

Peer Review History

BMJ Open-2010-000006

The NOTA STUDY: Non Operative Treatment for Acute Appendicitis. Study on Efficacy and Safety of Antibiotic Treatment (Amoxicillin and Clavulanic Acid) in Patients With Right Sided Lower Abdominal Pain

Reviewer 1: Lee, Steven

Steven Lee

UCLA, Pediatric Surgery

The Study	Yes	No
Is the research question clearly defined?	✓	
Is the overall study design appropriate and adequate to answer the research question?	✓	
Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described?	✓	
Are the patients representative of actual patients the evidence might affect?	✓	
Are the methods adequately described?	✓	
Is the main outcome measure clear?	✓	
Are the abstract/summary/key messages/limitations accurate?	✓	
Are the statistical methods described?	✓	
Are they appropriate?	✓	
Is the standard of written English acceptable for publication?	✓	
Are the references up to date and relevant? (If not, please provide details of significant omissions below.)	✓	
Do any supplemental documents e.g. a CONSORT checklist, contain information that should be better reported in the manuscript, or raise questions about the work?	✓	

RESULTS AND CONCLUSION (For articles reporting research findings only)	Yes	No
Do the results answer the research question?		
Are they credible?		
Are they well presented?		
Are the interpretation and conclusions warranted by and sufficiently derived from/focused on the data?		
Are they discussed in the light of previous evidence?		
Is the message clear?		

REPORTING AND ETHICS	Yes	No
Is the article reported in line with the appropriate reporting statement or checklist (e.g. CONSORT)?		
Are research ethics (e.g. consent, ethical approval) addressed appropriately?	✓	
Is the article free from any concerns about publication ethics (e.g. plagiarism, fabrication, redundant publication, undeclared conflicts of interest)?	✓	



Reviewer 2: Styrud, Johan

Johan Styrud

Karolinska Institutet, General Surgery

The Study	Yes	No
Is the research question clearly defined?		✓
Is the overall study design appropriate and adequate to answer the research question?		✓
Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described?		✓
Are the patients representative of actual patients the evidence might affect?	✓	
Are the methods adequately described?		✓
Is the main outcome measure clear?		✓
Are the abstract/summary/key messages/limitations accurate?		✓
Are the statistical methods described?	✓	
Are they appropriate?	✓	
Is the standard of written English acceptable for publication?	✓	
Are the references up to date and relevant? (If not, please provide details of significant omissions below.)	✓	
Do any supplemental documents e.g. a CONSORT checklist, contain information that should be better reported in the manuscript, or raise questions about the work?	✓	

If you answered No to any of the above, please supply details below.

- 1/ There are many authors of the article. The reason for this should be explained.
- 2/ The paper asks two questions; first on how to investigate the patients with suspected appendicitis and second how to treat those patients. It is of great importance to separate the two questions.
- 3/ In the setting of a study necessary that all patients are treated in the same way. The authors claim that radiological exams should be performed "when it is needed or helpful". How this is decided must be explained.

RESULTS AND CONCLUSION (For articles reporting research findings only)	Yes	No
Do the results answer the research question?		✓
Are they credible?		✓
Are they well presented?		✓
Are the interpretation and conclusions warranted by and sufficiently derived from/focused on the data?		✓
Are they discussed in the light of previous evidence?		✓
Is the message clear?		✓

If you answered No to any of the above, please supply details below.

4/ A nex paper should be written including all treated patients, since the setting of the study is unclear and all patients have not yet been included. The last patient is inrolled in this study in dec 2010. It is better to wait and see the result.

REPORTING AND ETHICS	Yes	No
Is the article reported in line with the appropriate reporting statement or checklist (e.g. CONSORT)?		✓
Are research ethics (e.g. consent, ethical approval) addressed appropriately?	✓	
Is the article free from any concerns about publication ethics (e.g. plagiarism, fabrication, redundant publication, undeclared conflicts of interest)?	✓	

If you answered No to any of the above, please supply details below or contact the editorial office.

