PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Acute Uncomplicated Appendicitis Study: Rationale and protocol for a multi-centre, prospective randomised controlled non-inferiority study to evaluate the safety and effectiveness of non-operative management in children with acute uncomplicated appendicitis
AUTHORS	Xu, Jane; Liu, Yingrui; Adams, Susan; Karpelowsky, Jonathan

VERSION 1 - REVIEW

REVIEWER	Dr. Salomone Di Saverio MD FACS FRCS Maggiore and Bellaria Hospital AUSL Bologna
REVIEW RETURNED	12-Aug-2016

GENERAL COMMENTS	Interesting randomized prospective study on a debated and well studied topic in adults. However answering the same question in a paediatric population would be of even more interest, given also the implications of imaging use and potential radiation exposure in children for diagnosing appendicitis and eventual follow up of non operatively treated cases vs the potential short and long term complications of surgery. The discussion of the Background section could be improved, with addition of the recommendations from the most up-to-date international evidence-based 2016 guidelines on diagnosis and management of AA, (see WSES Jerusalem guidelines for diagnosis and treatment of acute appendicitis. Di Saverio S, Birindelli A, Kelly MD, Catena F, Weber DG, Sartelli M, Sugrue M, De Moya M, Gomes CA, Bhangu A, Agresta F, Moore EE, Soreide K, Griffiths E, De Castro S, Kashuk J, Kluger Y, Leppaniemi A, Ansaloni L, Andersson M, Coccolini F, Coimbra R, Gurusamy KS, Campanile FC, Biffl W, Chiara O, Moore F, Peitzman AB, Fraga GP, Costa D, Maier RV, Rizoli S, Balogh ZJ, Bendinelli C, Cirocchi R, Tonini V, Piccinini A, Tugnoli G, Jovine E, Persiani R, Biondi A, Scalea T, Stahel P, Ivatury R, Velmahos G, Andersson R. World J Emerg Surg. 2016 Jul 18;11:34) especially when there is the sentence regarding "In fact, children with appendicitis complicated by perforation, abscess or phlegmon formation are often preferentially treated primarily non-operatively with antibiotic therapy, with or without percutaneous drainage – a management for which there is an evidence base.[8, 9]" as well as when discussing the morbidity - potential complications of open or laparoscopic appendectomy and the possibility of safety and efficacy on NOM that has been largely demonstrated in Adults (see the prospective cohort study in adults published on Ann Surg. 2014 Jul;260(1):109-17

	A further comments In the inclusion criteria "Clinical diagnosis by at least one paediatric surgeon of AUA based on a combination of clinical, laboratory and/or imaging findings; that before the study would have led to the decision to recommend appendicectomy." I think it would be better to make this criterion more objective and widely reproducible. Would you use a clinical score such as Alvarado or AIR score, for making a reliable diagnosis of AA?

REVIEWER	Daniel DeUgarte University of California Los Angeles, USA
REVIEW RETURNED	18-Aug-2016

GENERAL COMMENTS	1) There is no data in this report. I defer to the editor if papers describing study design are suitable for publication in BMJ. 2) Questions related to study design: a) Primary outcomes: Two primary outcomes are listed (unplanned/unnecessary operation AND complications). Are complications truly a primary outcome (incorporated into sample-size calculations)? If so, how? Or, are complications - in fact - another secondary outcome? How are complications being counted/weighted? Are surgical-site-infections being counted equal to sepsis or death? b) Primary outcome selection: It is my opinion that the primary outcome should be something that is comparable for both study arms. How can you only count 'failed' operations for the antibiotic group, when 100% of the patients in the appendectomy group get an appendectomy. This seems unfair. The 15% difference seems a bit arbitrary as was the adult RCT, which had a similar comparison. I think it would be better to find something that can be compared for both groups.

