminate colitis)
- 311 • Year of diagnosis
- 312 • Disease phenotype according to the Montreal classification[49]
- 313 • Presence of extra-intestinal manifestations
- 314 • Medication use for IBD
- 315 • IBD related surgery
- 316 • Comorbidities as defined by the self-administered comorbidity questionnaire (SCQ) with  
 317 inclusion of some extra questions as defined by ICHOM [50]
- 318 • Current or prior infection with tuberculosis, hepatitis B or human immunodeficiency virus
- 319 • Concomitant presence of primary sclerosing cholangitis
- 320 • Treating hospital

321

322 **Timing**

323 Patients can be included from one month before the start of the study (December 1<sup>st</sup> 2020) until the  
 324 end of the study (March 31<sup>st</sup> 2023). Outcomes will be measured at the following time points as  
 325 defined by ICHOM (see also Tables 2 and 3). The IBD-Control, MIBDI, EQ-5D-5L and the PROMIS-10  
 326 will be administered when a participant is included in the study and at six monthly intervals from the  
 327 start of the study. Cost questionnaires will be sent to patients at three monthly intervals from the  
 328 start of the study. Demographics and comorbidity questionnaires will be sent at inclusion, at the start  
 329 of the intervention period (t=15) and at the end of the study (t=27). Patient experience  
 330 questionnaires will be distributed once a year after an outpatient clinic visit. To reduce questionnaire  
 331 burden, some questionnaires at inclusion will not be sent if a patient is included two months (quality  
 332 of life) or three months (case mix) before the respective questionnaires would be sent again.  
 333

Table 2: Timing of questionnaires for patient included at or before T=0

|                  | Demographics | IBD-Control | MIBDI | SCQ | EQ-5D-5L/<br>PROMIS-10 | iPCQ | iMCQ | Patient costs |
|------------------|--------------|-------------|-------|-----|------------------------|------|------|---------------|
| 0m (study start) | X            | X           | X     | X   | X                      |      |      |               |
| 3m               |              |             |       |     |                        | X    | X    | X             |
| 6m               |              | X           | X     |     | X                      | X    | X    | X             |
| 9m               |              |             |       |     |                        | X    | X    | X             |
| 12m              |              | X           | X     |     | X                      | X    | X    | X             |
| 15m              | X            |             |       | X   |                        | X    | X    | X             |
| 18m              |              |             |       |     |                        | X    | X    | X             |
| 21m              |              | X           | X     |     | X                      | X    | X    | X             |
| 24m              |              |             |       |     |                        | X    | X    | X             |
| 27m              | X            | X           | X     | X   | X                      | X    | X    | X             |

IBD: Inflammatory bowel disease; MIBDI: Manitoba IBD Index; SCQ: self-administered comorbidity questionnaire; PROMIS-10: PROMIS-10 Global Health questionnaire; iMTA: Institute of Medical Technology Assessment; iPCQ: iMTA Productivity Cost Questionnaire; iMCQ: iMTA Medical Consumption Questionnaire

334

Table 3: Timing of questionnaires for a patient included at T=10m

|  | Demographics | IBD-Control | MIBDI | SCQ | EQ-5D-5L/<br>PROMIS-10 | iPCQ | iMCQ | Patient costs |
|--|--------------|-------------|-------|-----|------------------------|------|------|---------------|
|--|--------------|-------------|-------|-----|------------------------|------|------|---------------|

|                  |   |   |   |   |   |   |   |   |
|------------------|---|---|---|---|---|---|---|---|
| 0m (study start) |   |   |   |   |   |   |   |   |
| 3m               |   |   |   |   |   |   |   |   |
| 6m               |   |   |   |   |   |   |   |   |
| 9m               |   |   |   |   |   |   |   |   |
| 10m (inclusion)  | X |   |   |   |   |   |   |   |
| 12m              |   | X | X |   | X | X | X | X |
| 15m              | X |   |   | X |   | X | X | X |
| 18m              |   |   |   |   |   | X | X | X |
| 21m              |   | X | X |   | X | X | X | X |
| 24m              |   |   |   |   |   | X | X | X |
| 27m              | X | X | X | X | X | X | X | X |

IBD: Inflammatory bowel disease; MIBDI: Manitoba IBD Index; SCQ: self-administered comorbidity questionnaire; PROMIS-10: PROMIS-10 Global Health questionnaire; iMTA: Institute of Medical Technology Assessment; iPCQ: iMTA Productivity Cost Questionnaire; iMCQ: iMTA Medical Consumption Questionnaire

335

336

Other outcomes will be retrieved from the electronic health records retrospectively, biannually and annually as recommended by ICHOM. A subset of the data (e.g. age, gender, hospital healthcare use, anaemia, mortality, medication use) can be retrieved from the electronic health records anonymously. This data will be retrieved for the entire source population, as informed consent is not necessary for the use of anonymized data according to Dutch law. This can be used to study possible selection bias.

343

### Statistical considerations

344 Power

As our data are clustered longitudinally and per hospital, analytic sample size calculation is not appropriate. Thus, we used simulations to estimate power for different cluster sizes. The calculations were based on the following assumptions:

- a baseline IBD-Control score of 8 with a standard deviation (SD) of 4;[51, 52]
- because of the clustering of data at two levels (within patients over time and patients clustered within hospitals), the degree of clustering has to be accounted for. As this is not reported in the literature, we estimated random effects for patients and hospitals with standard deviations between 0 and 4 (corresponding to intraclass correlation coefficients between 0 and 0.25);
- a change in IBD-Control score of 1 as clinically meaningful. Research has shown minimal important differences of 0.5 SD for health-related quality of life instruments. However, as amelioration of a single symptom changes the score of the IBD Control by 0.25 SD, we powered our study on this effect size.[53]

359

The sample size calculation is further based on:

- simulating data based on the assumptions listed above;
- 8 hospitals of between 1 and 50 patients each, in steps of 5;
- 10,000 iterations per cluster size;
- dropout of 10%;
- type-1 error rate ( $\alpha$ ) of 0.05 two-sided;
- power of at least 80%;
- fitting a linear mixed effect model with random intercepts for patient and hospital and a fixed effect for intervention.

369

Power was defined as the number of iterations that found a statistically significant effect as a proportion of the total number of iterations. To account for our clustered data, 25 patients per hospital (a total of 200 patients) before the six month mark of the study would be required to have sufficient power (>80%) to identify a change of 1 point of the IBD-Control score. We are striving to

373

374 include all eligible patients to achieve a representative sample of the source population and to  
375 prevent selection bias.

376  
377 Business Intelligence (BI) departments in each of the participating hospitals will support patient  
378 screening and help reduce the logistic burden. The BI departments will use an algorithm to identify  
379 patients who meet the study inclusion criteria. These patients will receive a letter or e-mail from  
380 their hospital, asking for their consent to participate in the study. The algorithm will also identify the  
381 patient's care provider and next hospital visit. The care providers will be provided with this  
382 information to approach the patient for inclusion during the outpatient clinic visit. Patient  
383 recruitment should not be a time consuming process as the burden on the patient is low, the study is  
384 easy to explain and no randomisation or experimental treatment is used. Because all patients will  
385 receive an invitation letter to participate and care providers will remind them during their hospitals  
386 visit, we think that the minimum inclusion goal of 25 patients per hospital is feasible. Currently, 1001  
387 patients have been included.