See item 4



Reviewer 3: Vons, Corinne

Corinne Vons

HOPITAL JEAN VERDIER ASSISTANCE PUBLIQUE Hôpitaux de Paris

The Study	Yes	No
Is the research question clearly defined?		✓
Is the overall study design appropriate and adequate to answer the research question?		✓
Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described?		✓
Are the patients representative of actual patients the evidence might affect?	✓	
Are the methods adequately described?		✓
Is the main outcome measure clear?		✓
Are the abstract/summary/key messages/limitations accurate?		✓
Are the statistical methods described?	✓	
Are they appropriate?		✓
Is the standard of written English acceptable for publication?	✓	
Are the references up to date and relevant? (If not, please provide details of significant omissions below.)		✓
Do any supplemental documents e.g. a CONSORT checklist, contain information that should be better reported in the manuscript, or raise questions about the work?	✓	

If you answered No to any of the above, please supply details below.

The interest of the authors' question seems not important; the authors want to TREAT patients with a suspected appendicitis, but not needing emergency appendectomy, with antibiotics.
Do these patients have or not an appendicitis; if not what is the problem?: to treat patients with no appendicitis to evaluate the recurrence of appendicitis?
the criteria for the patients selection are not clear, what about the result of the TDM with regard to the question of appendicitis not needing emergency surgery
How the authors

RESULTS AND CONCLUSION (For articles reporting research findings only)	Yes	No
Do the results answer the research question?		✓
Are they credible?		✓
Are they well presented?		✓
Are the interpretation and conclusions warranted by and sufficiently derived from/focused on the data?		✓
Are they discussed in the light of previous evidence?		✓
Is the message clear?		✓

If you answered No to any of the above, please supply details below.

There are NO RESULTS

REPORTING AND ETHICS	Yes	No
Is the article reported in line with the appropriate reporting statement or checklist (e.g. CONSORT)?		✓
Are research ethics (e.g. consent, ethical approval) addressed appropriately?	✓	
Is the article free from any concerns about publication ethics (e.g. plagiarism, fabrication, redundant publication, undeclared conflicts of interest)?		✓

In compliance with the BMJ Open system of open peer review, please sign your review in the box below. Include your name, position, institution and country. Please also include a statement of competing interests. If you have filled out an ICMJE Conflicts of Interests form, please attach this using the box beneath instead.

Pr. Corinne Vons, APHP Paris FRANCE

Reviewer 4: Catena, Fausto

Fausto Catena

S. Orsola Malpighi University Hospital, General and Transplant Surgery

The Study	Yes	No
Is the research question clearly defined?	✓	
Is the overall study design appropriate and adequate to answer the research question?	✓	
Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described?	✓	
Are the patients representative of actual patients the evidence might affect?	✓	
Are the methods adequately described?	✓	
Is the main outcome measure clear?	✓	
Are the abstract/summary/key messages/limitations accurate?	✓	
Are the statistical methods described?	✓	
Are they appropriate?	✓	
Is the standard of written English acceptable for publication?		✓
Are the references up to date and relevant? (If not, please provide details of significant omissions below.)	✓	
Do any supplemental documents e.g. a CONSORT checklist, contain information that should be better reported in the manuscript, or raise questions about the work?		✓

If you answered No to any of the above, please supply details below.

- 1) The english needs revisions by an english mother tongue reviewer.
- 2) A manuscript reporting a Study Protocol needs supplemental documents reporting all the information regarding the study according to the current Guidelines for reporting Clinical Trials and/or Clinical Observational Studies. I would suggest the authors to add a flow diagram of the study showing the phases of the study as well as a Tempogram representation of the Non Operative Treatment plan of the patients and of the follow up plan. Including a checklist of the items included in reporting the Study may also be beneficial and improve the quality of reporting the Study.

