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

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ABSTRACT

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

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

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

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

STRENGTH AND LIMITATIONS OF THIS STUDY

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

INTRODUCTION

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

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

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

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

Implementing a care pathway in clinical practice seems promising for improving value, which was illustrated by a retrospective pilot study that evaluated a care pathway for IBD in a VBHC program. This care pathway showed a favourable effect on flares (-26%) and costs (-16%).[27] Other studies supported the effect of a care pathway for IBD on costs and also showed an improvement of care processes.[28, 29]. In other diseases the implementation of a care pathway was also accompanied by reduced variation.[30] Although these studies showed a promising effect on outcomes and processes, they suffered from low sample sizes, retrospective study designs and lacked patient-centred outcome measures. With the prospective multicentre IBD Value study we aim to assess the 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 2nd 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

- Have an IBD diagnosis of at least three months
- Treated with one of the currently registered biologics or small molecules for IBD treatment or new treatments registered during the study period, including: infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, or tofacitinib.

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

Intervention

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

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

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

The care pathway is a decision-making tool for care providers and patients, and presents treatment guidelines in a simple and interpretable format. It sets out the most appropriate steps in patient management at each therapy stage. Decision trees will be designed to give visual support to the care pathway. Because the treatment of IBD is rapidly changing and studies regularly provide new insights, the care pathway will be updated in IBD BeterKeten meetings after study closure. IBD specialists from IBD BeterKeten will safeguard implementation of the care pathway in their respective centres. They will be supported by a presentation of the working group to the care providers, educational tools and implementation and automatization of the care pathway in the electronic health records.

Comparison

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

Outcome

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

The other outcomes from the standard set are secondary outcomes:

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

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

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

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[45]
- Smoking status

- Diagnosis (Crohn's disease, ulcerative colitis, indeterminate)
- Year of diagnosis
- Disease phenotype according to the Montreal classification[46]
- 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 [47]
- 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 Table 1 and 2). 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 1: Timing of questionnaires for patient included at or before T=0

	Demographics	IBD-Control	MIBDI	SCQ	EQ-5D-5L/ 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

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

	Demographics	IBD-Control	MIBDI	SCQ	EQ-5D-5L/ 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

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;[48, 49]
- 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 intracluster 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.[50]

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 (α) 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.

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

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

Data analysis plan

All missing data will be assessed whether these data are likely to be missing (completely) at random. 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:

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

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); β_0 the intercept; η_j the cluster level random effect for cluster j; θ_{ij} the patient level random effect for patient i in cluster j; β_1 the estimated difference between standard care ($\iota = 0$) and the care pathway ($\iota = 1$); β_t a vector with coefficients for calendar time at the different time points t, captured as the vector υ_t with dummy variables for the different periods of follow-up; β_c a vector containing the coefficients for the case mix variables in the vector υ_c; and e_{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:

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

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

To assess the effect of the care pathway on variation, data from the six hospitals that implemented the care pathway will be analysed for the two periods using the aforementioned mixed effects model, without the coefficient for the care pathway. This model will be compared with a model that estimates a random effect per hospital for the baseline period and the care pathway period separately. The effect of the care pathway on variation will then be formally tested using a likelihood-ratio test comparing the two models.

Patient and public involvement

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

ETHICS AND DISSEMINATION

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

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

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COMPETING INTERESTS STATEMENT
Drs. van Linschoten has nothing to disclose.
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Dr. Birnie has nothing to disclose
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Dr. de Jonge has nothing to disclose
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LEGEND
Figure 1: Study Timeline

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Author Contributions: RCAvL, DvN, and RLW designed the study. NvL provided epidemiological expertise, DN provided statistical expertise and EB provided expertise in economic evaluation during the trial design. MS, CJvdW and JAH critically reviewed the study design. CvdW, RW, EV, VdJ, CJvdW and RCAvL participated in the design of the intervention. RCAvL drafted the manuscript and all authors read, critically revised and approved the final manuscript. Principal investigators are DvN and RLW. RCAvL ensures daily study management as study coordinator. DvN and RLW share last authorship.