388  
389 Data analysis plan

390 All missing data will be assessed whether these data are likely to be missing (completely) at random.  
391 If so, Multivariate Imputation by Chained Equations (MICE) will be used to impute missing data for  
392 variables used for adjustment. The primary outcome, IBD-Control-8 score, will be analysed on patient  
393 level using a linear mixed effects model of the form:

$$Y_{ijt} = \beta_0 + \eta_j + \theta_{ij} + \beta_1\iota + \beta_t v_t + \beta_c v_c + \varepsilon_{ijt}$$

394  
395  
396  
397 Where  $Y$  is the IBD-Control-8 score (0-16) of person  $i$  in cluster  $j$  at time  $t$  (0-6 months, 6-12 months,  
398 15-21 months, 21-27 months);  $\beta_0$  the intercept;  $\eta_j$  the cluster level random effect for cluster  $j$ ;  $\theta_{ij}$  the  
399 patient level random effect for patient  $i$  in cluster  $j$ ;  $\beta_1$  the estimated difference between standard  
400 care ( $\iota = 0$ ) and the care pathway ( $\iota = 1$ );  $\beta_t$  a vector with coefficients for calendar time at the  
401 different time points  $t$ , captured as the vector  $v_t$  with dummy variables for the different periods of  
402 follow-up;  $\beta_c$  a vector containing the coefficients for the case mix variables in the vector  $v_c$ ; and  $\varepsilon_{ijt}$  is  
403 the residual error.

404  
405 To adjust for case mix we will use the variables from the ICHOM IBD set. These are: age in years  
406 (continuous), sex at birth (dichotomous), education level (categorical: low, middle, high), smoking  
407 status (categorical: never, ex-smoker, current), comorbidities (self-administered comorbidity  
408 questionnaire, continuous), current or prior infection with tuberculosis (dichotomous), hepatitis B  
409 (dichotomous), and/or HIV (dichotomous), diagnosis (categorical: Crohn's disease, ulcerative colitis,  
410 unknown/indeterminate), disease duration in years (continuous), phenotype according to the  
411 Montreal classification (for Crohn's disease: age of onset, localisation, behaviour and for ulcerative  
412 colitis and IBD-U: extension, all categorical), presence of extra-intestinal manifestations (categorical:  
413 none, skin, joint, hepatobiliary, eye, other), and concomitant presence of primary sclerosing  
414 cholangitis (categorical). The secondary outcomes from the ICHOM Standard Set will be analysed on  
415 patient level with a (generalized) linear mixed model of the same form as described above.

416  
417 Cost-effectiveness

418 As the standard of care and the new care pathway will be analysed for a one-year period, this is also  
419 the time horizon for the CUA. No discounting of costs and effects will be applied to the one-year  
420 period. Costs will be determined by multiplying measured healthcare use and productivity loss with  
421 reference prices or cost estimates in line with recommendations of the National Health Care  
422 Institute.[46, 54] All costs will be transformed to the same year, adjusted for inflation using the  
423 consumer price index (CPI) if necessary. The friction cost method will be used to estimate  
424 productivity costs. A sensitivity analysis using the human capital approach will also be performed.

1  
2  
3 425  
4 426 To assess the cost-effectiveness of the care pathway compared to usual care, crude and adjusted  
5 427 differences in costs and quality of life in the before and after groups from the regression models will  
6 428 be used to estimate the incremental cost-effectiveness ratio (ICER). Robustness of results will be  
7 429 evaluated using probabilistic sensitivity analysis (PSA) using Monte Carlo simulation. For the PSA,  
8 430 non-parametric bootstrapping with 2,000 iterations will be used to determine uncertainty around the  
9 431 ICER. To support decision making, calculation of the net monetary/health benefits at the relevant  
10 432 willingness to pay levels, acceptability curves and Value of Information Analysis will be added.  
11 433

#### 12 434 Variation

13 435 To assess the variation in outcomes and costs between hospitals the intraclass correlation coefficient  
14 436 (ICC) will be used. The ICC is defined as:  
15 437

$$16 438 \quad ICC (Cluster) = \frac{\sigma_{\eta}^2}{\sigma_{\eta}^2 + \sigma_{\theta}^2 + \sigma_{\varepsilon}^2}$$

17 439  
18 440 which can be interpreted as the variance explained by the hospital as a proportion of the total  
19 441 variance. For the baseline period, data will be analysed using the aforementioned mixed effects  
20 442 models omitting the coefficient for the care pathway.  
21 443

22 444 To assess the effect of the care pathway on variation, data from the six hospitals that implemented  
23 445 the care pathway will be analysed for the two periods using the aforementioned mixed effects  
24 446 model, without the coefficient for the care pathway. This model will be compared with a model that  
25 447 estimates a random effect per hospital for the baseline period and the care pathway period  
26 448 separately. The effect of the care pathway on variation will then be formally tested using a  
27 449 likelihood-ratio test comparing the two models.  
28 450

#### 29 451 Patient and public involvement

30 452 Crohn & Colitis NL (Dutch Crohn's and Colitis Patient Organisation) collaborated in the design of this  
31 453 study. They critically revised the study design and helped in piloting the questionnaires. They will be  
32 454 involved in the working group that is responsible for the development of the care pathway.  
33 455

#### 34 456 ETHICS AND DISSEMINATION

35 457 The study was deemed to not be subject to the Wet medisch-wetenschappelijk onderzoek met  
36 458 mensen (WMO; Medical Research Involving Human Subjects Act) by the Medical Ethics Committee  
37 459 Erasmus MC, the Netherlands (registration number MEC-2020-075). The study is not subject to the  
38 460 Medical Research Involving Human Subjects Act as the implementation of the care pathway is a  
39 461 change in the local standard of care, patients aren't randomised to different treatment groups, and  
40 462 patients do not undergo invasive procedures for the study. Informed consent for questionnaires and  
41 463 chart review will be obtained by local investigators (online supplementary file 2). Data of all  
42 464 participating centres will be collected using electronic CRFs and entered in Castor EDC, an electronic  
43 465 database that is ISO27001 certified.[55] Data will be coded and handled based on the General Data  
44 466 Protection Regulation (GDPR). A data monitoring committee is not necessary as the intervention  
45 467 under study is a change in the standard of care.  
46 468

47 469 The principal investigators and study coordinator will have access to the final dataset. The dataset  
48 470 will be available on reasonable request. The study team is responsible for data analysis and  
49 471 reporting. Results will be fed back to participating centres and disseminated through peer-reviewed  
50 472 journals and presented at (inter)national conferences. The study team will make the decision to  
51 473 publish, and the funder and sponsor had and will have no influence on the research question, study  
52 474 design, data collection or analysis, or decision to publish.  
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60



## DISCUSSION

The IBD Value study aims to assess the effect of a care pathway for IBD patients treated with biologicals on health outcomes and cost-effectiveness as compared to current care. The study design is a longitudinal multicentre non-randomised parallel cluster trial with a baseline period. This design was chosen because the care pathway is an intervention on hospital level making a patient level study infeasible. A randomised cluster trial was logistically not possible as the care pathway will be developed by the six intervention hospitals and they can therefore not be blinded to the intervention. A randomised stepped wedge cluster trial would run into problems with contamination of the control period as the care pathway would need to be developed before the first clusters moved to the intervention group. This would lead to providers from the control cluster not being blinded to the intervention as they would be in the working group.

