PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A value-based care pathway for inflammatory bowel disease: protocol for the multicentre longitudinal non-randomised parallel cluster IBD Value study with baseline period
AUTHORS	van Linschoten, Reinier; van Leeuwen, Nikki; Nieboer, Daan; Birnie, Erwin; Scherpenzeel, Menne; Verweij, Karen Evelyne; de Jonge, Vincent; Hazelzet, Jan; van der Woude, Christien Janneke; West, Rachel; van Noord, Desirée

VERSION 1 – REVIEW

REVIEWER	Saibeni, S Gastroenterology Unit, Rho Hospital
REVIEW RETURNED	20-Apr-2021

GENERAL COMMENTS	In this paper, van Linschoten et al. suggested the design and the implementation of an uniform care pathway for IBD treatment in order to potentially reduce practice variation and improve several outcomes. The study design is clearly exposed and the project appears to be realizable in the scheduled times. Major concern I disagree with authors when they state to refer to as biologics small molecules (rows 81 and 82). Since small molecules are not biologics, I think they should be considered apart. I also think that small molecules could be excluded from the present study. Minor concerns Row 75: to add signs to symptoms for the clinical manifestations of IBD Rows 87: among the US papers that explored variation among healthcare providers in IBD treatment, I would suggest to cite also an Italian study assessing the barriers to antiTNFalpha prescription (Bezzio et al. GastroHep 2019;1: 93–99). Rows 89-90: to add costs and safety among the different outcomes related to treatment variation Rows 95-102: the concept exposed by the authors is acceptable, but I also think that they should more underline the relevant differences between RCT and real-world experience, besides treatment variation. Rows 115: authors could specify in which other diseases the implementation of a care pathway was accompanied by reduced variation (and which variation also). Rows 232: is it possible to add other secondary outcomes to those already identified by ICHOM? I would suggest: objective measures of disease activity (e.g. clinical and endoscopic indices, serum and faecal biomarkers), incidence of other neoplasms than CRC, clinical course or development ex novo of concomitant IMID. Rows 251: in the cost-unit analysis, it would be interesting also to

	consider the number and the type of instrumental techniques (e.g. endoscopies, US, MR, radiology) as well as the number of blood chemistry performed between the two periods. Rows 277: please add “colitis” after “indeterminate” Rows 279: please consider also IMID Table 1 an Table 2: please add legends for the several acronyms

REVIEWER	Dulai, Parambir University of California San Diego
REVIEW RETURNED	01-Aug-2021

GENERAL COMMENTS	This is an important topic, and one that is understudied in a prospective manner. Therefore, the impact of this care pathway study if positive will be substantial. The methodology, cohort, inclusion/exclusion criteria, statistical analysis plan, and key stakeholders are outlined in sufficient detail and are of appropriate methodology. My only main comment is for the authors to consider and highlight how they plan to address continue variation after the implementation of the value care pathway. The use of biologics, choice of biologics, decision to switch therapy, is a patient preference sensitive decision and some patients may not agree to follow the care pathway outlined. Would those be considered drop outs and treated as non-adherent/non-responders and factor into continued variability? The authors are attempting to focus on provider variability but patient acceptance as a driver of variability will be important to understand. Consideration could be given to including patient preference assessments at baseline during the observational pre-exposure period to account for this in the comparison.

REVIEWER	Szigethy, Eva University of Pittsburgh, Department of Psychiatry and Medicine
REVIEW RETURNED	11-Aug-2021

GENERAL COMMENTS	This study design addresses a critical issue of a data-driven clinical pathway to provide a more cost-effective algorithm in prescribing biologics, one of the most expensive treatments for IBD, to IBD patients. The overall study objectives and design are appropriate, the main commentary are in two major areas- 1) better connecting objectives and study design strategies discussed, and 2) providing more details about the decision-making process on how this care-pathway will be determined (e.g. better mapping out key decision points based on the variables being probed. Specific comments are below. 1) The Abstract lacks key details such as the duration of the study, study assessment timepoints and description of the "non-equivalent control group". 2) The aims and study design could be better linked. The first aim appears to be assessing baseline biologic prescription practices and their effects in both the control and active sites for the first 12 months of the study. For aims 2 and 3 ("uncover areas of improvement", and "develop and implement a care pathway"- there is very little detail on the process, how consensus decisions will be made and weighted? Perhaps the incorporation of methodology from implementation science would be useful here, particularly since this is a methods paper. 3) Please justify the non-equivalent parallel control group design and discuss other design configurations considered (e.g. propensity