RESULTS AND CONCLUSION (For articles reporting research findings only)	Yes	No
Do the results answer the research question?		
Are they credible?		
Are they well presented?		
Are the interpretation and conclusions warranted by and sufficiently derived from/focused on the data?		
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REPORTING AND ETHICS	Yes	No
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Are research ethics (e.g. consent, ethical approval) addressed appropriately?	✓	
Is the article free from any concerns about publication ethics (e.g. plagiarism, fabrication, redundant publication, undeclared conflicts of interest)?	✓	

If you answered No to any of the above, please supply details below or contact the editorial office.

3) Again the Study Protocol manuscript is missing an accurate reporting Statement either as a Flow Diagram and/or a Checklist.

In 2007 a network of methodologists, researchers, and journal editors developed recommendations for reporting observational research: the strengthening the reporting of observational studies in epidemiology (STROBE) statement.

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.

BMJ. 2007 Oct 20; 335(7624):806-8
PLoS Med. 2007 Oct 16; 4(10):e296
Lancet. 2007 Oct 20; 370(9596):1453-7
Ann Intern Med. 2007 Oct 16; 147(8):573-7.

Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M; STROBE initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration.
PLoS Med. 2007 Oct 16; 4(10):e297
Ann Intern Med. 2007 Oct 16; 147(8):W163-94

As highlighted in these publications, much of the research into the cause of diseases relies on cohort, case-control, or cross sectional studies. Observational studies also have a role in research into the benefits and harms of medical interventions. Randomised trials cannot answer all important questions about a given intervention. For example, observational studies are more suitable to detect rare or late adverse effects of treatments, and are more likely to provide an indication of what is achieved in daily medical practice.

Research should be reported transparently so that readers can follow what was planned, what was done, what was found, and what conclusions were drawn. The credibility of research depends on a critical assessment by others of the strengths and weaknesses in study design, conduct, and analysis. Transparent reporting is also needed to judge whether and how results can be included in systematic reviews. However, in published observational research important information is often missing or unclear.

Recommendations on the reporting of research can improve reporting quality. The consolidated standards of reporting trials (CONSORT) statement was developed in 1996.

The STROBE statement is a checklist of items that should be addressed in articles reporting on the three main study designs of analytical epidemiology: cohort, case-control, and cross sectional studies. The intention is solely to provide guidance on how to report observational research well: these recommendations are not prescriptions for designing or conducting studies. Also, while clarity of reporting is a prerequisite to evaluation, the checklist is not an instrument to evaluate the quality of observational research.

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Dr. Fausto Catena MD PhD
Consultant General Surgeon
Emergency Surgery Unit
General and Multivisceral Transplant Unit
S. Orsola Malpighi University Hospital
University of Bologna
ITALY

Authors Response to Decision Letter for (BMJ Open-2010-000006)

The NOTA STUDY: Non Operative Treatment for Acute Appendicitis. Study on Efficacy and Safety of Antibiotic Treatment (Amoxicillin and Clavulanic Acid) in Patients With Right Sided Lower Abdominal Pain

Dear Editor,
Dear Reviewers,

We greatly appreciate the opportunity to revise in light of reviewers' comments our paper and resubmit it for publication on BMJ OPEN.
Enclosed. please find the revised version of our manuscript. previously submitted to your attention as

BMJ Open-2010-000006 "The NOTA STUDY: Non Operative Treatment for Acute Appendicitis. Study on Efficacy and Safety of Antibiotic Treatment (Amoxicillin and Clavulanic Acid) in Patients With Right Sided Lower Abdominal Pain" in the section STUDY PROTOCOL. We made our best efforts in order to make the requested revisions in light of the editor and reviewer's comments. Below you can find an itemized, point-by-point detailed response to all the questions and comments of the reviewers. We hope our paper is now suitable for publication on BMJ OPEN in its present form and we are now resubmitting it to your attention.

Reviewer #1 COMMENTS:
Reviewer: Steven Lee
"There are no comments".
Thanks.

