PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Control Crohn Safe with episodic adalimumab monotherapy as first line treatment study (CoCroS): study protocol for a randomized controlled trial
AUTHORS	Janssen, Laura; Romberg-Camps, Mariëlle; van Bodegraven, Ad; Haans, Jeoffrey; Aquarius, Michèl; Boekema, Paul; Munnecom, Tamara; Brandts, Lloyd; Joore, Manuela; Masclee, Adrian; Jonkers, D; Pierik, M

VERSION 1 – REVIEW

REVIEWER	Naftali, Timna Clalit Health Services
REVIEW RETURNED	29-Oct-2020

GENERAL COMMENTS	Is the study design appropriate to answer the research question? the control arm can recieve either infliximab or adalimumab, whereas the reaserch arm can only recieve adalimumab, It would have been better to compare one drug to itself and not to another drug. Are the methods described sufficiently to allow the study to be repeated? the answer is yes, but the studt population is only dutch speaking people who have a smartphone, so the results may only be applicable to this population.

REVIEWER	de Ridder, Lissy Erasmus MC Sophia Children Hospital, Paediatric gastroenterology
REVIEW RETURNED	17-Nov-2020

GENERAL COMMENTS	In this manuscript the authors describe the study protocol of the CoCros trial was in detail. The hypothesis of the trial is that episodic adalimumab monotherapy as first line treatment for CD in combination with close disease activity monitoring after drug discontinuation improves long-term outcome and reduces drug-related side effects, while still preventing overtreatment. The manuscript is well written, and the SPIRIT protocol guidelines were taken into account in this manuscript. The research question definitely is of interest. I do have some suggestions which may further improve this manuscript, including some questions. - How is this study funded, or is it performed without funding? - Has the trial been rregistered, eg on Clinicaltrial.gov?

	- I suggest to clarify the term episodic adalimumab treatment in the abstract, based on the abstract it is not clear how these patients are treated. - Line 23-27 page 5: In these sentences is stated that stopping and re-initiation is a relative contra indication for monotherapy or intermittent treatment with IFX. The cited study of Sandborn et al. is primarily focused on differences between mono or combo with azathioprine and not on intermittent treatment. I suggest to reframe these sentences or use another reference to support this statement. - However, though the risk to develop immunogenicity to adalimumab is smaller than to infliximab, it still is a risk (see Pants study). Please discuss this risk. - Please describe the randomisation procedure in more detail. - On page 7, authors report so far 9 patients have been included, while the study started in Dec 2019. In total, 158 patients need to be included. That seems a slow start. Please comment why this is so and if the expectancies this study is feasible despite this slow start. - Inclusion criteria on page 7; last endoscopy performed <12 months before screening while MRE should be performed at diagnosis. Why is such a long interval between endoscopy and study enrolment allowed? This is a very long interval, please elaborate why this is the case - Exclusion criteria page 7; steroid use > 4 months. So, steroid use < 4 months in the year before screening is allowed. But before enrolment, a patient is allowed to use max 20 mg prednisolone for max 2 weeks. How long should the interval between previous steroid use be? So, a patient with a flare of Crohn's, having had steroids for 3 months prior, then is eligible and can be randomised to steroids (step-up care). Is this a patient you indeed want to enrol in this trial? - Is TDM in patients treated with ada part of the protocol? - Adalimumab monotherapy vs step up care, means sc treatment vs oral. Do authors envisage problems with enrolment because of this difference? And in case yes, how to overcome this? - Table 1 shows a complete overview of the study schedule. It would be helpful to add a figure showing the most important information in this table. - Line 37 page 15, here is stated to assess the efficacy of adalimumab monotherapy… Which is not really the case. I would suggest to adjust this: eg. as episodic adalimumab or induction with adalimumab - A challenge which needs further discussion is the comparability of both strategies. For example: primary outcome: the number of yearly quarters of corticosteroid free clinical remission and biochemical remission at week 96. In the step-up group STEP 2 includes prolonged use of CS, while this is not the case for adalimumab monotherapy treated patients. - Primary endpoint focusses on steroid free remission. What if patients restarted adalimumab? - Figure 1: add to the adalimumab monotherapy column 1

	that the duration of adalimumab induction treatment is 24 weeks. - I do not fully understand the sequence (Figure 1). Ada mono: step 3 is dose optimization while step is already switch to ifx. Why not peform TDM and optimize before switch? - What about quality of life, PK, thiopurine levels?

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1

Comments to the Author
-Is the study design appropriate to answer the research question?
the control arm can recieve either infliximab or adalimumab, whereas the reaserch arm can only recieve adalimumab, It would have been better to compare one drug to itself and not to another drug.