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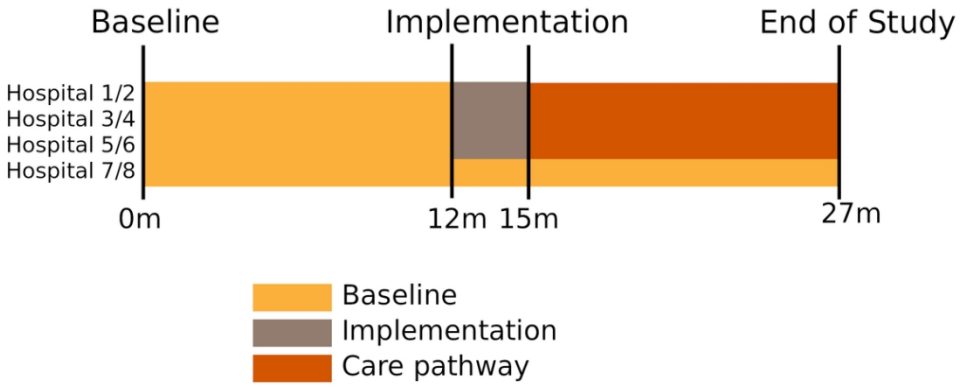

Figure 1: Study Timeline

50x21mm (600 x 600 DPI)

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1 - 13
Protocol version	#3	Date and version identifier	4
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	12
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12 - 13
Introduction			

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4 - 5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	NA
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	5

Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are	NA

		assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if	8 - 9

		not in the protocol	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8 - 9
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8 - 9
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg,	4, 11

		investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8, 11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised	Supplementary file 2

		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

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.

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

9. Gebruik en bewaren van uw gegevens

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

Vertrouwelijkheid van uw gegevens

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

Toegang tot uw gegevens voor controle

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

Bewaren en gebruik van gegevens

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

Intrekken toestemming

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

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

Meer informatie over uw rechten bij verwerking van gegevens

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

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

Registratie van het onderzoek

Informatie over dit onderzoek is ook opgenomen in een overzicht van medisch-wetenschappelijke onderzoeken namelijk (https://www.trialregister.nl/trial/8276). Daarin zijn geen gegevens opgenomen die naar u herleidbaar zijn. Na het onderzoek kan de website een samenvatting van de resultaten van dit onderzoek tonen.

10. Geen vergoeding voor meedoen

Het meedoen aan het onderzoek kost u niets. U wordt niet betaald voor het meedoen aan dit onderzoek.

11. Heeft u vragen?

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

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

12. Ondertekening toestemmingsformulier

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

Dank voor uw aandacht.

13. Bijlagen bij deze informatie

A. Contactgegevens

B. Toestemmingsformulier(en)

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 (voor alle locaties)

Functionaris Gegevensbescherming (alle locaties)**:**

Mw. L. Pollinger

E-mail: 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 : __ / __ / __

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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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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ABSTRACT

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

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

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

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

STRENGTH AND LIMITATIONS OF THIS STUDY

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

INTRODUCTION

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

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

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

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

Implementing a care pathway in clinical practice seems promising for improving value, which was illustrated by a retrospective pilot study that evaluated a care pathway for IBD in a VBHC program. This care pathway showed a favourable effect on flares (-26%) and costs (-16%).[27] Other studies supported the effect of a care pathway for IBD on costs and also showed an improvement of care processes.[28, 29]. In inguinal hernia repair, chronic heart failure and total hip replacement the implementation of a care pathway was also accompanied by reduced variation in processes and outcomes.[30] Although these studies showed a promising effect on outcomes and processes, they suffered from low sample sizes, retrospective study designs and lacked patient-centred outcome measures. With the prospective multicentre IBD Value study we aim to assess the impact of a care pathway for the treatment of IBD with biologics and new small molecules 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). 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 2nd 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.

Population

The study population comprises all IBD patients being treated with a biologic agent or new small molecule in the eight participating hospitals. The care pathway also covers patients treated with new small molecules, as these belong to the same group as patients treated with a biologic: complex disease and a high cost of treatment. Approximately 3,200 patients are treated with the aforementioned medication 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
- Have an IBD diagnosis of at least three months
- Treated with one of the currently registered biologics or new small molecules for IBD treatment or new treatments registered during the study period, including: infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, or tofacitinib.

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

Intervention

Design

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

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

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

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

Content

The care pathway will address the following issues.

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

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

Implementation & Adherence

IBD specialists from IBD BeterKeten will safeguard implementation of the care pathway in their respective centres. They will be supported by a presentation of the working group to the care providers. To facilitate working according to the care pathway, we will implement the care pathway in electronic health records. Care providers will be able to schedule follow-up or diagnostics according to the care pathway with a single action. We will assess adherence to the care pathway by randomly sampling patients and comparing treatment decisions made for these patients with the treatment algorithms set out in the care pathway.