Strengths of this study are the baseline period and control group, as well as blinding of the control group. The baseline period and control group make it possible to control for time trends, such as a change in practice over time, when analysing the effect of the care pathway. By comparing the change in outcomes of the intervention group with the change in the control group, it is possible to distinguish the effect of the care pathway from time trends that impact outcomes or costs. A present-day example would be the impact of the COVID-19 pandemic on IBD healthcare.[56] Blinding of the control group to the intervention prevents contamination of the control group. If not blinded to the intervention, the control group could (subconsciously) change standard of care to incorporate the care pathway, and bias the effect of the care pathway towards the null.

The main weakness of our study design is the lack of randomisation. As hospitals are allocated to the intervention and control groups non-randomly there might be differences in confounders both on the cluster and patient level. Even though we correct for the average trend in outcomes or costs, there might be residual confounding because of systematic differences in hospitals between the intervention and control groups. Confounding at the patient level can occur because of differences in case-mix between the intervention and control group. To reduce bias, we will control for case-mix variables at the patient level as specified in the ICHOM IBD Standard Set.[25]

The main challenge of our study is implementation of and adherence to the intervention. To effectively implement the care pathway we will take several steps during the design and implementation phases.[57] First, the care pathway will be developed by a mixed group of stakeholders to ensure involvement of all hospitals and patients. Second, the care pathway was adjusted to the local context as to not disrupt local processes. Third, implementation of the care pathway in the participating hospitals will be done by the respective IBD specialists to ensure support from the rest of the medical staff. Fourth, the care pathway will be supported in the electronic health records to reduce burden on physicians and nurses. Last, adherence to the care pathway will be reported to the participating hospitals to evaluate implementation and detect potential barriers for implementation.

1  
2  
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5 517

6 518 **COMPETING INTERESTS STATEMENT**

7 519 Drs. van Linschoten has nothing to disclose.

8 520 Dr. van Leeuwen has nothing to disclose.

9 521 Drs. Nieboer has nothing to disclose.

10 522 Dr. Birnie has nothing to disclose

11 523 Drs. Scherpenzeel, MPM has nothing to disclose

12 524 Dr. de Jonge has nothing to disclose

13 525 Drs. Verweij has nothing to disclose

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16 528 Celltrion outside the submitted work.

17 529 Dr. van Noord reports personal fees from Janssen and Takeda outside the submitted work.

18 530 Dr. West reports personal fees from AbbVie, Janssen and Pfizer outside the submitted work.

19 531

20 532 **LEGEND**

21 533 Figure 1: Study Timeline

22 534

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30 542 *Author Contributions:* RCAvL, DvN, and RLW designed the study. NvL provided epidemiological

31 543 expertise, DN provided statistical expertise and EB provided expertise in economic evaluation during

32 544 the trial design. MS, CJvdW and JAH critically reviewed the study design. CJvdW, RLW, KEV, VdJ and

33 545 RCAvL participated in the design of the intervention. RCAvL drafted the manuscript and all authors

34 546 read, critically revised and approved the final manuscript. Principal investigators are DvN and RLW.

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42 554

43 555 **KEYWORDS**

44 556 Clinical trial; gastroenterology; inflammatory bowel disease; health economics; value-based

45 557 healthcare; health services research; care pathway;

46 558

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606 inflammatory bowel disease is increasing due to biologics and varies between continents.  
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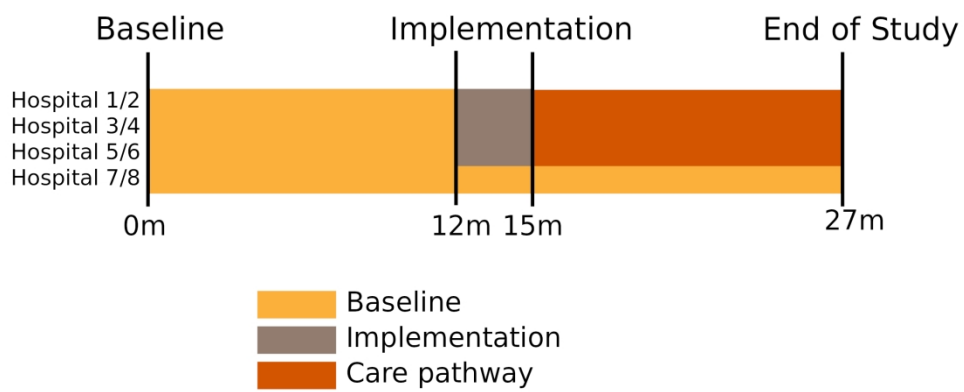


Figure 1: Study Timeline

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|    | Reporting Item  | Page Number  |         |
|----|---|--|---------|
| 1  |   |  |         |
| 2  |   |  |         |
| 3  |   |  |         |
| 4  | <b>Administrative</b>                                   |  |         |
| 5  | <b>information</b>                                      |  |         |
| 6  |   |  |         |
| 7  | Title   | <a href="#">#1</a> Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym  | 1       |
| 8  |   |  |         |
| 9  |   |  |         |
| 10 |   |  |         |
| 11 |   |  |         |
| 12 | Trial registration                                      | <a href="#">#2a</a> Trial identifier and registry name. If not yet registered, name of intended registry   | 2       |
| 13 |   |  |         |
| 14 |   |  |         |
| 15 |   |  |         |
| 16 | Trial registration: data set                            | <a href="#">#2b</a> All items from the World Health Organization Trial Registration Data Set   | 1 - 13  |
| 17 |   |  |         |
| 18 |   |  |         |
| 19 |   |  |         |
| 20 | Protocol version  | <a href="#">#3</a> Date and version identifier   | 4       |
| 21 |   |  |         |
| 22 | Funding   | <a href="#">#4</a> Sources and types of financial, material, and other support   | 13      |
| 23 |   |  |         |
| 24 |   |  |         |
| 25 |   |  |         |
| 26 | Roles and responsibilities: contributorship             | <a href="#">#5a</a> Names, affiliations, and roles of protocol contributors  | 13      |
| 27 |   |  |         |
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| 30 |   |  |         |
| 31 | Roles and responsibilities: sponsor contact information | <a href="#">#5b</a> Name and contact information for the trial sponsor   | 13      |
| 32 |   |  |         |
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| 38 | Roles and responsibilities: sponsor and funder          | <a href="#">#5c</a> 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 | 11      |
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| 48 | Roles and responsibilities: committees                  | <a href="#">#5d</a> 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)                         | 13 - 14 |
| 49 |   |  |         |
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| 58 | <b>Introduction</b>                                     |  |         |
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| 60 |   |  |         |