Reviewer #2 COMMENTS:
Reviewer: Johan Styru
"1/ There are many authors of the article. The reason for this should be explained.
2/ The paper asks two questions; first on how to investigate the patients with suspected appendicitis and second how to treat those patients. It is of great importance to separate the two questions.
3/ In the setting of a study necessary that all patients are treated in the same way. The authors claim that radiological exams should be performed "when it is needed or helpful". How this is decided must be explained.
4/ A next paper should be written including all treated patients, since the setting of the study is unclear and all patients have not yet been included. The last patient is enrolled in this study in Dec 2010. It is better to wait and see the result".
1) The reason of the number of authors is because the overall sample size includes 160 patients. All authors have been involved at various degrees in enrolling, treating, following the patients, as well as in the design and conduction of the study, analysis and interpretation of the data and drafting the manuscript.
2) We do agree with you. The aim of the study protocol are both:
Evaluate the outcome of patients treated conservatively (Short and Long Term Efficacy of Antibiotic Treatment, Safety, Secondary Outcomes
Additional Objective: Identify clinical, laboratory or imaging findings that are predictive of failure of conservative treatment and/or relapse of appendicitis and need for appendectomy within 1 year time. The several different aims of the study have been clearly separated in the statement of the objectives within the Protocol and the results of the study will clarify this issue.
3) Imaging exams such as Ultrasound, may be helpful but are not usually necessary in diagnosing acute appendicitis and deciding its further treatment (Operative or non operative). Worldwide and from the literature the Scores such as Alvarado and AIR only includes clinical and laboratory characteristics. Therefore only the clinical signs and symptoms and laboratory values are routinely evaluated and assessed in the patient with suspected acute appendicitis for deciding its further treatment. However adjunctive radiological exams such as US maybe requested by the treating surgeon /doctor if deemed helpful.
This explanation has been added in the manuscript.
4) This is the paper presenting the study protocol and not yet reporting the results. The patients have all now been enrolled and the results with a proper follow up period will be available shortly and presented during 2011. The results will be submitted and published in due course.

Reviewer #3 COMMENTS:
Reviewer: Corinne Vons
"The interest of the authors' question seems not important; the authors want to TREAT patients with a suspected appendicitis, but not needing emergency appendectomy, with antibiotics.
Do these patients have or not an appendicitis; if not what is the problem?: to treat patients with no appendicitis to evaluate the recurrence of appendicitis?
The criteria for the patients selection are not clear, what about the result of the TDM with regard to the question of appendicitis not needing emergency surgery
How the authors".
Dear Prof. Vons,
Unfortunately your comments are quite unclear and the review is rather confusing than helpful to improve the manuscript. As far as I can understand:
-The question if these patients have or not appendicitis is rather philosophy!!! Do you know when you assess a patient with RIF pain and suspected appendicitis if he really has an appendicitis or not unless operating on this patient??? Do you operate all patients with RIF pain??? Can you really discriminate which patients really had an appendicitis between those with RIF pain observed and conservatively treated???

- As written in the manuscript:
the Inclusion Criteria are:
1. Age >14 years
 2. Lower / RIF Abdominal Pain
 3. Clinical Suspicion of Acute Appendicitis:
i.e.
 - o Alvarado Score 5-6 (equivocal for acute appendicitis)
 - o Alvarado Score 7-8 (probably appendicitis)
 - o Alvarado Score 9-10 (highly likely appendicitis)
 4. Informed consent (patient or legal representative)

Exclusion Criteria are:

1. Diffuse peritonitis
2. Antibiotic (Penicillin) documented allergy
3. Ongoing previously started antibiotic therapy
4. Previous appendectomy
5. Positive pregnancy test
6. IBD history or suspicion of IBD recrudescence

- Do you really think the author's question and the topic are not important??? It does not seem like the questions we are trying to answer are not important to you, Prof. Vons...
<http://www.druglib.com/trial/03/NCT00135603.html>

Reviewer #1 COMMENTS:

Reviewer: Fausto Catena

"1) The english needs revisions by an english mother tongue reviewer.