This study is designed to compare a novel treatment strategy to standard step-up care, and not to compare two drugs. First line treatment with adalimumab monotherapy is the treatment strategy of interest and is compared to the step-up approach, and not so much to infliximab or adalimumab specific. Both patients in the control arm and in the research arm can receive infliximab. In the control arm patients can receive infliximab if thiopurine maintenance fails, and in the research arm patients can switch to infliximab if adalimumab fails.

-Are the methods described sufficiently to allow the study to be repeated?
the answer is yes, but the study population is only Dutch speaking people who have a smartphone, so the results may only be applicable to this population.

To participate in this study, a tight control approach with three monthly measuring of the disease activity score and fecal calprotectin is necessary to enable timely treatment optimization or reintroduction of medical therapy after discontinuation of maintenance treatment. The same tight monitoring is possible with fecal laboratory tests and paper questionnaires, or any other system used to send patients questionnaires according to GDPR requirements. The electronic patient diary myIBDcoach is used to facilitate data collection. Every recent drug trial in IBD uses electronic patient diaries for this purpose. Hence, the study results can be used in every health care system with excess to fecal calprotectin testing.

REVIEWER 2
Comments to the Author
In this manuscript the authors describe the study protocol of the CoCroS trial in detail. The hypothesis of the trial is that episodic adalimumab monotherapy as first line treatment for CD in combination with close disease activity monitoring after drug discontinuation improves long-term outcome and reduces drug-related side effects, while still preventing overtreatment. The manuscript is well written, and the SPIRIT protocol guidelines were taken into account in this manuscript. The research question definitely is of interest. I do have some suggestions which may further improve this manuscript, including some questions.

- How is this study funded, or is it performed without funding?

The study is funded by ZonMW grant number 848050009.

- Has the trial been registered, eg on Clinicaltrial.gov?

The study is registered at Clinicaltrials.gov (http://clinicaltrials.gov/show/NCT03917303).

- **I suggest to clarify the term episodic adalimumab treatment in the abstract, based on the abstract it is not clear how these patients are treated.**

Episodic adalimumab monotherapy means treatment during (at least) 24 weeks. In case of endoscopic remission during the ileocolonoscopy at week 24, adalimumab will be discontinued. If no endoscopic remission, adalimumab will be prolonged and/or intensified.
This aspect of time (i.e. 24 weeks) has been added to methods in the abstract to clarify the meaning of episodic adalimumab monotherapy.

- **Line 23-27 page 5: In these sentences is stated that stopping and re-initiation is a relative contra indication for monotherapy or intermittent treatment with IFX. The cited study of Sandborn et al. is primarily focused on differences between mono or combo with azathioprine and not on intermittent treatment. I suggest to reframe these sentences or use another reference to support this statement.**

We rephrased the sentence and added another reference as suggested.

- However, though the risk to develop immunogenicity to adalimumab is smaller than to infliximab, it still is a risk (see Pants study). Please discuss this risk.

Adalimumab is not chimeric, but a humanized monoclonal antibody and subsequently the risk to develop immunogenicity to adalimumab is smaller than to infliximab. Addition of azathioprine to adalimumab had only a marginal effect on antidrug antibody formation as shown by the DIAMOND study. Furthermore, addition of azathioprine to adalimumab had no significant effect on the endoscopic responses and clinical remission after one year in this trial. We based the protocol on the available data in 2018. The in 2019 published PANTS trial indeed showed higher immunogenicity in patients treated with adalimumab monotherapy compared to patients treated with combination therapy.
In the treatment of Crohn's disease, balancing risk and safety is necessary at every important decision during the patient's journey. Each treatment (strategy) brings along certain risks, including for example immunogenicity and drug-related side effects. Patients with a mild disease course are at risk of overtreatment with a top-down approach, while patients with a complicated disease course are at risk of under-treatment with the step-up care approach. In this study, we try to find the balance between the risks of a step-up approach and of adalimumab monotherapy as first line treatment. While trying to prevent overtreatment and drug-related side effects by using adalimumab monotherapy instead of combination therapy and by stopping adalimumab in patients with endoscopic remission at week 24, the possibility of having to reinitiate adalimumab arises and the risk of lower response rates due to immunogenicity. Given the additional risk of combination therapy and the number needed to treat (11 at week 56 in the Pants study) to prevent antidrug antibody formation associated with lower responses, we still consider the study protocol to be valid. Furthermore, in the 2019 ECCO guidelines on medical treatment in Crohn's disease adalimumab monotherapy is recommended over combination therapy.

- Please describe the randomisation procedure in more detail.