|    |                           |                      |  |       |
|----|---------------------------|----------------------|--|-------|
| 1  | Background and            | <a href="#">#6a</a>  | Description of research question and justification for   | 3     |
| 2  | rationale                 |                      | undertaking the trial, including summary of relevant     |       |
| 3  |                           |                      | studies (published and unpublished) examining            |       |
| 4  |                           |                      | benefits and harms for each intervention                 |       |
| 5  |                           |                      |  |       |
| 6  |                           |                      |  |       |
| 7  |                           |                      |  |       |
| 8  | Background and            | <a href="#">#6b</a>  | Explanation for choice of comparators                    | 6     |
| 9  | rationale: choice of      |                      |  |       |
| 10 | comparators               |                      |  |       |
| 11 |                           |                      |  |       |
| 12 |                           |                      |  |       |
| 13 | Objectives                | <a href="#">#7</a>   | Specific objectives or hypotheses                        | 4     |
| 14 |                           |                      |  |       |
| 15 | Trial design              | <a href="#">#8</a>   | Description of trial design including type of trial (eg, | 4     |
| 16 |                           |                      | parallel group, crossover, factorial, single group),     |       |
| 17 |                           |                      | allocation ratio, and framework (eg, superiority,        |       |
| 18 |                           |                      | equivalence, non-inferiority, exploratory)               |       |
| 19 |                           |                      |  |       |
| 20 |                           |                      |  |       |
| 21 |                           |                      |  |       |
| 22 | <b>Methods:</b>           |                      |  |       |
| 23 | <b>Participants,</b>      |                      |  |       |
| 24 | <b>interventions, and</b> |                      |  |       |
| 25 | <b>outcomes</b>           |                      |  |       |
| 26 |                           |                      |  |       |
| 27 |                           |                      |  |       |
| 28 |                           |                      |  |       |
| 29 | Study setting             | <a href="#">#9</a>   | Description of study settings (eg, community clinic,     | 4     |
| 30 |                           |                      | academic hospital) and list of countries where data      |       |
| 31 |                           |                      | will be collected. Reference to where list of study      |       |
| 32 |                           |                      | sites can be obtained                                    |       |
| 33 |                           |                      |  |       |
| 34 |                           |                      |  |       |
| 35 |                           |                      |  |       |
| 36 | Eligibility criteria      | <a href="#">#10</a>  | Inclusion and exclusion criteria for participants. If    | 4 - 5 |
| 37 |                           |                      | applicable, eligibility criteria for study centres and   |       |
| 38 |                           |                      | individuals who will perform the interventions (eg,      |       |
| 39 |                           |                      | surgeons, psychotherapists)                              |       |
| 40 |                           |                      |  |       |
| 41 |                           |                      |  |       |
| 42 |                           |                      |  |       |
| 43 | Interventions:            | <a href="#">#11a</a> | Interventions for each group with sufficient detail to   | 5 - 6 |
| 44 | description               |                      | allow replication, including how and when they will      |       |
| 45 |                           |                      | be administered  |       |
| 46 |                           |                      |  |       |
| 47 |                           |                      |  |       |
| 48 | Interventions:            | <a href="#">#11b</a> | Criteria for discontinuing or modifying allocated        | NA    |
| 49 | modifications             |                      | interventions for a given trial participant (eg, drug    |       |
| 50 |                           |                      | dose change in response to harms, participant            |       |
| 51 |                           |                      | request, or improving / worsening disease)               |       |
| 52 |                           |                      |  |       |
| 53 |                           |                      |  |       |
| 54 |                           |                      |  |       |
| 55 | Interventions:            | <a href="#">#11c</a> | Strategies to improve adherence to intervention          | 6     |
| 56 | adherence                 |                      | protocols, and any procedures for monitoring             |       |
| 57 |                           |                      | adherence (eg, drug tablet return; laboratory tests)     |       |
| 58 |                           |                      |  |       |
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|----|---------------------------|----------------------|--|--------|
| 1  | Interventions:            | <a href="#">#11d</a> | Relevant concomitant care and interventions that         | NA     |
| 2  | concomitant care          |                      | are permitted or prohibited during the trial             |        |
| 3  |                           |                      |  |        |
| 4  | Outcomes                  | <a href="#">#12</a>  | Primary, secondary, and other outcomes, including        | 6 - 8  |
| 5  |                           |                      | the specific measurement variable (eg, systolic          |        |
| 6  |                           |                      | blood pressure), analysis metric (eg, change from        |        |
| 7  |                           |                      | baseline, final value, time to event), method of         |        |
| 8  |                           |                      | aggregation (eg, median, proportion), and time point     |        |
| 9  |                           |                      | for each outcome. Explanation of the clinical            |        |
| 10 |                           |                      | relevance of chosen efficacy and harm outcomes is        |        |
| 11 |                           |                      | strongly recommended                                     |        |
| 12 |                           |                      |  |        |
| 13 | Participant timeline      | <a href="#">#13</a>  | Time schedule of enrolment, interventions (including     | 8 - 9  |
| 14 |                           |                      | any run-ins and washouts), assessments, and visits       |        |
| 15 |                           |                      | for participants. A schematic diagram is highly          |        |
| 16 |                           |                      | recommended (see Figure)                                 |        |
| 17 |                           |                      |  |        |
| 18 | Sample size               | <a href="#">#14</a>  | Estimated number of participants needed to achieve       | 9 - 10 |
| 19 |                           |                      | study objectives and how it was determined,              |        |
| 20 |                           |                      | including clinical and statistical assumptions           |        |
| 21 |                           |                      | supporting any sample size calculations                  |        |
| 22 |                           |                      |  |        |
| 23 |                           |                      |  |        |
| 24 | Recruitment               | <a href="#">#15</a>  | Strategies for achieving adequate participant            | 10     |
| 25 |                           |                      | enrolment to reach target sample size                    |        |
| 26 |                           |                      |  |        |
| 27 |                           |                      |  |        |
| 28 |                           |                      |  |        |
| 29 |                           |                      |  |        |
| 30 |                           |                      |  |        |
| 31 | <b>Methods:</b>           |                      |  |        |
| 32 | <b>Assignment of</b>      |                      |  |        |
| 33 | <b>interventions (for</b> |                      |  |        |
| 34 | <b>controlled trials)</b> |                      |  |        |
| 35 |                           |                      |  |        |
| 36 | Allocation: sequence      | <a href="#">#16a</a> | Method of generating the allocation sequence (eg,        | 4      |
| 37 | generation                |                      | computer-generated random numbers), and list of          |        |
| 38 |                           |                      | any factors for stratification. To reduce predictability |        |
| 39 |                           |                      | of a random sequence, details of any planned             |        |
| 40 |                           |                      | restriction (eg, blocking) should be provided in a       |        |
| 41 |                           |                      | separate document that is unavailable to those who       |        |
| 42 |                           |                      | enrol participants or assign interventions               |        |
| 43 |                           |                      |  |        |
| 44 |                           |                      |  |        |
| 45 |                           |                      |  |        |
| 46 |                           |                      |  |        |
| 47 |                           |                      |  |        |
| 48 |                           |                      |  |        |
| 49 |                           |                      |  |        |
| 50 |                           |                      |  |        |
| 51 |                           |                      |  |        |
| 52 |                           |                      |  |        |
| 53 | Allocation                | <a href="#">#16b</a> | Mechanism of implementing the allocation sequence        | NA     |
| 54 | concealment               |                      | (eg, central telephone; sequentially numbered,           |        |
| 55 | mechanism                 |                      | opaque, sealed envelopes), describing any steps to       |        |
| 56 |                           |                      | conceal the sequence until interventions are             |        |
| 57 |                           |                      |  |        |
| 58 |                           |                      |  |        |
| 59 |                           |                      |  |        |
| 60 |                           |                      |  |        |

