PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Selecting children with suspected inflammatory bowel disease for endoscopy with the calgranulin C or calprotectin stool test: protocol of the CACATU study.
AUTHORS	Heida, Anke; Vijver, Els; Muller Kobold, Anneke; Rheenen, Patrick

VERSION 1 - REVIEW

REVIEWER	Dr Paul Henderson Consultant Paediatric Gastroenterologist Dept of Paediatric Gastroenterology and Nutrition Royal Hospital for Sick Children Sciennes Road Edinburgh EH9 1LF
REVIEW RETURNED	23-Jan-2017

GENERAL COMMENTS	This is a very useful and interesting study to assess whether calgranulin C out performs FC in the diagnosis of paediatric IBD. A few comments: 1. Can the authors explain more fully with a protein released by granulocytes would be more specific for IBD? 2. Is it not standard practice for all patients with expected IBD to be seen and clinically assessed by a paediatric gastroenterologist? Would a paediatrician be expected to refer a child straight for endoscopy based on biomarkers alone? 3. Is the study to include patients up to 19yrs of age? (i.e. 6-18yrs). This is a very high age range foe paediatric IBD, especially given the Paris classification etc (i.e. 17yrs). 4. Why is the decision for endoscopy based on the FC result (in addition to symptoms and blood tests). I am slightly concerned that patients with an FC <50, while highly unlikely to have IBD, may still have bowel pathology requiring endoscopic assessment. I am concerned that clinicians (and not always gastroenterologists) will get an email saying "your patient is at low risk of IBD - suggest do not scope". This may be inappropriate for this patient as other pathologies may have a normal calprotectin but require endoscopy (coeliac disease etc). 5. Table 1 is quite vague and I would argue that a patient with two episodes of abdominal pain with diarrhoea in 6 months would not be at "high risk" of IBD. Similarly, with rectal blood loss, there are many differentials for this (polyps etc) so again ALL patients with this finding would not be suspected of IBD. Again, looking at the minor criteria, according to this protocol, a patient with a CRP of 11 and anaemia would be classed as "suspected IBD" which may be very inappropriate. Although I appreciate that he authors are attempting to use this in a real world scenario, I am concerned that many children's treatment/management will be influenced by this study.

	6. Can the authors comment on the number of children in the Netherlands/Belgium that they would expect to be diagnosed with IBD each year? Although they have given some power calculations it seems as though, with the current data available, they would be expecting to diagnose ~200 patients per year? Some basic numbers of IBD diagnoses per year would be useful to assess feasibility. Overall this is a study that needs performed but I am concerned that FC and Cal C are being used exclusively in the context of IBD with other diagnoses not taken into consideration during the study protocol.

REVIEWER	Barbara Lisowska-Myjak Department of Biochemistry and Clinical Chemistry, Medical University of Warsaw. Warsaw, Poland
REVIEW RETURNED	01-Mar-2017

GENERAL COMMENTS	Introduction of new diagnostic strategies supported by the validation of employed tests and scientific grounds for their interpretation is an important contribution to the improvement of health care. The paper submitted by Heida Anke uses faecal calprotectin , a well-established marker of intestinal inflammation in IBD and compares it with a new parameter (S100A12). The choice of S100A12 is well justified theoretically, because increases in S100A12 levels reflect both the presence of granulocytes at the site of inflammation and their activation. Demonstrating a higher specificity of S100A12 compared to faecal calprotectin is a step forward in the diagnosis of IBD. Also worthy of note is the idea behind the study - to find the most effective and at the same time the least invasive diagnostic tests for this special patient population, i.e. paediatric patients with IBD.

VERSION 1 – AUTHOR RESPONSE

Manuscript ID: bmjopen-2016-015636
Title: "Selecting children with suspected inflammatory bowel disease for endoscopy with the calgranulin C or calprotectin stool test: protocol of the CACATU study"
Authors: Heida A, Van de Vijver E, Muller Kobold AC, van Rheenen PF
Re: Detailed response to the comments of reviewer #1 (Dr. Paul Henderson)

1. Can the authors explain more fully why a protein released by granulocytes would be more specific for IBD?

In the introduction we added a paragraph to lay out the rationale for comparing the test characteristics of the relative unknown marker S100A12 and the more established marker calprotectin.

2. Is it not standard practice for all patients with expected IBD to be seen and clinically assessed by a paediatric gastroenterologist? Would a paediatrician be expected to refer a child straight for endoscopy based on biomarkers alone?