2) A manuscript reporting a Study Protocol needs supplemental documents reporting all the information regarding the study according to the current Guidelines for reporting Clinical Trials and/or Clinical Observational Studies. I would suggest the authors to add a flow diagram of the study showing the phases of the study as well as a Tempogram representation of the Non Operative Treatment plan of the patients and of the follow up plan. Including a checklist of the items included in reporting the Study may also be beneficial and improve the quality of reporting the Study.

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Ann Intern Med. 2007 Oct 16; 147(8):573-7.

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STROBE initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration.

PLoS Med. 2007 Oct 16; 4(10):e297

Ann Intern Med. 2007 Oct 16; 147(8):W163-94

As highlighted in these publications, much of the research into the cause of diseases relies on cohort, case-control, or cross sectional studies. Observational studies also have a role in research into the benefits and harms of medical interventions. Randomised trials cannot answer all important questions about a given intervention. For example, observational studies are more suitable to detect rare or late adverse effects of treatments, and are more likely to provide an indication of what is achieved in daily medical practice.

Research should be reported transparently so that readers can follow what was planned, what was done, what was found, and what conclusions were drawn. The credibility of research depends on a critical assessment by others of the strengths and weaknesses in study design, conduct, and analysis. Transparent reporting is also needed to judge whether and how results can be included in systematic reviews. However, in published observational research important information is often missing or unclear.

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The intention is solely to provide guidance on how to report observational research well: these recommendations are not prescriptions for designing or conducting studies. Also, while clarity of

reporting is a prerequisite to evaluation, the checklist is not an instrument to evaluate the quality of observational research.

Thanks for the opportunity of reviewing this Study Protocol for BMJ Open.

This is an interesting study carrying important implications on the management of the most common surgical disease worldwide such as appendicitis and one of the most common reasons of access to Emergency Department which is the lower / right sided abdominal pain. RIF / lower abdo pain is the extremely common in all ages and both genders and implies an insidious and multidisciplinary differential diagnosis.

Non operative treatment of a suspected appendicitis implies also relevant safety considerations, both in terms of delaying surgery or performing an unnecessary surgical procedure and appendectomy. In fact delaying surgical treatment may possibly increase risk of perforated appendicitis, intra-abdominal abscesses, localized or diffuse peritonitis, wound infection, increased risk of adhesions and subsequent ASBO and infertility. On the other hand, surgery and appendectomy are not without risk, as correctly underlined by the authors, carrying a possible risk of anesthesiological complications, intraoperative complications (either with laparoscopic or open approach, such as vascular lesions, enterotomies, urinary tract lesions etc), early surgical postoperative complications (hematoma/bleeding, colonic fistula, SSI, IAA, adhesions and ileus/obstruction) with subsequent rate of re-operation, late surgical postoperative complications (adhesions and subsequent ASBO and tubal infertility) and general postoperative complications.

Surgery may be associated with a longer length of hospital stay and higher costs compared with NOM with antibiotics but a delayed treatment and occurrence of perforated appendix may worsen morbidity, sick leave times and costs.

However NOM with antibiotics may be a cost-effective alternative to surgery in a large percentage of patients without increasing the risk, and may reduce hospital stay and costs in both developed and third world countries.

This NOTA study is welcome in order to clarify these issues and better identify the subset of patients where NOM with antibiotics may be more safe and more effective.

However I suggest the authors to better discuss the above issues in the Background section and possibly specify the reported incidence from the literature of the known risk associated with surgical procedure. This would give to the reader and all general practitioner a better overview of the risks and benefits of the treatment in order to better identify and select the patients whose potentially benefit from NOM rather than surgery. Giving the references for these described complications of the surgical treatment should also be done."

Thanks for your valuable suggestions. All points gave useful contribution in improving the study and the manuscript.