assigned

|    |                        |                      |   |
|----|------------------------|----------------------|---|
| 1  |                        |                      |   |
| 2  |                        |                      |   |
| 3  | Allocation:            | <a href="#">#16c</a> | Who will generate the allocation sequence, who will       |
| 4  | implementation         |                      | enrol participants, and who will assign participants to   |
| 5  |                        |                      | interventions   |
| 6  |                        |                      |   |
| 7  |                        |                      |   |
| 8  | Blinding (masking)     | <a href="#">#17a</a> | Who will be blinded after assignment to interventions     |
| 9  |                        |                      | (eg, trial participants, care providers, outcome          |
| 10 |                        |                      | assessors, data analysts), and how                        |
| 11 |                        |                      |   |
| 12 |                        |                      |   |
| 13 | Blinding (masking):    | <a href="#">#17b</a> | If blinded, circumstances under which unblinding is       |
| 14 | emergency              |                      | permissible, and procedure for revealing a                |
| 15 | unblinding             |                      | participant's allocated intervention during the trial     |
| 16 |                        |                      |   |
| 17 |                        |                      |   |
| 18 | <b>Methods: Data</b>   |                      |   |
| 19 | <b>collection,</b>     |                      |   |
| 20 | <b>management, and</b> |                      |   |
| 21 | <b>analysis</b>        |                      |   |
| 22 |                        |                      |   |
| 23 |                        |                      |   |
| 24 |                        |                      |   |
| 25 | Data collection plan   | <a href="#">#18a</a> | Plans for assessment and collection of outcome,           |
| 26 |                        |                      | baseline, and other trial data, including any related     |
| 27 |                        |                      | processes to promote data quality (eg, duplicate          |
| 28 |                        |                      | measurements, training of assessors) and a                |
| 29 |                        |                      | description of study instruments (eg, questionnaires,     |
| 30 |                        |                      | laboratory tests) along with their reliability and        |
| 31 |                        |                      | validity, if known. Reference to where data collection    |
| 32 |                        |                      | forms can be found, if not in the protocol                |
| 33 |                        |                      |   |
| 34 |                        |                      |   |
| 35 |                        |                      |   |
| 36 |                        |                      |   |
| 37 |                        |                      |   |
| 38 | Data collection plan:  | <a href="#">#18b</a> | Plans to promote participant retention and complete       |
| 39 | retention              |                      | follow-up, including list of any outcome data to be       |
| 40 |                        |                      | collected for participants who discontinue or deviate     |
| 41 |                        |                      | from intervention protocols                               |
| 42 |                        |                      |   |
| 43 |                        |                      |   |
| 44 |                        |                      |   |
| 45 | Data management        | <a href="#">#19</a>  | Plans for data entry, coding, security, and storage,      |
| 46 |                        |                      | including any related processes to promote data           |
| 47 |                        |                      | quality (eg, double data entry; range checks for data     |
| 48 |                        |                      | values). Reference to where details of data               |
| 49 |                        |                      | management procedures can be found, if not in the         |
| 50 |                        |                      | protocol  |
| 51 |                        |                      |   |
| 52 |                        |                      |   |
| 53 |                        |                      |   |
| 54 |                        |                      |   |
| 55 | Statistics: outcomes   | <a href="#">#20a</a> | Statistical methods for analysing primary and             |
| 56 |                        |                      | secondary outcomes. Reference to where other              |
| 57 |                        |                      | details of the statistical analysis plan can be found, if |
| 58 |                        |                      |   |
| 59 |                        |                      |   |
| 60 |                        |                      |   |

not in the protocol

|    |                        |  |        |
|----|------------------------|--|--------|
| 1  |                        |  |        |
| 2  |                        |  |        |
| 3  | Statistics: additional | <a href="#">#20b</a>                                     | 9 - 10 |
| 4  | analyses               | Methods for any additional analyses (eg, subgroup        |        |
| 5  |                        | and adjusted analyses)                                   |        |
| 6  | Statistics: analysis   | <a href="#">#20c</a>                                     | 9 - 10 |
| 7  | population and         | Definition of analysis population relating to protocol   |        |
| 8  | missing data           | non-adherence (eg, as randomised analysis), and          |        |
| 9  |                        | any statistical methods to handle missing data (eg,      |        |
| 10 |                        | multiple imputation)                                     |        |
| 11 |                        |  |        |
| 12 |                        |  |        |
| 13 | <b>Methods:</b>        |  |        |
| 14 | <b>Monitoring</b>      |  |        |
| 15 |                        |  |        |
| 16 |                        |  |        |
| 17 | Data monitoring:       | <a href="#">#21a</a>                                     | 12     |
| 18 | formal committee       | Composition of data monitoring committee (DMC);          |        |
| 19 |                        | summary of its role and reporting structure;             |        |
| 20 |                        | statement of whether it is independent from the          |        |
| 21 |                        | sponsor and competing interests; and reference to        |        |
| 22 |                        | where further details about its charter can be found,    |        |
| 23 |                        | if not in the protocol. Alternatively, an explanation of |        |
| 24 |                        | why a DMC is not needed                                  |        |
| 25 |                        |  |        |
| 26 |                        |  |        |
| 27 |                        |  |        |
| 28 | Data monitoring:       | <a href="#">#21b</a>                                     | NA     |
| 29 | interim analysis       | Description of any interim analyses and stopping         |        |
| 30 |                        | guidelines, including who will have access to these      |        |
| 31 |                        | interim results and make the final decision to           |        |
| 32 |                        | terminate the trial                                      |        |
| 33 |                        |  |        |
| 34 |                        |  |        |
| 35 | Harms                  | <a href="#">#22</a>                                      | NA     |
| 36 |                        | Plans for collecting, assessing, reporting, and          |        |
| 37 |                        | managing solicited and spontaneously reported            |        |
| 38 |                        | adverse events and other unintended effects of trial     |        |
| 39 |                        | interventions or trial conduct                           |        |
| 40 |                        |  |        |
| 41 |                        |  |        |
| 42 | Auditing               | <a href="#">#23</a>                                      | NA     |
| 43 |                        | Frequency and procedures for auditing trial conduct,     |        |
| 44 |                        | if any, and whether the process will be independent      |        |
| 45 |                        | from investigators and the sponsor                       |        |
| 46 |                        |  |        |
| 47 | <b>Ethics and</b>      |  |        |
| 48 | <b>dissemination</b>   |  |        |
| 49 |                        |  |        |
| 50 |                        |  |        |
| 51 | Research ethics        | <a href="#">#24</a>                                      | 11     |
| 52 | approval               | Plans for seeking research ethics committee /            |        |
| 53 |                        | institutional review board (REC / IRB) approval          |        |
| 54 |                        |  |        |
| 55 | Protocol               | <a href="#">#25</a>                                      | 4, 11  |
| 56 | amendments             | Plans for communicating important protocol               |        |
| 57 |                        | modifications (eg, changes to eligibility criteria,      |        |
| 58 |                        | outcomes, analyses) to relevant parties (eg,             |        |
| 59 |                        |  |        |
| 60 |                        |  |        |

