PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	VAlidation of an 8-item-questionnaire predictive for a positive CaLprotectin tEst and Real-life implemenTation in primary care to reduce diagnostic delay in inflammatory bowel disease (ALERT): protocol for a prospective diagnostic study
AUTHORS	Hasler, Susann; Zahnd, Nadine; Müller, Salomé; Vavricka, Stephan; Rogler, Gerhard; Tandjung, Ryan; Rosemann, Thomas

VERSION 1 - REVIEW

REVIEWER	Andreas Zeller Institute of Primary Health Care University of Basel Switzerland
REVIEW RETURNED	18-Jan-2015

GENERAL COMMENTS	Diagnosing inflammatory bowel disease in primary care is challenging. Earlier and appropriate calprotectin testing may reduce diagnostic delay regarding the presence of inflammatory bowel disease. However, fecal calprotectin testing is “more complicated” for patients than filling in a short questionnaire, fecal calprotectin testing is more expensive, and needs laboratory infrastructure. Questionnaires are readily available, can be filled in by patients in the waiting room, and provide immediate information (e.g. during the consultation, no waiting time for laboratory result). Hasler S et al. present a study protocol of a prospective observational trial assessing the predictive performance of an 8-item questionnaire developed to increase pre-test probability for a positive result of fecal calprtectin levels. The study consists two parts assessing patients referred for endoscopic evaluation (part A) and patients presenting to their GPs because of unspecific gastrointestinal symptoms (part B). In my view the protocol is scientifically credible and presented in an appropriate context. The methodological aspects are clearly described and sound. Background information is comprehensive and the reader is left with sufficient information. The references are up to date. Basically, I feel the study is feasible in busy general practice (part B) since the questionnaire itself is short and the information requested is part of history taking and physical examination by GPs assessing patients with gastrointestinal symptoms. Minor points:

	♣ On page 2/22, line 15 I would prefer “gastrointestinal symptoms” instead of “stomach ache”. ♣ I wonder what does” gastroentereologists, specialised for IBD” (p 5/14, line 18) exactly mean. In my view every gastroenterologist performing endoscopic evaluation should be able to manage or give therapeutic advice how to tailor the treatment of a patient with IBD. ♣ Figure “study design” on page 15/22. What is the meaning/point of the arrow in the middle of the graph? Thanks ever so much for having given me the opportunity to review this study protocol. I’m looking forward to the results of this interesting evaluation.

REVIEWER	D'Haens, Geert AMC Amsterdam
REVIEW RETURNED	21-Jan-2015

GENERAL COMMENTS	This is an interesting study proposal meeting a clinical ‘need’ in the community to facilitate an earlier diagnosis of IBD. THE PAPER ONLY DESCRIBES THE STUDY DESIGN AND HAS NO RESULTS YET Although the protocol is already ongoing, there are a few remarks to be made: 1. Early intervention is beneficial in CD but there is no data it is helpful in UC. 2. A calpro <50 does not exclude Crohn’s disease. In fact a significant proportion of patients with Crohn’s ileitis have NORMAL calprotectin. The authors should recognize this and probably this should also have an effect on the sample calculation. 3. The seminal paper by D’Haens et al. about the correlation between endoscopic lesions and calpro values in UC and CD should be included. 4. Patients diagnose with IBD are asked about the duration for their symptoms (delay). It would be preferable to ask that question before the endoscopy to avoid bias. 5. The authors already state that the sample size may not be reached at the GP practices. Efforts should be made, however, to avoid this eg by including more participating practices/GP’s. 6. Before a diagnosis of IBD is considered and an endoscopy scheduled it is generally recommended to exclude gastrointestinal infections, bacterial and parasitic. To make the study more scientifically sound it would be advisable to exclude this infections with stool examinations before patients are enrolled in this program.

VERSION 1 – AUTHOR RESPONSE

Comments of reviewer Andreas Zeller

Diagnosing inflammatory bowel disease in primary care is challenging. Earlier and appropriate calprotectin testing may reduce diagnostic delay regarding the presence of inflammatory bowel disease. However, fecal calprotectin testing is “more complicated” for patients than filling in a short questionnaire, fecal calprotectin testing is more expensive, and needs laboratory infrastructure.

Questionnaires are readily available, can be filled in by patients in the waiting room, and provide immediate information (e.g. during the consultation, no waiting time for laboratory result).

Hasler S et al. present a study protocol of a prospective observational trial assessing the predictive performance of an 8-item questionnaire developed to increase pre-test probability for a positive result of fecal calprotectin levels.

The study consists two parts assessing patients referred for endoscopic evaluation (part A) and patients presenting to their GPs because of unspecific gastrointestinal symptoms (part B).

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Minor points:

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§ I wonder what does” gastroentereologists, specialised for IBD” (p 5/14, line 18) exactly mean. In my view every gastroenterologist performing endoscopic evaluation should be able to manage or give therapeutic advice how to tailor the treatment of a patient with IBD.