- 1) The English form has been reviewed by Dr. Di Saverio's wife, Mrs O. Pillay, English mother tongue.
- 2) Both a Tempogram (Fig. 2) showing the steps of Non Operative Treatment as well as the follow up plan of the Study as well as a Flow Diagram (Fig. 1), have been designed and included in the paper. The citations have also been added in the main text.
- 3) Thanks again for this extremely valuable observation and suggestion. In fact the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement is exactly fitting to our observational study and therefore we have included this checklist to our study manuscript. We have checked the fulfilment of all items of STROBE Checklist by our study. Most of the items were already included in the previous version including Title and Abstract, Introduction, Methods and Funding. The items relating to the Results and Discussion will be included and fulfilled in the reporting phase and in the article which will report the results of our NOTA STUDY. The STROBE Checklist has been included in the manuscript as Table 1 and the explanation and elaboration of STROBE Statement as well as the role of Observational Studies in daily medical practice, have been discussed further within the Rationale section.
- 4) Finally the risks and benefits of conservative vs surgical treatment for acute appendicitis have been discussed and added in the background section, specifying also the incidence of the surgical risks and giving appropriate references for that. The background section has overall been widely extended.

FROM THE BMJ OPEN EDITORIAL OFFICE

Please support the claim 'The study population estimated sample size is 160 patients in one year' with data showing the past two or three years' rates of suspected appendicitis at your department - reported in the context of the hospital's catchment population of over 14yr olds - and to compare those rates, if possible, with some previous literature on average incidence of suspected appendicitis per 100,000 population. The crude incidence of acute appendicitis was 86 per 100,000 inhabitants per year, varying between 74 and 96 per 100,000 during the 5-year period in Norway from an urban and rural catchment area with 265,000 inhabitants. A peak incidence of acute appendicitis was found in patients 13 to 40 years of age, and males were more frequently encountered in this age group (ratio 1.34:1.00). Among small children and elderly people, significantly ($p < 0.002$) more females were found to have acute appendicitis.

World Journal of Surgery Volume 21, Number 3, 313-317 Incidence of Acute Nonperforated and Perforated Appendicitis: Age-specific and Sex-specific Analysis Hartwig Körner, Karl Söndena, Jon Arne Söreide, Egil Andersen, Arne Nysted, Tone H. Lende, Kjell H. Kjellevoid

A further paper reported the incidence of appendicitis to be about 100 per 100,000 person-years in Europe/America. Whereas the appendectomy rate is still decreasing, the incidence of appendicitis is now nearly stable. During the last 30 years the incidence of perforated appendicitis has not changed (approximately 20 per 100,000 person-years). These data suggest the operative for acute appendicitis is decreasing, in an attempt to operate the truly complicated appendicitis really needing surgery and avoid unnecessary appendectomies.

Chirurg. 2002 Aug; 73(8):769-76. [Status report on epidemiology of acute appendicitis]. Ohmann C, Franke C, Kraemer M, Yang Q.

The catchment population of Bologna is half million people. Maggiore Hospital is the largest hospital of Bologna and covers the northern part of the urban area, the southern part being covered by another hospital.

These comments have been added to the paper

Thanks in advance for your attention and your interest in our work

Yours faithfully,

Dr. Salomone Di Saverio, MD

Dr. Gregorio Tugnoli, MD

BMJ Open-2010-000006.R1

The NOTA STUDY: Non Operative Treatment for Acute Appendicitis. Study on Efficacy and Safety of Antibiotic Treatment (Amoxicillin and Clavulanic Acid) in Patients With Right Sided Lower Abdominal Pain

Reviewer 4: Catena, Fausto

Fausto Catena

S. Orsola Malpighi University Hospital, General and Transplant Surgery

The Study	Yes	No
Is the research question clearly defined?	✓	
Is the overall study design appropriate and adequate to answer the research question?	✓	
Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described?	✓	
Are the patients representative of actual patients the evidence might affect?	✓	
Are the methods adequately described?	✓	
Is the main outcome measure clear?	✓	
Are the abstract/summary/key messages/limitations accurate?	✓	
Are the statistical methods described?	✓	
Are they appropriate?	✓	
Is the standard of written English acceptable for publication?	✓	
Are the references up to date and relevant? (If not, please provide details of significant omissions below.)	✓	
Do any supplemental documents e.g. a CONSORT checklist, contain information that should be better reported in the manuscript, or raise questions about the work?	✓	