|    |                       |  |               |
|----|-----------------------|--|---------------|
| 1  |                       | investigators, REC / IRBs, trial participants, trial                       |               |
| 2  |                       | registries, journals, regulators)  |               |
| 3  |                       |  |               |
| 4  | Consent or assent     | <a href="#">#26a</a> Who will obtain informed consent or assent from       | 9             |
| 5  |                       | potential trial participants or authorised surrogates,                     |               |
| 6  |                       | and how (see Item 32)  |               |
| 7  |                       |  |               |
| 8  |                       |  |               |
| 9  | Consent or assent:    | <a href="#">#26b</a> Additional consent provisions for collection and use  | NA            |
| 10 | ancillary studies     | of participant data and biological specimens in                            |               |
| 11 |                       | ancillary studies, if applicable   |               |
| 12 |                       |  |               |
| 13 |                       |  |               |
| 14 | Confidentiality       | <a href="#">#27</a> How personal information about potential and           | 9, 11         |
| 15 |                       | enrolled participants will be collected, shared, and                       |               |
| 16 |                       | maintained in order to protect confidentiality before,                     |               |
| 17 |                       | during, and after the trial  |               |
| 18 |                       |  |               |
| 19 |                       |  |               |
| 20 |                       |  |               |
| 21 | Declaration of        | <a href="#">#28</a> Financial and other competing interests for principal  | 13            |
| 22 | interests             | investigators for the overall trial and each study site                    |               |
| 23 |                       |  |               |
| 24 |                       |  |               |
| 25 | Data access           | <a href="#">#29</a> Statement of who will have access to the final trial   | 11            |
| 26 |                       | dataset, and disclosure of contractual agreements                          |               |
| 27 |                       | that limit such access for investigators                                   |               |
| 28 |                       |  |               |
| 29 |                       |  |               |
| 30 | Ancillary and post    | <a href="#">#30</a> Provisions, if any, for ancillary and post-trial care, | NA            |
| 31 | trial care            | and for compensation to those who suffer harm from                         |               |
| 32 |                       | trial participation  |               |
| 33 |                       |  |               |
| 34 |                       |  |               |
| 35 |                       |  |               |
| 36 | Dissemination policy: | <a href="#">#31a</a> Plans for investigators and sponsor to communicate    | 11            |
| 37 | trial results         | trial results to participants, healthcare professionals,                   |               |
| 38 |                       | the public, and other relevant groups (eg, via                             |               |
| 39 |                       | publication, reporting in results databases, or other                      |               |
| 40 |                       | data sharing arrangements), including any                                  |               |
| 41 |                       | publication restrictions   |               |
| 42 |                       |  |               |
| 43 |                       |  |               |
| 44 |                       |  |               |
| 45 | Dissemination policy: | <a href="#">#31b</a> Authorship eligibility guidelines and any intended    | NA            |
| 46 | authorship            | use of professional writers  |               |
| 47 |                       |  |               |
| 48 |                       |  |               |
| 49 | Dissemination policy: | <a href="#">#31c</a> Plans, if any, for granting public access to the full | 11            |
| 50 | reproducible          | protocol, participant-level dataset, and statistical                       |               |
| 51 | research              | code   |               |
| 52 |                       |  |               |
| 53 |                       |  |               |
| 54 |                       |  |               |
| 55 | <b>Appendices</b>     |  |               |
| 56 |                       |  |               |
| 57 | Informed consent      | <a href="#">#32</a> Model consent form and other related                   | Supplementary |
| 58 | materials             | documentation given to participants and authorised                         | file 2        |
| 59 |                       |  |               |
| 60 |                       |  |               |

surrogates

1  
2  
3 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

NA

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For peer review only

# Informatie voor deelname aan medisch-wetenschappelijk onderzoek

## Verbeteren van de zorg voor mensen met een chronische darmontsteking

*Officiële titel: Waardegedreven zorg voor inflammatoire darmziekten: het verbeteren van (kosten-)effectiviteit*

### Inleiding

Geachte heer/mevrouw,

U ontvangt deze brief omdat u een chronische darmontsteking (ziekte van Crohn of colitis ulcerosa) heeft en gaat starten met een behandeling met krachtige ontstekingsremmers (biological) of deze al gebruikt. Wij vragen u om mee te doen aan een medisch-wetenschappelijk onderzoek. Dit onderzoek gaat over de verbetering van de zorg voor mensen met een chronische darmontsteking. Meedoen is vrijwillig. Om mee te doen, hebben wij wel uw schriftelijke toestemming nodig.

Voordat u beslist of u wilt meedoen aan dit onderzoek, krijgt u uitleg over wat het onderzoek inhoudt. Lees deze informatie rustig door en vraag de onderzoeker om uitleg als u vragen heeft. U kunt ook de onafhankelijk deskundige, die aan het eind van deze brief genoemd wordt, om aanvullende informatie vragen. U kunt er ook over praten met uw partner, vrienden of familie.

### 1. Achtergrond van het onderzoek

Mensen met een chronische darmontsteking kunnen veel klachten hebben en moeten soms dure ontstekingsremmende medicijnen gebruiken. Er wordt steeds meer onderzoek gedaan naar chronische darmontsteking. Ook komen er steeds meer medicijnen om chronische darmontsteking te behandelen. Door de nieuwe informatie en behandelingen wordt de zorg voor chronische darmontsteking ingewikkelder. Daarom werken MDL-artsen in het Zuidwesten van Nederland samen om de zorg te verbeteren. Er wordt een zorgpad ontwikkeld, zodat iedereen op een vergelijkbare manier wordt behandeld in de regio. Een zorgpad is een stappenplan, met daarin praktische adviezen over keuzes tijdens de behandeling van chronische darmontsteking.

### 2. Doel van het onderzoek

Het doel van het onderzoek is om de zorg te verbeteren voor mensen met een chronische darmontsteking die sterke ontstekingsremmers krijgen. Door gegevens te verzamelen over de uitkomsten van uw behandeling kunnen wij kijken wat er goed gaat, en wat er beter kan.

Daarnaast kijken wij ook naar de kosten van de behandeling, en de kosten die u zelf maakt. Wij hopen met dit onderzoek de kwaliteit van zorg te verbeteren en de kosten te reduceren.

### 3. Wat meedoen inhoudt

Meedoen houdt in dat u tot maart 2023 vragenlijsten invult over de zorg die u krijgt. U krijgt dezelfde behandeling als normaal. De ziekenhuizen zijn ingedeeld in twee groepen, een groep ziekenhuizen die volgens het nieuwe zorgpad werkt en een groep ziekenhuizen die dit niet doet. Door deze twee groepen te vergelijken kunnen we kijken of het zorgpad ook echt beter is dan de huidige situatie.

Door de COVID-19 pandemie kan het gebeuren dat de start van deze studie moet worden uitgesteld. Als de start wordt uitgesteld begint u later met het invullen van vragenlijsten. In dat geval loopt de studie langer door en vragen wij u ook om door te gaan met het invullen van de vragenlijsten. Mocht dit het geval zijn, dan laten wij u dat weten.

#### Anders dan bij gebruikelijke zorg

Als u meedoet met het onderzoek wordt u niet anders behandeld dan normaal. Eerst willen wij de zorg die u nu krijgt evalueren. Daarom vragen wij u om vragenlijsten in te vullen. In december 2021 zal het zorgpad geïntroduceerd worden. Dit is voor alle patiënten, dus ook als u niet meedoet aan het onderzoek. Dit kan bijvoorbeeld betekenen dat de MDL-artsen afspreken dat u vaker, of minder vaak op de polikliniek moet komen. Wij willen dan kijken of deze verandering beter is.