	matching, equivalent control groups). 4) In the study design, " the development of the care pathway will be completed by the working group" but no description on what process will be used. In the design, there is no consideration that the carepath may be different for Crohn's disease versus ulcerative colitis patients. How are medical and mental comorbidities or surgical histories going to handled in the decision-making? How is fidelity/adherence to this care pathway in the "active" groups going to be measured? 5) For outcomes- how will side effects/lack of tolerability to biologics be included? A clearer description (perhaps even Table) of the source of each outcome, and perhaps even organizing outcomes by aims would be helpful- for example, self-report, clinician report, medical record, claims data, etc. 6) The abstract states that 200 patients will be included but the statistical methods sections states that " 588 patients have been included" Please clarify. 7. The statistical plan is comprehensive and well described.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. S Saibeni, Gastroenterology Unit, Rho Hospital

- In this paper, van Linschoten et al. suggested the design and the implementation of an uniform care pathway for IBD treatment in order to potentially reduce practice variation and improve several outcomes. The study design is clearly exposed and the project appears to be realizable in the scheduled times.

Author's reply: Thank you for your kind words. We have used your feedback to improve our manuscript.

Major concern

- I disagree with authors when they state to refer to as biologics small molecules (rows 81 and 82). Since small molecules are not biologics, I think they should be considered apart. I also think that small molecules could be excluded from the present study.

Author's reply: The care pathway also covers patients treated with new small molecules (i.e. tofacitinib), as these belong to the same group as patients treated with a biologic: complex disease and a high cost of treatment. We have clarified why we also include these patients in lines 183-188. We agree that small molecules areot biologics. We have changed our manuscript so that tofacitinib is not referred to as a biologic anymore (i.e. lines 86-87).

Minor concerns

- Row 75: to add signs to symptoms for the clinical manifestations of IBD

Author's reply: We have added 'signs' to line 79.

- Rows 87: among the US papers that explored variation among healthcare providers in IBD treatment, I would suggest to cite also an Italian study assessing the barriers to antiTNFalpha prescription (Bezzio et al. GastroHep 2019;1: 93–99 PubMed).

Author's reply: Thank you for this suggestion. We have also cited this paper at the suggested place in line 92 to show variation in treatment with biologics in an European context.

- Rows 89-90: to add costs and safety among the different outcomes related to treatment variation

Author's reply: We have added costs and side effects as outcomes that could also be related to treatment variation (line 95).

- Rows 95-102: the concept exposed by the authors is acceptable, but I also think that they should more underline the relevant differences between RCT and real-world experience, besides treatment variation.

Author's reply: We have added a line on the differences between RCTs and real-world studies concerning the study designs and patient populations (line 103-105).

- Rows 115: authors could specify in which other diseases the implementation of a care pathway was accompanied by reduced variation (and which variation also).

Author's reply: We have specified which other diseases (inguinal hernia repair, chronic heart failure and total hip replacement) were studied and what variation (both variation in processes and outcomes) was reduced in lines 121-123.

- Rows 232: is it possible to add other secondary outcomes to those already identified by ICHOM? I would suggest: objective measures of disease activity (e.g. clinical and endoscopic indices, serum and faecal biomarkers), incidence of other neoplasms than CRC, clinical course or development ex novo of concomitant IMID.

Author's reply: Thank you for your suggestion. The ICHOM Standard Set that we use for our outcome measures already contains objective measures of disease activity: clinical remission as judged by the provider, endoscopic remission, and serum and faecal biomarkers (see lines 285-286 and Table 1). As the study has started on December 1st 2020 it is unfortunately not possible to adjust our outcome measures to incorporate your suggestions.

- Rows 251: in the cost-unit analysis, it would be interesting also to consider the number and the type of instrumental techniques (e.g. endoscopies, US, MR, radiology) as well as the number of blood chemistry performed between the two periods.

Author's reply: Thank you for this suggestion. We are considering the number and type of instrumental techniques and blood chemistry for the cost-utility analysis. We have clarified this in line 310.

- Rows 277: please add "colitis" after "indeterminate"

Author's reply: We have added the word "colitis" after "indeterminate" in line 330.

- Rows 279: please consider also IMID

Author's reply: Thank you for this suggestion. At baseline we consider several immune-mediated inflammatory diseases as comorbidities which are measured with the self-administered comorbidity questionnaire (lines 336-337). As the study has already started we unfortunately cannot change data collection at baseline or during follow-up.

