PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Using laxatives and/or enemas to accelerate the diagnosis in children presenting with acute abdominal pain: a randomized controlled trial study protocol
AUTHORS	Timmerman, Marjolijn; Trzpis, Monika; Broens, Paul

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Bob Phillips Institution and Country: Centre for Reviews and Dissemination, UK Competing interests: None
REVIEW RETURNED	23-Aug-2018

GENERAL COMMENTS	This is a paper exploring a protocol for an ongoing trial of laxatives & enemas to reduce pain and increase speed to diagnosis in children presenting to the emergency department with a low suspicion of acute appendicitis, but no clear diagnosis having been reached. The protocol is slightly confused, in that it describes itself (during the sample size calculation) as a pilot study, yet no-where else is this mentioned nor does it have any outcomes related to it being a pilot. These I would expect to be; descriptions of the rates of randomisation below which it would be unfeasible to undertake a study; rates of outcome assessment &/or completion; practical aspects of study management or assessments of the views of those included in the study. As written, it seems like this is a phase III study of the management approach, but inadequately powered, and so designated 'pilot'. The study is written strongly describing how this technique will speed the diagnosis of constipation, yet the primary outcome is of abdominal pain measurements, and a hoped reduction in pain with the use of laxatives and enemas. This is another area where the description and the design do not match. The suggested analysis techniques appear sensible for a full study, but they seem inappropriate when the target number of patients is 15 in each group. With this number of patients, the risk of false conclusions appears high. This sample size also differs from the size on the trial registry (n=60). The study appears to need the child to return for a second visit. To me, this would be better described in the inclusion criteria with a phrase more like that in the first line of the 'Intervention' section: "If children do not receive a conclusive diagnosis after the first consultation at the emergency room and need to return for a second consultation," As I read the study, it is not all children with abdominal pain who are recruited, but those who are not definitively diagnosed AND need at least one more visit. The discussion section appears to have information about the first four years of undertaking this study within it.

	It would be better if this would be clearly explained, setting out when the trial was opened, the challenges far and the alterations which have been undertaken to address these. The protocol has a couple of phrases which do not 'read well' in English: "The code of resistance of minors will also be taken into account." - I do not understand this phrase "suffering acute abdominal pain, but who were not diagnosed after first consultation," – I would suggest making clearer with the phrase – ""suffering acute abdominal pain, but who DID NOT HAVE A DEFINITIVE DIAGNOSIS MADE after first consultation,"

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment 1. This is a paper exploring a protocol for an ongoing trial of laxatives & enemas to reduce pain and increase speed to diagnosis in children presenting to the emergency department with a low suspicion of acute appendicitis, but no clear diagnosis having been reached. The protocol is slightly confused, in that it describes itself (during the sample size calculation) as a pilot study, yet no-where else is this mentioned nor does it have any outcomes related to it being a pilot. These I would expect to be; descriptions of the rates of randomization below which it would be unfeasible to undertake a study; rates of outcome assessment &/or completion; practical aspects of study management or assessments of the views of those included in the study. As written, it seems like this is a phase III study of the management approach, but inadequately powered, and so designated 'pilot'.

Response: The protocol described in our manuscript has indeed been set up as a pilot study, since our local Medical Ethical Committee would not allow us to perform this study without a power analysis. Since we did not have any data /starting point to calculate this power, we described the study as a pilot. The committee has accepted this pilot study to be described as if it was already a randomized controlled trial. Because later on, once the data needed for power analysis are gained, we can directly follow the same protocol with only adjusting the number of patients required for the final randomized controlled trial. The idea behind it is that by performing such a pilot, one can more accurately calculate the sample size and also eventually figure out possible weak points, and then adjust the protocol accordingly after the pilot phase, before the final randomized study. In other words, after performing the pilot study, the local Medical Ethical Committee receives an amendment in which the sample size is adjusted to the sample size calculation, and eventual improvements on the protocol are introduced, if necessary. This is the reason we have presented a detailed study protocol prepared for a randomized controlled trial but with a small sample size. To clarify this issue, we have added an explanation to the Methods (page 6, lines 124-129) and Discussion (page 12, lines 285-190). In addition, as mentioned in our answer to the second comment of the reviewer, we have also added information regarding outcome measurement (page 8, lines 178-180).

2. The study is written strongly describing how this technique will speed the diagnosis of constipation, yet the primary outcome is of abdominal pain measurements, and a hoped reduction in pain with the use of laxatives and enemas. This is another area where the description and the design do not match. The suggested analysis techniques appear sensible for a full study, but they seem inappropriate when the target number of patients is 15 in each group. With this number of patients, the risk of false conclusions appears high.

Response: We agree that the mentioned primary and secondary outcome are only appropriate for a study with a bigger simple size. This issue can be indeed confusing if the reader has not been explained that our protocol has been designed for both:

a pilot study (with a limited sample size) and final study (with a sufficient sample size). To clarify this point, have added information about the outcome measures specifically for the pilot study, namely the binary variable ‘’diminishing of abdominal pain in the consecutive consultation’’ (page 8, lines 178-180).

3. This sample size also differs from the size on the trial registry (n=60).

Response: Our apologies for the confusion. The original protocol that was accepted by the Medical Ethical Committee consisted of two parts with similar inclusion criteria but with different research questions, namely: 1. “Does supporting fecal production with laxatives and/or enemas accelerates the final diagnosis in children with acute abdominal pain?” and “Are acute cytomegalovirus and human herpes virus 6 infection correlated with acute appendicitis in children?”. The Medical Ethical Committee obliged us to combine these studies and to register them together in the trial register. The sample size of 60 in the trial register was meant for the study on the correlation of viruses and acute appendicitis (the manuscript has already been submitted to Virology Journal). It was unfortunately not possible to add two different sample sizes for both parts in this trial registry, and therefore the number of patients we have aimed to use for the first part of the protocol (n = 30) was not reported in the trial register, while it was reported in the first part of our protocol. If either the reviewer or the editor finds this information to be important to be placed in the manuscript, we are willing to do it.

4. The study appears to need the child to return for a second visit. To me, this would be better described in the inclusion criteria with a phrase more like that in the first line of the ‘Intervention’ section: “If children do not receive a conclusive diagnosis after the first consultation at the emergency room and need to return for a second consultation,” As I read the study, it is not all children with abdominal pain who are recruited, but those who are not definitively diagnosed AND need at least one more visit.

Response: To improve the points raised by the reviewer, we have revised the fragments according to his /her suggestions (page 6, lines 133-135).

5. The discussion section appears to have information about the first four years of undertaking this study within it. It would be better if this would be clearly explained, setting out when the trial was opened, the challenges far and the alterations which have been undertaken to address these.

Response: We revised the order of the discussion to make the course of our study more clear. We have however, not introduced any alteration until now, because for these we need to obtain agreement of the medical ethics committee. We aim to apply for the permission to extend the protocol to a multicenter study, and we have added this information to the revised discussion.

6. The protocol has a couple of phrases which do not ‘read well’ in English:

“The code of resistance of minors will also be taken into account.” - I do not understand this phrase

“suffering acute abdominal pain, but who were not diagnosed after first consultation,” – I would suggest making clearer with the phrase – ““suffering acute abdominal pain, but who DID NOT HAVE A DEFINITIVE DIAGNOSIS MADE after first consultation,”

Response: We have adjusted the abovementioned phrases in accordance with the advice of the reviewer in the Introduction (page 5, line 112) and in the Methods (page 7, lines 149-150 and page 9, lines 200-200).