#### Vragenlijsten

Voor dit onderzoek willen wij u vragen om enkele vragenlijsten in te vullen.

- Aan het begin van het onderzoek, en elk jaar krijgt u een vragenlijst opgestuurd via de e-mail om te kijken naar uw persoonlijke omstandigheden, de aanwezigheid van andere ziekten en uw leefstijl. Het invullen kost u ongeveer 5 minuten.
- U krijgt elke drie maanden een vragenlijst toegestuurd via de e-mail. Deze vragen gaan over hoe de ziekte uw werk beïnvloedt, en de (zorg)kosten die u maakt door uw ziekte. Het invullen kost u ongeveer 5 minuten.
- Daarnaast krijgt u elke 6 maanden een vragenlijst toegestuurd via de mail om de invloed van de ziekte op uw leven en uw kwaliteit van leven te meten. Het invullen kost u ongeveer 10 minuten.

Daarnaast zullen wij ook aan uw behandelend specialist gegevens vragen over de uitkomsten van uw behandeling. Dit gaat bijvoorbeeld over het verloop van uw ziekte, en welke medicijnen u gebruikt.

### 4. Afspraken

Om het onderzoek goed te laten verlopen, is het belangrijk dat u de vragenlijsten invult volgens de uitleg.



Het is belangrijk dat u contact opneemt met de onderzoeker:

- als u niet meer wilt meedoen aan het onderzoek.
- als uw contactgegevens wijzigen.

## 5. Mogelijke voor- en nadelen

Het is belangrijk dat u de mogelijke voor- en nadelen goed afweegt voordat u besluit mee te doen. Als u meedoet aan dit onderzoek betekent het niet dat u minder last krijgt van uw ziekte. Maar u draagt wel bij aan meer kennis over de behandeling van chronische darmziekten, en aan de verbetering hiervan. Een nadeel van het meedoen aan het onderzoek kan zijn dat het invullen van de vragenlijsten u tijd kost.

## 6. Als u niet wilt meedoen of wilt stoppen met het onderzoek

U beslist zelf of u meedoet aan het onderzoek. Deelname is vrijwillig. Als u niet wilt meedoen, wordt u op de gebruikelijke manier behandeld voor uw chronische darmziekte. Dit is niet anders dan als u wel mee zou doen met het onderzoek.

Als u wel meedoet, kunt u zich altijd bedenken en toch stoppen, ook tijdens het onderzoek. U wordt dan op dezelfde manier behandeld voor uw chronische darmziekte. U hoeft niet te zeggen waarom u stopt. Wel moet u dit direct melden aan de onderzoeker. De gegevens die tot dat moment zijn verzameld, worden gebruikt voor het onderzoek.

Als er nieuwe informatie over het onderzoek is die belangrijk voor u is, laat de onderzoeker dit aan u weten. U wordt dan gevraagd of u blijft meedoen.

## 7. Algemene informatie

Dit onderzoek is opgezet door het Franciscus Gasthuis & Vlietland en wordt gedaan door artsen in verschillende ziekenhuizen in de regio Rotterdam. Voor dit onderzoek worden alle patiënten benaderd die in de regio Rotterdam behandeld worden met een sterke ontstekingsremmer voor een chronische darmontsteking.

De studie is aangemeld bij de medisch-ethische toetsingscommissie (METC) Erasmus MC die heeft bepaald dat deze studie niet valt onder de wet medische wetenschappelijk onderzoek met mensen. Dat betekent dat deze studie niet door de METC goedgekeurd hoeft te worden.

## 8. Einde van het onderzoek

Uw deelname aan het onderzoek stopt als

- alle vragenlijsten ingevuld zijn
- u zelf kiest om te stoppen
- de onderzoeker het beter voor u vindt om te stoppen
- het Franciscus Gasthuis & Vlietland of de overheid besluit om het onderzoek te stoppen.

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4  
5 Het hele onderzoek is afgelopen als alle deelnemers klaar zijn. Na het verwerken van alle  
6 gegevens informeert de onderzoeker u over de belangrijkste uitkomsten van het onderzoek.  
7 Dit gebeurt ongeveer 6 maanden na uw deelname. Als u dit niet wilt, dan kunt u dit tegen de  
8 onderzoeker zeggen. Hij mag het u dan niet vertellen.  
9

## 10 11 12 **9. Gebruik en bewaren van uw gegevens**

13 Voor dit onderzoek worden uw persoonsgegevens verzameld, gebruikt en bewaard. Het gaat  
14 om gegevens zoals uw naam, geboortjaar en om gegevens over uw gezondheid. Het  
15 verzamelen, gebruiken en bewaren van uw gegevens is nodig om de vragen die in dit  
16 onderzoek worden gesteld te kunnen beantwoorden en de resultaten te kunnen publiceren.  
17 Wij vragen voor het gebruik van uw gegevens uw toestemming.  
18  
19

### 20 21 **Vertrouwelijkheid van uw gegevens**

22 Om uw privacy te beschermen krijgen uw gegevens een code. Uw naam en andere  
23 gegevens die u direct kunnen identificeren worden daarbij weggelaten. Alleen met de sleutel  
24 van de code zijn gegevens tot u te herleiden. De sleutel van de code blijft veilig opgeborgen  
25 in de lokale onderzoeksinstelling. De gegevens die naar de opdrachtgever worden gestuurd,  
26 bevatten alleen de code en uw e-mailadres om de vragenlijsten te versturen, maar niet uw  
27 naam of andere gegevens waarmee u kunt worden geïdentificeerd. Ook in rapporten en  
28 publicaties over het onderzoek zijn de gegevens niet tot u te herleiden.  
29  
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31

### 32 33 **Toegang tot uw gegevens voor controle**

34 Sommige personen kunnen op de onderzoekslocatie toegang krijgen tot al uw gegevens.  
35 Ook tot de gegevens zonder code. Dit is nodig om te kunnen controleren of het onderzoek  
36 goed en betrouwbaar is uitgevoerd. Personen die ter controle inzage krijgen in uw gegevens  
37 zijn: onderzoekers en studenten die hen hierbij assisteren, een monitor die voor de  
38 opdrachtgever van het onderzoek werkt, en nationale en internationale toezichthoudende  
39 autoriteiten, bijvoorbeeld, de Inspectie Gezondheidszorg en Jeugd. Zij houden uw gegevens  
40 geheim. Wij vragen u voor deze inzage toestemming te geven.  
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### 45 46 **Bewaren en gebruik van gegevens**

47 Uw gegevens moeten 15 jaar worden bewaard op de onderzoekslocatie en 15 jaar bij de  
48 opdrachtgever. Uw gegevens kunnen na afloop van dit onderzoek ook nog van belang zijn  
49 voor ander wetenschappelijk onderzoek op het gebied van chronische darmontsteking. U  
50 kunt op het toestemmingsformulier aangeven of u hier wel of niet mee instemt. Indien u hier  
51 niet mee instemt, kunt u gewoon deelnemen aan het huidige onderzoek. Uw bewaarde  
52 gegevens zullen dan niet gebruikt worden voor ander wetenschappelijk onderzoek.  
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### 56 57 **Intrekken toestemming**