Thank you for these comments. Changes were made accordingly. However, real life practice shows that a dedicated IBD gastroenterologist is far more than a person who is able to do endoscopy. In contrast to the reviewers view definitely not every gastroenterologist that is able to perform endoscopic evaluation is able to tailor treatment of IBD patients. In fact many gastroenterologists that do more or less exclusively endoscopy do not even want to (but this is not subject of this study).

§ Figure “study design” on page 15/22. What is the meaning/point of the arrow in the middle of the graph?

The study consists of two independent parts. Thus we deleted the arrow.

Comments of reviewer Geert D'Haens

This is an interesting study proposal meeting a clinical ‘need’ in the community to facilitate an earlier diagnosis of IBD.
THE PAPER ONLY DESCRIBES THE STUDY DESIGN AND HAS NO RESULTS YET

Although the protocol is already ongoing, there are a few remarks to be made:

1. Early intervention is beneficial in CD but there is no data it is helpful in UC.
Thank you for this comment. Indeed data from the Swiss IBD cohort study (among others) showed that a diagnostic delay in CD causes an increased rate of surgeries in the first year after diagnosis (Schoepfer and Vavricka). In the meantime we have further data showing that a start of 5-ASA treatment in patients with UC may be of disadvantage for the further disease course (manuscript submitted).

2. A calpro <50 does not exclude Crohn’s disease. In fact a significant proportion of patients with

Crohn's ileitis have NORMAL calprotectin. The authors should recognize this and probably this should also have an effect on the sample calculation.

Thank you for this comment. While planning of the study we were well aware of this fact. The purpose of the study is not to exclude CD in the study population. The main goal is to study whether a questionnaire can increase the pre-test probability for calprotectin testing. The sample size calculation was done with respect to this goal.
Accordingly, the primary endpoint in part A (gastroenterologists) is the prospective validation and evaluation of sensitivity and specificity of the 8-item questionnaire (CalproQuest) for 1) a positive Calprotectin test result greater than or equal 50 µg/g feces and for 2) a positive Calprotectin test result greater than or equal 50 µg/g feces and positive IBD-diagnosis. All the patients in part A will undergo an endoscopy, patients with Crohn's ileitis and normal calprotectin will be diagnosed.
Subsequently, taking this into account, the sample size was calculated according to the formula of Flahault et al. [1] (Ncontrols = Ncases x [(1-prevalence)/prevalence]). As we don't know the prevalence of fecal Calprotectin-testing in Switzerland, we used an estimated prevalence of 20% of immune bowel disease (confirmed by endoscopy) in our gastroenterologic practices. It is an approximation, other studies about diagnostic accuracy of fecal calprotectin in patients with inflammatory bowel disease were performed in a sample with a prevalence of 42-82% [2]. Calculating the formula of Flahault with a prevalence of 40% would lead to a lower sample size, i.e. around 62 patients.

3. The seminal paper by D'Haens et al. about the correlation between endoscopic lesions and calpro values in UC and CD should be included.

Thank you for the reference, which is now included in the protocol. We just want to point out that there are usually less cited but nevertheless excellent manuscripts on the same topic by Schoepfer et al.

4. Patients diagnose with IBD are asked about the duration for their symptoms (delay). It would be preferable to ask that question before the endoscopy to avoid bias.

As we will include patient without known diagnosis, we decided to ask these questions only after appropriate diagnoses. In fact, with this procedure we have to account a "recall bias", which we are aware of. The recall bias cannot be completely avoided even asking the question before endoscopy. We discuss this now as a limitation of the study which is inevitable and thank the reviewer for this comment.

5. The authors already state that the sample size may not be reached at the GP practices. Efforts should be made, however, to avoid this eg by including more participating practices/GP's.

In part B the primary endpoint is the feasibility. The number of 80 patients was based on previous studies investigating the feasibility of a new implemented tool in primary care. However we could finally recruit about 35 GPs, recruiting 1-5 patients each. Therefore, we are quite confident, that we will reach the inclusion number in the GP practices.

6. Before a diagnosis of IBD is considered and an endoscopy scheduled it is generally recommended to exclude gastrointestinal infections, bacterial and parasitic. To make the study more scientifically sound it would be advisable to exclude this infections with stool examinations before patients are enrolled in this program.

Thank you for your remark. In part A, we assume that this sort of clarification has already been done by the GP before referral to a gastroenterologist. It will be checked, whether this has happened and otherwise it will be done before endoscopy. In part B (primary endpoint: feasibility), a screening list

was added, where the GP are requested to tick a box, whether the symptom or the history of the patient is more probable to be an infectious disease. Subsequently the patient should not be included into the study.

[1] Flahault A, Cadilhac M and Thomas G (2005) Sample size calculation should be performed for design accuracy in diagnostic test studies. Journal of clinical epidemiology 58: 859-862.
[2] Lin JF, Chen JM, Zuo JH, Yu A, Xiao ZJ, et al. (2014) Meta-analysis: fecal calprotectin for assessment of inflammatory bowel disease activity. Inflammatory bowel diseases 20: 1407-1415.