Patients will be randomly assigned 1:1 to open label adalimumab or step-up care starting with corticosteroids. The minimization method is used to balance differences between treatment groups in the prognostic factors disease location (ileal vs. colon, ileocolon and upper gastro-intestinal tract) and disease behavior (inflammatory vs. structuring and penetrating). Center is added as stratification factor to balance the difference in initial costs of treatment per center. This explanation has been added to page 11 of the manuscript.

At inclusion, a member of the study team fills out the electronic case report form in MACRO, including these stratification factors. Automatic randomization is performed centrally with the randomisation service of ALEA after completing this form.

Minimisation settings used in ALEA:

- Rule to calculate the amount of variation for each treatment: use the range
- Rule to calculate the level of imbalance for each treatment: use the sum
- Rule to assign a probability to each treatment: use a custom rule with one threshold level → when the highest imbalance exceeds a boundary of 2 assign an odds ratio of 90% to the treatment resulting in the lowest imbalance

- On page 7, authors report so far 9 patients have been included, while the study started in Dec 2019. In total, 158 patients need to be included. That seems a slow start. Please comment why this is so and if the expectancies this study is feasible despite this slow start.

The first patient was included in the Maastricht Medical University Center+ (MUMC+) in December 2019. At that time, the MUMC+ was yet the only center including patients, since local approval was pending in the other participating centers. In July 2020, when this manuscript was first submitted, the study was ongoing in the MUMC+, and the Zuyderland Medical Center just started inclusion. Currently, in November 2020, 24 patients have been included in these two centers.
Due to the COVID-19 crisis, fewer eligible patients could be identified, since colonoscopies, among other standard care examinations, were postponed. In addition, obtaining local approval in the other participating centers took longer than anticipated due to the COVID-19 crisis, but has recently been obtained in three other participating centers. These centers started identifying potential subjects this month. Therefore, despite the slow start, we expect the study to be feasible.

- Inclusion criteria on page 7; last endoscopy performed <12 months before screening while MRE should be performed at diagnosis. Why is such a long interval between endoscopy and study enrolment allowed? This is a very long interval, please elaborate why this is the case

Patients with newly diagnosed Crohn's disease or a flare can be included, in other words patients with active disease. Newly diagnosed CD patients will have had an ileocolonoscopy recently. Patients with a flare might not have had a recent ileocolonoscopy, since their flare can be objectified by imaging and increased inflammatory biomarkers, such as CRP or fecal calprotectin, and not necessarily by endoscopy. In line with the pragmatic design, a longer interval between endoscopy and study enrollment is allowed. Objectification with endoscopy or MRI is warranted at inclusion for every patients.

- **Exclusion criteria page 7; steroid use > 4 months. So, steroid use < 4 months in the year before screening is allowed. But before enrolment, a patient is allowed to use max 20 mg prednisolone for max 2 weeks. How long should the interval between previous steroid use be? So, a patient with a flare of Crohn's, having had steroids for 3 months prior, then is eligible and can be randomised to steroids (step-up care). Is this a patient you indeed want to enrol in this trial?**

We include patients without prior use of thiopurines and biologicals, and preferably with a short disease duration and without prior steroids, so both treatment strategies are truly used as first line treatment. In a previous version of the protocol, one of the inclusion criteria was 'without medical IBD treatment for at least one year'. This criterion has been replaced by the exclusion criterion 'use of corticosteroids for a duration longer than 4 months in the year before screening', to prevent the criteria from being too strict and to not miss potential participants with a flare in the subsequent year after diagnosis. However, in clinical practice most patients needing a second course of steroids are started on maintenance therapy, and consequently are not eligible for this study.

Currently, a certain interval between previous steroid use is not required. In line with the comment, an amendment to the protocol has been submitted to adjust this exclusion criterion and to make a distinction

between the use of prednisone and budesonide. The exclusion criterion 'Use of corticosteroids for a duration longer than 4 months in the year before screening' will be replaced by the exclusion criteria 'Use of prednisone in the year before screening (excluding prednisone used as bridging before the start of study medication)' and 'Use of budesonide for a duration longer than 3 months in the year before screening'.

Prednisolone or budesonide for max 2 weeks before starting medication according to the assigned study group is permitted, since eligible patients get at least one week to decide whether they want to participate or not after being informed about the study. After this week, patients can be included and randomized. During this week and/or after this week, if the biological screening results are awaited for patients randomized in the adalimumab group, it can be desirable to bridge this waiting time. The prednisone dose for this bridging has been chosen lower than usually, so it can be stopped without tapering if randomized in the adalimumab group.

- Is TDM in patients treated with ada part of the protocol?