58 U kunt uw toestemming voor gebruik van uw persoonsgegevens altijd weer intrekken. Dit  
59 geldt voor dit onderzoek en ook voor het bewaren en het gebruik voor het toekomstige  
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4 onderzoek. De onderzoeksgegevens die zijn verzameld tot het moment dat u uw  
5 toestemming intrekt, worden nog wel gebruikt in het onderzoek.  
6  
7

### 8 **Meer informatie over uw rechten bij verwerking van gegevens**

9 Voor algemene informatie over uw rechten bij verwerking van uw persoonsgegevens kunt u  
10 de website van de Autoriteit Persoonsgegevens raadplegen. Bij vragen over uw rechten kunt  
11 u contact opnemen met de verantwoordelijke voor de verwerking van uw persoonsgegevens.  
12 Voor dit onderzoek is dat: het Franciscus Gasthuis & Vlietland. Zie bijlage A voor  
13 contactgegevens en website.  
14  
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16

17 Bij vragen of klachten over de verwerking van uw persoonsgegevens raden we u aan eerst  
18 contact op te nemen met de onderzoekslocatie. U kunt ook contact opnemen met de  
19 Functionaris voor de Gegevensbescherming van de instelling (zie bijlage A) of de Autoriteit  
20 Persoonsgegevens.  
21  
22

### 23 **Registratie van het onderzoek**

24 Informatie over dit onderzoek is ook opgenomen in een overzicht van medisch-  
25 wetenschappelijke onderzoeken namelijk (<https://www.trialregister.nl/trial/8276>). Daarin zijn  
26 geen gegevens opgenomen die naar u herleidbaar zijn. Na het onderzoek kan de website  
27 een samenvatting van de resultaten van dit onderzoek tonen.  
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## 32 **10. Geen vergoeding voor meedoen**

33 Het meedoen aan het onderzoek kost u niets. U wordt niet betaald voor het meedoen aan dit  
34 onderzoek.  
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## 38 **11. Heeft u vragen?**

39 Bij vragen kunt u contact opnemen met de onderzoeker. Voor onafhankelijk advies over  
40 meedoen aan dit onderzoek kunt u terecht bij de onafhankelijke arts. Hij weet veel over het  
41 onderzoek, maar heeft niets te maken met dit onderzoek.  
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45 Indien u klachten heeft over het onderzoek, kunt u dit bespreken met de onderzoeker of uw  
46 behandelend arts. Wilt u dit liever niet, dan kunt u zich wenden tot de klachtenfunctionaris of  
47 klachtencommissie van het Franciscus Gasthuis & Vlietland. Alle gegevens vindt u in bijlage  
48 A: Contactgegevens.  
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## 52 **12. Ondertekening toestemmingsformulier**

53 Indien u besluit mee te doen met dit onderzoek, vragen wij u dit op de bijbehorende  
54 toestemmingsverklaring schriftelijk te bevestigen. Door uw schriftelijke toestemming geeft u  
55 aan dat u de informatie heeft begrepen en instemt met deelname aan het onderzoek. Zowel  
56 uzelf als de onderzoeker ontvangen een getekende versie van deze toestemmingsverklaring.  
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Dank voor uw aandacht.

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**13. Bijlagen bij deze informatie**

- A. Contactgegevens
- B. Toestemmingsformulier(en)

For peer review only

## Bijlage A: contactgegevens voor Franciscus Gasthuis & Vlietland

Als u nog vragen heeft over dit onderzoek, neem dan contact op met de onderzoeksarts of zijn of haar onderzoeksmedewerkers:

- de hoofdonderzoekers: dr. D. Leemreis-van Noord en dr. R.L. West, 010-4616161
- de coördinerend onderzoeker: drs. R.C.A. van Linschoten, 010-4617838
- de onafhankelijk arts: Dr. G.J. Braunstahl, 010-4616161
- Buiten kantooruren kunt u met het algemene nummer van het ziekenhuis bellen:
  - Franciscus Gasthuis: 010-461 61 61
  - Franciscus Vlietland: 010-893 93 93

en vragen naar de dienstdoend arts van de Maag-, Darm-, en Leverziekten.

### Cliëntvertrouwenspersoon:

Deze studie wordt uitgevoerd met toestemming van de Raad van Bestuur van dit ziekenhuis. Het *Franciscus Gasthuis & Vlietland* vindt het belangrijk dat patiënten, proefpersonen en bezoekers tevreden zijn. Toch kan het gebeuren dat u niet tevreden bent en een klacht wilt indienen. In dat geval kunt u het beste eerst praten met de onderzoeksarts of uw behandelend arts. Als u dat liever niet doet, kunt u ook contact opnemen met de cliëntvertrouwenspersoon van het ziekenhuis. Dit kan zowel telefonisch als door het invullen van het online klachtenformulier.

Contact met de cliëntvertrouwenspersoon voor compliment, suggestie of klacht:

### **Franciscus Gasthuis en Franciscus Berkel**

Telefoonnummer: 010 – 461 6701

### **Franciscus Vlietland, Franciscus Haven, Franciscus Hoogvliet en Franciscus Maassluis**

Telefoonnummer: 010 – 893 4125

Digitaal via [www.franciscus.nl/klacht](http://www.franciscus.nl/klacht) (voor alle locaties)

### **Functionaris Gegevensbescherming (alle locaties):**

Mw. L. Pollinger

E-mail: [fg@franciscus.nl](mailto:fg@franciscus.nl)

Telefoonnummer: 010-4616898

## Bijlage B: toestemmingsformulier deelnemer

### Waardegedreven zorg voor inflammatoire darmziekten: IBD Value

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn voldoende beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen of te stoppen met het onderzoek. Daarvoor hoef ik geen reden te geven.
- Ik geef toestemming om, in het geval ik tijdens de looptijd van het onderzoek zou komen te overlijden, mijn officiële doodsoorzaakgegevens op te vragen bij het Centraal Bureau voor de Statistiek.
- Ik geef toestemming voor het opvragen van informatie bij mijn specialist(en) die mij behandelt over de uitkomsten van de behandeling van mijn chronische darmontsteking.
- Ik geef toestemming voor het verzamelen en gebruiken van mijn gegevens voor de beantwoording van de onderzoeksvraag in dit onderzoek.
- Ik weet dat voor de controle van het onderzoek sommige mensen toegang tot al mijn gegevens kunnen krijgen. Die mensen staan vermeld in deze informatiebrief. Ik geef toestemming voor die inzage door deze personen.
- Ik geef toestemming om mijn e-mailadres aan het onderzoeksteam door te geven, zodat de vragenlijsten naar mij verstuurd kunnen worden.
- Ik geef  **wel**  **geen**  
toestemming om mijn persoonsgegevens langer te bewaren en te gebruiken voor toekomstig onderzoek op het gebied van chronische darmontsteking.
- Ik geef  **wel**  **geen**  
toestemming om mij na dit onderzoek opnieuw te benaderen voor een vervolgonderzoek.
- Ik wil  **wel**  **niet**  
geïnformeerd worden over de uitkomsten van dit onderzoek.
- Ik wil meedoen aan dit onderzoek.

Naam deelnemer:

E-mailadres:

Handtekening:

Datum : \_\_ / \_\_ / \_\_

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*De deelnemer krijgt een volledige informatiebrief mee.*