Comparison

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

Outcome

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

The other outcomes from the standard set are secondary outcomes:

- IBD-attributable mortality;
- Remission, both clinician-reported (biochemical, radiological, endoscopic, histologic) and patient-reported (Manitoba IBD Index; MIBDI);[38]
- Incidence of colorectal cancer;
- Presence of anaemia;
- Number of A&E visits;
- Number and cumulative length of hospital admissions;

- Number of complications of any intervention for IBD;
- Long-term (>3 months) steroid use;
- Presence of fistulae symptoms;
- BMI as a proxy for nutritional status;

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

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

Outcome	**Source**
Primary	
Patient-reported disease control	Patient-reported (IBD-Control)[36, 37]
Secondary	
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/ 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

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

	Demographics	IBD-Control	MIBDI	SCQ	EQ-5D-5L/ 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

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 intracluster 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 (α) 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.

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

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

Data analysis plan

All missing data will be assessed whether these data are likely to be missing (completely) at random. 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:

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

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); β_0 the intercept; η_j the cluster level random effect for cluster j; θ_{ij} the patient level random effect for patient i in cluster j; β_1 the estimated difference between standard care ($\iota = 0$) and the care pathway ($\iota = 1$); β_t a vector with coefficients for calendar time at the different time points t, captured as the vector υ_t with dummy variables for the different periods of follow-up; β_c a vector containing the coefficients for the case mix variables in the vector υ_c; and e_{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.[46, 54] 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:

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

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

To assess the effect of the care pathway on variation, data from the six hospitals that implemented the care pathway will be analysed for the two periods using the aforementioned mixed effects model, without the coefficient for the care pathway. This model will be compared with a model that estimates a random effect per hospital for the baseline period and the care pathway period separately. The effect of the care pathway on variation will then be formally tested using a likelihood-ratio test comparing the two models.

Patient and public involvement

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

ETHICS AND DISSEMINATION

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

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

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Drs. van Linschoten has nothing to disclose.
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LEGEND
Figure 1: Study Timeline

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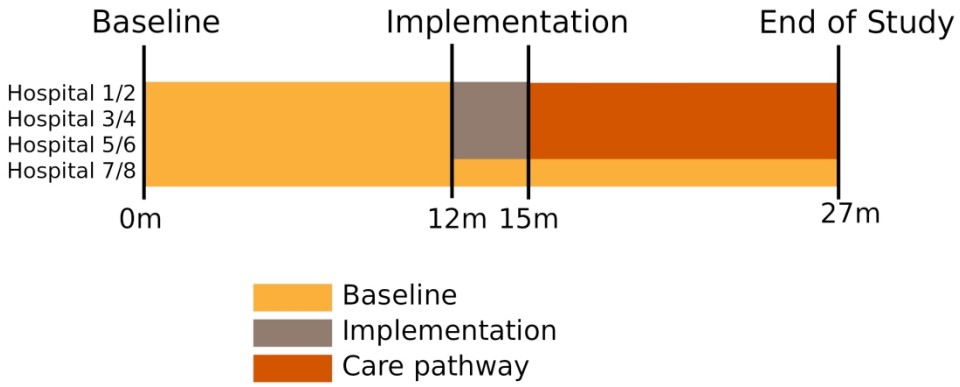

Figure 1: Study Timeline

50x21mm (1200 x 1200 DPI)

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1 - 13
Protocol version	#3	Date and version identifier	4
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	13
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13 - 14
Introduction			

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5 - 6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	NA
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6

Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6 - 8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8 - 9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9 - 10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are	NA

		assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7 - 8
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7 - 8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if	10 - 11

		not in the protocol	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10 - 11
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10 - 11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg,	4, 12

		investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10, 12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised	Supplementary file 2

		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

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.

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

9. Gebruik en bewaren van uw gegevens

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

Vertrouwelijkheid van uw gegevens

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

Toegang tot uw gegevens voor controle

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

Bewaren en gebruik van gegevens

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

Intrekken toestemming

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

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

Meer informatie over uw rechten bij verwerking van gegevens

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

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

Registratie van het onderzoek

Informatie over dit onderzoek is ook opgenomen in een overzicht van medisch-wetenschappelijke onderzoeken namelijk (https://www.trialregister.nl/trial/8276). Daarin zijn geen gegevens opgenomen die naar u herleidbaar zijn. Na het onderzoek kan de website een samenvatting van de resultaten van dit onderzoek tonen.