Therapeutic drug monitoring in patients treated with adalimumab is indeed part of the protocol. TDM will be performed at week 24 for the patients in the adalimumab group. Additionally, TDM is performed before adjusting medication or escalation to the next drug according to the study algorithms, as part of dose optimization. The sentence 'Therapeutic drug monitoring for thiopurines and TNF-blockers will be performed before escalation to another drug.' has been added to the manuscript on page 10.

- Adalimumab monotherapy vs step up care, means sc treatment vs oral. Do authors envisage problems with enrolment because of this difference? And in case yes, how to overcome this?

We did not envisage the randomisation between subcutaneous and oral treatment to be an enrollment problem. The administration of adalimumab has both disadvantages and advantages over oral treatment. Subcutaneous administration might be a difficulty for patients afraid of needles. At the same time, taking medication orally might be a problem for patients who have difficulty swallowing tablets. In addition, adalimumab is administered weekly or every other week, whereas oral medication has to be taken every day. So far, the administration route has not been a reason for eligible patients to decline participation.

- Table 1 shows a complete overview of the study schedule. It would be helpful to add a figure showing the most important information in this table.

We have added an overview of the study design with the assessments during follow-up, see figure 1.

- Line 37 page 15, here is stated to assess the efficacy of adalimumab monotherapy… Which is not really the case. I would suggest to adjust this: eg. as episodic adalimumab or induction with adalimumab

The sentence on page 15 is adjusted accordingly to 'To assess the efficacy of episodic adalimumab monotherapy as first line treatment, the primary outcome of this trial is the number of yearly quarters of corticosteroid free remission'.

- **A challenge which needs further discussion is the comparability of both strategies. For example: primary outcome: the number of yearly quarters of corticosteroid free clinical remission and biochemical remission at week 96. In the step-up group STEP 2 includes prolonged use of CS, while this is not the case for adalimumab monotherapy treated patients.**

Since treatment is not curative and disease course is unpredictable, it is important to evaluate the effect of a treatment strategy during induction and maintenance. To take into account the entire study duration while comparing both strategies, and to overcome the difference in time to maximum effect of the different drugs used, the primary outcome is defined by yearly quarters.

Corticosteroid sparing is an important treatment goal. One of the reasons for this study is the need for reduced CS use (and corresponding drug related side effects) in the treatment of Crohn's disease. Therefore, steroid-free is part of the primary outcome definition. Prolonged use of CS is generally part of the first quarter when the primary outcome is already not met, since the patients are not in remission. Therefore, prolonged use of CS is not expected to make a difference in primary outcome between the two groups.

- Primary endpoint focusses on steroid free remission. What if patients restarted adalimumab?

The primary outcome focusses on steroid-free clinical and biochemical remission. Whether a patient needs steroids or restarts adalimumab because of disease activity, in both situations the patient does not meet the primary endpoint.
If a patient is in remission with steroids he does not meet the primary outcome. Steroids are solely meant as induction therapy, not as maintenance, however some patients become steroid dependent.
If a patient is in remission with adalimumab he meets the primary outcome. Adalimumab is meant as induction and maintenance. If a patient need to restart adalimumab, this patient is not in remission at that moment and hence does not meet the primary endpoint.

- Figure 1: add to the adalimumab monotherapy column 1 that the duration of adalimumab induction treatment is 24 weeks.

In the column of adalimumab monotherapy in this figure (revised figure 2), the duration of treatment with adalimumab (at least 24 weeks) has been added.

- I do not fully understand the sequence (Figure 1). Ada mono: step 3 is dose optimization while step is already switch to ifx. Why not peform TDM and optimize before switch?

In the protocol, it is noted that TDM is performed in both study arms before escalation to the next drug according to the study algorithms, so TDM for adalimumab is also performed before switch. To clarify this, the step of dose optimization of adalimumab has been added in between step 2 and 3 in this figure (revised figure 2).

- What about quality of life, PK, thiopurine levels?

Patient reported outcomes on quality of life are part of the secondary outcomes, and measured three monthly by questionnaires in the telemedicine tool myIBDcoach. welke
Pharmacokinetics are part of the methods of the study, but not of the outcomes. TDM for thiopurines and TNF-blockers will be performed before adjusting medication. PK data is not collected given the goal of this pragmatic strategy study with registered drugs

VERSION 2 – REVIEW

REVIEWER	de Ridder, Lissy Erasmus MC Sophia Children Hospital, Paediatric gastroenterology
REVIEW RETURNED	17-Dec-2020

GENERAL COMMENTS	Thank you very much for the thorough rebuttal of the comments. Congratulations with the nice manuscript and good luck with your interesting study.