We hypothesize that these two questions arise from a misunderstanding of our patient spectrum. The CACATU-study is a so-called phase III diagnostic study. Similar to development of new drugs, diagnostic test development goes through several phases. In Phase I of the development of the S100A12 test researchers showed that patients with IBD had different test results from healthy individuals. In Phase II researchers compared faecal S100A12 levels between preselected groups of healthy individuals and of those with severe IBD and showed that the test can discriminate under ideal circumstances. In this phase III study we aim to evaluate whether faecal S100A12 can identify those with IBD in a group of consecutive patients with chronic gastrointestinal complaints. These patients can enter the study through the consultation room of the general paediatrician or the paediatric gastroenterologist. Both will base the need for endoscopic confirmation on the combination of symptoms, blood results and stool examination. Indeed it is standard practice for all patients referred for endoscopy to be first seen and clinically assessed by a paediatric gastroenterologist.
We adjusted the text in the paragraph entitled “Intervention” to make this more clear.

3. Is the study to include patients up to 19yrs of age? (i.e. 6-18yrs). This is a very high age range foe paediatric IBD, especially given the Paris classification etc (i.e. 17yrs).

In the Netherlands and Belgium paediatricians care for patients until they reach the age of 18. We changed the text about eligibility criteria accordingly.

4. Why is the decision for endoscopy based on the FC result (in addition to symptoms and blood tests). I am slightly concerned that patients with an FC <50, while highly unlikely to have IBD, may still have bowel pathology requiring endoscopic assessment. I am concerned that clinicians (and not always gastroenterologists) will get an email saying "your patient is at low risk of IBD - suggest do not scope". This may be inappropriate for this patient as other pathologies may have a normal calprotectin but require endoscopy (coeliac disease etc).

Apparently the reviewer has concerns that this study interferes with normal differential diagnostic reasoning. We can assure that the normal diagnostic work-up of the paediatrician is not disturbed, and we adjusted the text to make this more clear.

Notwithstanding the automated e-mail “your patient is at low risk of IBD”, we advise to contact the paediatric gastroenterologist if it is felt that endoscopy is required.

5. Table 1 is quite vague and I would argue that a patient with two episodes of abdominal pain with diarrhoea in 6 months would not be at "high risk" of IBD. Similarly, with rectal blood loss, there are many differentials for this (polyps etc) so again ALL patients with this finding would not be suspected of IBD. Again, looking at the minor criteria, according to this protocol, a patient with a CRP of 11 and anaemia would be classed as "suspected IBD" which may be very inappropriate. Although I appreciate that he authors are attempting to use this in a real world scenario, I am concerned that many children's treatment/management will be influenced by this study.

This comment made us realize that the legend of table 1 is not correct. We adjusted the text “Table 1: Study inclusion criteria.
One major criterion or two minor criteria are required to make the patient eligible for participation in the CACATU study.”

6. Can the authors comment on the number of children in the Netherlands/Belgium that they would expect to be diagnosed with IBD each year? Although they have given some power calculations it seems as though, with the current data available, they would be expecting to diagnose ~200 patients per year? Some basic numbers of IBD diagnoses per year would be useful to assess feasibility.

We aim to include at least 250 participants. To assess the feasibility of the study we asked the participating centers to count the number of patients that fulfilled the eligibility criteria in the year before the start of the study. The estimates of the centers convinced us that reaching the target sample size is realistic. We expect, based on a previous study in our region, that among all participants 36% will be diagnosed with IBD.(Van de Vijver 2012)
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Title: "Selecting children with suspected inflammatory bowel disease for endoscopy with the calgranulin C or calprotectin stool test: protocol of the CACATU study"
Authors: Heida A, Van de Vijver E, Muller Kobold AC, van Rheenen PF

Re: Detailed response to the comments of reviewer #2 Barbara Lisowska-Myjak

Introduction of new diagnostic strategies supported by the validation of employed tests and scientific grounds for their interpretation is an important contribution to the improvement of health care. The paper submitted by Heida Anke uses faecal calprotectin , a well-established marker of intestinal inflammation in IBD and compares it with a new parameter (S100A12). The choice of S100A12 is well justified theoretically, because increases in S100A12 levels reflect both the presence of granulocytes at the site of inflammation and their activation. Demonstrating a higher specificity of S100A12 compared to faecal calprotectin is a step forward in the diagnosis of IBD.
Also worthy of note is the idea behind the study - to find the most effective and at the same time the least invasive diagnostic tests for this special patient population, i.e. paediatric patients with IBD.

VERSION 2 – REVIEW

REVIEWER	Dr Paul Henderson Royal Hospital For Sick Children Scotland, UK
REVIEW RETURNED	29-Mar-2017

GENERAL COMMENTS	No further comments - all queries answered appropriately and clearly