- Table 1 and Table 2: please add legends for the several acronyms

Author's reply: We have added legends for the acronyms in Tables 1, 2, and 3. No acronym was added for the EQ-5D-5L as this is the name of the instrument.

Reviewer: 2

Dr. Parambir Dulai, University of California San Diego

Comments to the Author:

- This is an important topic, and one that is understudied in a prospective manner. Therefore, the impact of this care pathway study if positive will be substantial. The methodology, cohort, inclusion/exclusion criteria, statistical analysis plan, and key stakeholders are outlined in sufficient detail and are of appropriate methodology. My only main comment is for the authors to consider and highlight how they plan to address continue variation after the implementation of the value care pathway. The use of biologics, choice of biologics, decision to switch therapy, is a patient preference sensitive decision and some patients may not agree to follow the care pathway outlined. Would those be considered drop outs and treated as non-adherent/non-responders and factor into continued variability? The authors are attempting to focus on provider variability but patient acceptance as a driver of variability will be important to understand. Consideration could be given to including patient preference assessments at baseline during the observational pre-exposure period to account for thiin the comparison.

Author's reply: Thank you for your kind comments on our manuscript. Patient preference and shared decision making are important topics in the care pathway. The care pathway aims to guarantee the same level of care for IBD patients in all participating hospitals, but also takes into account patient preference and uncertainty in the evidence concerning IBD treatment. The care pathway thus allows deviation in cases where the provider and patient deem this necessary. In cases of uncertainty, the

care pathway focusses on informing the patient with information leaflets and medical animations, so they can make treatment decisions together with their provider.

Because this is a pragmatic study, which looks at the implementation of a care pathway in daily practice, non-adhering patients are not considered drop-outs. We aim to study what happens if a care pathway is implemented, and removing non-adherent patients would overestimate the effect of the care pathway outside a study setting. Because the study has started on December 1st 2020, we unfortunately cannot add patient preference assessment in the baseline period. We will assess adherence to the care pathway to evaluate whether implementation was successful and why the care pathway did or did not have an effect. We have clarified this in lines 263 – 265.

Reviewer: 3
Dr. Eva Szigethy, University of Pittsburgh

- This study design addresses a critical issue of a data-driven clinical pathway to provide a more cost-effective algorithm in prescribing biologics, one of the most expensive treatments for IBD, to IBD patients. The overall study objectives and design are appropriate, the main commentary are in two major areas- 1) better connecting objectives and study design strategies discussed, and 2) providing more details about the decision-making process on how this care-pathway will be determined (e.g. better mapping out key decision points based on the variables being probed. Specific comments are below.

Author's reply: Thank you for your feedback and comments, we have incorporated them to improve our manuscript. Please see our reply for each specific comment.

- The Abstract lacks key details such as the duration of the study, study assessment timepoints and description of the "non-equivalent control group".

Author's reply: We have clarified the study design, study duration, assessment time points and control group in lines 48-51 and line 57.

- The aims and study design could be better linked. The first aim appears to be assessing baseline biologic prescription practices and their effects in both the control and active sites for the first 12 months of the study. For aims 2 and 3 ("uncover areas of improvement", and "develop and implement a care pathway"- there is very little detail on the process, how consensus decisions will be made and weighted? Perhaps the incorporation of methodology from implementation science would be useful here, particularly since this is a methods paper.

Author's reply: Thank you for this suggestion. The first aim is indeed to assess variation between hospitals in outcomes and costs of treatment of IBD with biologics and new small molecules. The process concerning aims 2 and 3 is clarified below and in the manuscript in lines 204-232:

We did not use a formal process from implementation science to design the care pathway, but followed the following steps. First the main topics of what the care pathway should cover were drafted by the project manager and discussed in the working group. When there was consensus on what topics should be covered, the project manager drafted the care pathways on the basis of (inter)national guidelines. These drafts were then discussed in a working group meeting, where exact content and timing of the components of the care pathway were established. In case of disagreement on best practices, we searched for scientific literature and the information found was then summarised and discussed in the working group, after which consensus was reached.

Results from the baseline period will be analysed according to the definitions of the International Consortium of Health Outcomes Measurement (ICHOM) and stratified by centre. These results and their consequences for the care pathway will be discussed in a working group meeting, after which the care pathway will be adjusted based on this discussion. The final draft of the care pathway will then be presented to the IBD specialists of the six hospitals in the intervention group for approval.