10. Geen vergoeding voor meedoen

Het meedoen aan het onderzoek kost u niets. U wordt niet betaald voor het meedoen aan dit onderzoek.

11. Heeft u vragen?

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

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

12. Ondertekening toestemmingsformulier

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

Dank voor uw aandacht.

13. Bijlagen bij deze informatie

A. Contactgegevens

B. Toestemmingsformulier(en)

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:

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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**

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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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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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ABSTRACT

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

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

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

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

STRENGTH AND LIMITATIONS OF THIS STUDY

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

INTRODUCTION

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

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

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

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

Implementing a care pathway in clinical practice seems promising for improving value, which was illustrated by a retrospective pilot study that evaluated a care pathway for IBD in a VBHC program. This care pathway showed a favourable effect on flares (-26%) and costs (-16%).[27] Other studies supported the effect of a care pathway for IBD on costs and also showed an improvement of care processes.[28, 29]. In inguinal hernia repair, chronic heart failure and total hip replacement the implementation of a care pathway was also accompanied by reduced variation in processes and outcomes.[30] Although these studies showed a promising effect on outcomes and processes, they suffered from low sample sizes, retrospective study designs and lacked patient-centred outcome measures. With the prospective multicentre IBD Value study we aim to assess the impact of a care pathway for the treatment of IBD with biologics and new small molecules 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). 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). 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 2nd 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.

Population

The study population comprises all IBD patients being treated with a biologic agent or new small molecule in the eight participating hospitals. The care pathway also covers patients treated with new small molecules, as these belong to the same group as patients treated with a biologic: complex disease and a high cost of treatment. Approximately 3,200 patients are treated with the aforementioned medication 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
- Have an IBD diagnosis of at least three months
- Treated with one of the currently registered biologics or new small molecules for IBD treatment or new treatments registered during the study period, including: infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, or tofacitinib.

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

Intervention

Design

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

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

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

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

Content

The care pathway will address the following issues.

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

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

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

Implementation & Adherence

IBD specialists from IBD BeterKeten will safeguard implementation of the care pathway in their respective centres. They will be supported by a presentation of the working group to the care providers. To facilitate working according to the care pathway, we will implement the care pathway in electronic health records. Care providers will be able to schedule follow-up or diagnostics according to the care pathway with a single action. We will assess adherence to the care pathway by randomly sampling patients and comparing treatment decisions made for these patients with the treatment algorithms set out in the care pathway.

Comparison

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

Outcome

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

The other outcomes from the standard set are secondary outcomes:

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

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

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

Outcome	**Source**
Primary	
Patient-reported disease control	Patient-reported (IBD-Control)[36, 37]
Secondary	
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 from one month before the start of the study (December 1st 2020) until the end of the study (March 31st 2023). 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/ 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

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

	Demographics	IBD-Control	MIBDI	SCQ	EQ-5D-5L/ 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

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 intracluster 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 (α) 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.

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

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

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

Data analysis plan

All missing data will be assessed whether these data are likely to be missing (completely) at random. 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:

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

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); β_0 the intercept; η_j the cluster level random effect for cluster j; θ_{ij} the patient level random effect for patient i in cluster j; β_1 the estimated difference between standard care ($\iota = 0$) and the care pathway ($\iota = 1$); β_t a vector with coefficients for calendar time at the different time points t, captured as the vector υ_t with dummy variables for the different periods of follow-up; β_c a vector containing the coefficients for the case mix variables in the vector υ_c; and e_{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.[46, 54] 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:

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

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

To assess the effect of the care pathway on variation, data from the six hospitals that implemented the care pathway will be analysed for the two periods using the aforementioned mixed effects model, without the coefficient for the care pathway. This model will be compared with a model that estimates a random effect per hospital for the baseline period and the care pathway period separately. The effect of the care pathway on variation will then be formally tested using a likelihood-ratio test comparing the two models.

Patient and public involvement

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

ETHICS AND DISSEMINATION

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

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

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.