REVIEWER	Dr M.Muthucumaru Canberra hospital, Canberra Australia.
REVIEW RETURNED	22-Aug-2016

GENERAL COMMENTS	primary outcome- OM group - normal appendix at operation is considered an unnecessary operation rather than an exclusion criteria from the study. why is it not considered as exclusion from the appendicectomy group?. failure of the NOM should be assessed in the first admission and if on operation found other pathology needs to be excluded from the study.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
The introduction has been edited and the important references noted by Dr. Salomone Di Saverio have been included.

With respect to the question on the inclusion of an appendicitis scoring system as part of the study "Clinical diagnosis by at least one paediatric surgeon of AUA based on a combination of clinical, laboratory and/or imaging findings; that before the study would have led to the decision to recommend appendicectomy."
I think it would be better to make this criterion more objective and widely reproducible. Would you use a clinical score such as Alvarado or AIR score, for making a reliable diagnosis of AA?

The entry point into this study is when the treating team feels there is enough evidence to subject a child to surgery for an appendicectomy. We contemplated using one of the standardised appendicitis scores such as Alvarado or the Paediatric Appendicitis Score (PAS), however these scores are not routinely used within clinical practice in Australia (apart from one prospective emergency department triage study currently underway). Furthermore, as noted by S Di Saverio et al in World J Emerg Surg. 2016 Jul 18;11:34 “Statement 1.2 The Alvarado score is not sufficiently specific in diagnosing acute appendicitis [EL 1, GoR A]”. An important aspect for the authors during study design was to ensure that the results from this study were generalisable, thus a more pragmatic point of entry was chosen representing the way appendicitis is diagnosed and managed daily. It was for a similar reason that we chose not to mandate imaging for entry into the study. As noted by Brockman SF, et al. ANZ J Surg. 2013; 83(10):744–7, only 25% of Australian patients get routine imaging during the workup for appendicectomy.

Reviewer 2

We would like to thank Dr DeUgarte for his insightful questions. He has highlighted the most challenging aspect of this study design. We assessed paediatric studies in this area to date. The Cochrane review defined efficacy was defined as cure within two weeks of intervention, along with the absence of major complications (including recurrence), Wilms IM, et al Cochrane Database of Sys Rev. 2011;11:1-34. The only another small RCT undertaken on non-operative management in paediatric appendicitis, Svensson J, et al Annals of Surgery 2015;261:67-71 used a similar primary outcome measure. In order to maintain consistency and improve further systematic review and meta-analysis a similar primary outcome was used. “The primary outcome for the study is the treatment efficacy for both NOM and OM in AUA based on the following within 30 days of randomisation”. There is this a single outcome measure. The subsequent definitions are representative of treatment efficiency. As the treatments are so discrepant it is challenging to find a single of come of efficacy.

With regards the second question, if complications have been weighted for the primary, the answer is no as as the primary outcome is binary. The presence of a complication relates for the purpose of the primary outcome to treatment efficiency. The spectrum and severity of complications is a secondary outcome number 3 “Treatment-related complications”. Finally, we have a DMSB who will assess the severity of complications in order to ensure patient safety.

Finally, with regards the “The 15% difference seems a bit arbitrary”. This was chosen for several reasons. A difference to power the study is always needed. The rationale for that number is twofold. Firstly, it is similar to prior studies. Secondly it represents a middle ground of success for non-operative management trials in children (92%) and adults (68%).

Reviewer 3

Thank you to Dr M.Muthucumaru for her question. The reason for negative appendicectomy being included in the primary outcome is that it represents an unnecessary operation and as such would affect treatment efficacy of surgery, our primary outcome. It was similarly included as a failure of or unnecessary treatment in Svensson J, et al Annals of Surgery 2015;261:67-71.
With respect to NOM being assessed on the first admission the primary outcome extends to 30 days as while there may be an initial early success on the first admission, prior studies have documented that there is a real incidence of recurrence following discharge. We thus would look at any unplanned or unnecessary admission at any time within the first 30 days.

Should there be any further questions, would be happy to provide further comment.