- Please justify the non-equivalent parallel control group design and discuss other design configurations considered (e.g. propensity matching, equivalent control groups).

Author's reply: We have clarified our design choice in lines 153-161. In short, we have chosen a longitudinal non-randomised parallel cluster trial with a baseline period because of logistical

reasons: the six hospitals represented in the care pathway working grop could not participate in the control group because they could not be blinded to the intervention.

- In the study design, " the development of the care pathway will be completed by the working group" but no description on what process will be used. In the design, there is no consideration that the carepath may be different for Crohn's disease versus ulcerative colitis patients. How are medical and mental comorbidities or surgical histories going to be handled in the decision-making? How is fidelity/adherence to this care pathway in the "active" groups going to be measured?

Author's reply: We have clarified the process of the development of the care pathway in lines 205-232. As IBD is a heterogeneous disease, we do not aim to completely encapsulate all possible treatment decisions and medical/surgical histories in the care pathway, but to create the same level of care for all intervention hospitals. We have clarified this in lines 207-210. The care pathway will take diagnosis (Crohn's disease versus ulcerative colitis) into account.

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. We have clarified this in lines 257-265. As the care pathway will be finalised shortly before the implementation period and hospitals in the control group need to be blinded to the intervention, we cannot go into further detail about the exact contents of the care pathway.

- For outcomes- how will side effects/lack of tolerability to biologics be included? A clearer description (perhaps even Table) of the source of each outcome, and perhaps even organizing outcomes by aims would be helpful- for example, self-report, clinician report, medical record, claims data, etc.

Author's reply: Thank you for this suggestion. Side effects/lack of tolerability are included under the outcome: 'Complications of any intervention for IBD' (line 291). We have clarified the source of each outcome in a new table (see Table 1, lines 319-320).

- The abstract states that 200 patients will be included but the statistical methods sections states that " 588 patients have been included" Please clarify.

Author's reply: The power calculation indicated that a minimum of 200 patients are necessary to show an effect of 1 of the care pathway on the IBD-Control score. To evaluate treatment differences and variation during the baseline period we would like to include all patients in the source population. This means that our minimum inclusion goal is 200 patients, but we will continue to include patients so that power can be increased and a representative sample from the source population can be obtained. We have clarified this in the abstract (line 58) and further information can be found in lines 390-395. At the time of first submission of the manuscript, 588 patients were included. Currently, 1 001 patients are participating in our study (line 407).

- The statistical plan is comprehensive and well described.

Author's reply: Thank you for this compliment.

VERSION 2 – REVIEW

REVIEWER	Saibeni, S Gastroenterology Unit, Rho Hospital Lecture fees and/or advisory board for Janssen, AbbVie, Takeda, Gilead, Arena, MSD
REVIEW RETURNED	31-Oct-2021

GENERAL COMMENTS	Authors provided exhaustive answers to my previous comments.

REVIEWER	Szigethy, Eva University of Pittsburgh, Department of Psychiatry and Medicine

REVIEW RETURNED	07-Dec-2021

GENERAL COMMENTS	The authors adequately addressed reviewer concerns. One minor point is that there is no discussion section addressing limitations. Authors do list other study designs considered in the methods section. It may be clearer if these considerations as well as other limitations (e.g. keeping fidelity of control group, bias introduced by non-randomization, change in practice over time) could impact findings.

VERSION 2 – AUTHOR RESPONSE

REVIEWERS' COMMENTS TO AUTHOR:
Reviewer: 2
Dr. Eva Szigethy, University of Pittsburgh

- The authors adequately addressed reviewer concerns. One minor point is that there is no discussion section addressing limitations. Authors do list other study designs considered in the methods section. It may be clearer if these considerations as well as other limitations (e.g. keeping fidelity of control group, bias introduced by non-randomization, change in practice over time) could impact findings.

Author's reply: *Thank you for this suggestion. We have moved the design considerations from the design section (lines 150-156) to the discussion and elaborated on strengths and weaknesses of the study in the discussion (lines 488 – 526). In short, main strengths of the study are the baseline period and control group to control for changes over time. The main weakness is the absence of randomisation because of confounding bias, for which we aim to control by adjusting for case-mix. We have also elaborated on implementation of the care pathway and how we aim to effectively implement the care pathway, as this is the main challenge for these types of studies.*