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COMPETING INTERESTS STATEMENT
Drs. van Linschoten has nothing to disclose.
Dr. van Leeuwen has nothing to disclose.
Drs. Nieboer has nothing to disclose.
Dr. Birnie has nothing to disclose
Drs. Scherpenzeel, MPM has nothing to disclose
Dr. de Jonge has nothing to disclose
Drs. Verweij has nothing to disclose
Prof. Dr. Hazelzet has nothing to disclose.
Prof. Dr. van der Woude reports grants from Pfizer and Janssen and personal fees from AbbVie and Celltrion outside the submitted work.
Dr. van Noord reports personal fees from Janssen and Takeda outside the submitted work.
Dr. West reports personal fees from AbbVie, Janssen and Pfizer outside the submitted work.

LEGEND
Figure 1: Study Timeline

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Author Contributions: RCAvL, DvN, and RLW designed the study. NvL provided epidemiological expertise, DN provided statistical expertise and EB provided expertise in economic evaluation during the trial design. MS, CJvdW and JAH critically reviewed the study design. CJvdW, RLW, KEV, VdJ and RCAvL participated in the design of the intervention. RCAvL drafted the manuscript and all authors read, critically revised and approved the final manuscript. Principal investigators are DvN and RLW. RCAvL ensures daily study management as study coordinator. DvN and RLW share last authorship.

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KEYWORDS
Clinical trial; gastroenterology; inflammatory bowel disease; health economics; value-based healthcare; health services research; care pathway;

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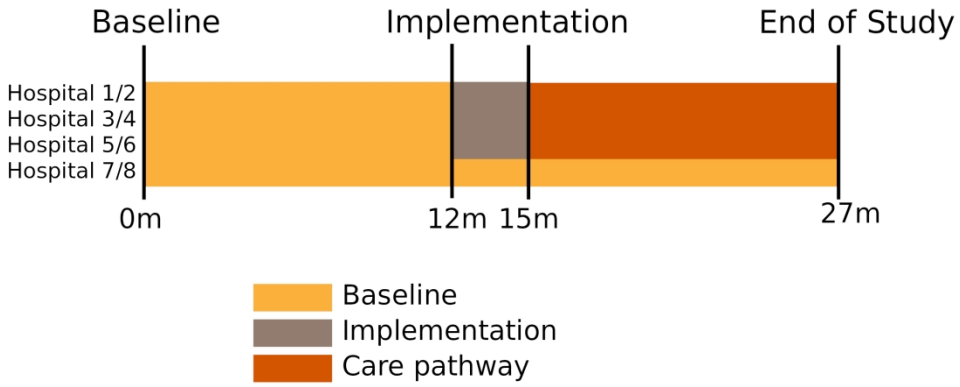

Figure 1: Study Timeline

50x21mm (1200 x 1200 DPI)

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1 - 13
Protocol version	#3	Date and version identifier	4
Funding	#4	Sources and types of financial, material, and other support	13
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	13
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	13
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13 - 14
Introduction			

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	6
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4 - 5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5 - 6
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	NA
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6

Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6 - 8
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8 - 9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9 - 10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	4
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are	NA

		assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6 - 7
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6 - 7
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if	9 - 10

		not in the protocol	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9 - 10
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9 - 10
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	11
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg,	4, 11

		investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9, 11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	NA
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised	Supplementary file 2

		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

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.

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

9. Gebruik en bewaren van uw gegevens

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

Vertrouwelijkheid van uw gegevens

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

Toegang tot uw gegevens voor controle

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

Bewaren en gebruik van gegevens

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

Intrekken toestemming

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

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

Meer informatie over uw rechten bij verwerking van gegevens

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

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

Registratie van het onderzoek

Informatie over dit onderzoek is ook opgenomen in een overzicht van medisch-wetenschappelijke onderzoeken namelijk (https://www.trialregister.nl/trial/8276). Daarin zijn geen gegevens opgenomen die naar u herleidbaar zijn. Na het onderzoek kan de website een samenvatting van de resultaten van dit onderzoek tonen.

10. Geen vergoeding voor meedoen

Het meedoen aan het onderzoek kost u niets. U wordt niet betaald voor het meedoen aan dit onderzoek.

11. Heeft u vragen?

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

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

12. Ondertekening toestemmingsformulier

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

Dank voor uw aandacht.

13. Bijlagen bij deze informatie

A. Contactgegevens

B. Toestemmingsformulier(en)

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 (voor alle locaties)

Functionaris Gegevensbescherming (alle locaties)**:**

Mw. L. Pollinger

E-mail: 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 : __ / __ / __

De deelnemer krijgt een volledige informatiebrief mee.