RESULTS AND CONCLUSION (For articles reporting research findings only)	Yes	No
Do the results answer the research question?	✓	
Are they credible?	✓	
Are they well presented?	✓	
Are the interpretation and conclusions warranted by and sufficiently derived from/focused on the data?	✓	
Are they discussed in the light of previous evidence?	✓	
Is the message clear?	✓	

If you answered No to any of the above, please supply details below.

not applicable (Protocol Paper)

REPORTING AND ETHICS	Yes	No
Is the article reported in line with the appropriate reporting statement or checklist (e.g. CONSORT)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Are research ethics (e.g. consent, ethical approval) addressed appropriately?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Is the article free from any concerns about publication ethics (e.g. plagiarism, fabrication, redundant publication, undeclared conflicts of interest)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>

req BMJ Open uses compulsory open peer review. Your name and institution will be returned to the authors and will be published with this review if the article is accepted. Therefore please sign your review in the box below. Include your name, position, institution and country. Please also include a statement of competing interests. If you have filled out an ICMJE Conflicts of Interests form - please attach this using the box beneath instead.

Dr. Fausto Catena MD PhD
Emergency Surgery Unit
Department of General and Transplant Surgery
S. Orsola Malpighi University Hospital
University of Bologna, ITALY

Comments from the previous review:

Thanks for the opportunity of reviewing this Study Protocol for BMJ Open.

This is an interesting study carrying important implications on the management of the most common surgical disease worldwide such as appendicitis and one the most common reasons of access to Emergency Department which is the lower / right sided abdominal pain. RIF / lower abdominal pain is the extremely common in all ages and both genders and implies an insidious and multidisciplinary differential diagnosis.

Non operative treatment of a suspected appendicitis implies also relevant safety considerations, both in terms of delaying surgery or performing an unnecessary surgical procedure and appendectomy. In fact delaying surgical treatment may possibly increase risk of perforated appendicitis, intra-abdominal abscesses, localized or diffuse peritonitis, wound infection, increased risk of adhesions and subsequent ASBO and infertility. On the other hand surgery and Appendectomy are not without risk, as correctly underlined by the authors, carrying a possible risk of anesthesiological complications, intraoperative complications (either with laparoscopic or open approach, such as vascular lesions, enterotomies, urinary tract lesions etc), early surgical postoperative complications (hematoma/bleeding, colonic fistula, SSI, IAA, adhesions and ileus/obstruction) with subsequent rate of re-operation, late surgical postoperative complications (adhesions and subsequent ASBO and tubal infertility) and general postoperative complications. Surgery may be associated with a longer length of hospital stay and higher costs compared with NOM with antibiotics but a delayed treatment and occurrence of perforated appendix may worsen morbidity, sick leave times and costs.

However NOM with antibiotics may be a cost-effective alternative to surgery in a large percentage of patients without increasing the risk, and may reduce hospital stay and costs in both developed and third world countries.

This NOTA study is welcome in order to clarify these issues and better identify the subset of patients where NOM with antibiotics may be more safe and more effective.

The reader and all general practitioner should always keep in mind the risks and benefits of the treatment in order to better identify and select the patients whose potentially benefit from NOM rather than surgery.

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Ann Intern Med. 2007 Oct 16;147(8):573-7.

Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M; STROBE initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration.

PLoS Med. 2007 Oct 16;4(10):e297
Ann Intern Med. 2007 Oct 16;147(8):W163-94

As highlighted in these publications, much of the research into the cause of diseases relies on cohort, case-control, or cross sectional studies. Observational studies also have a role in research into the benefits and harms of medical interventions. Randomised trials cannot answer all important questions about a given intervention. For example, observational studies are more suitable to detect rare or late adverse effects of treatments, and are more likely to provide an indication of what is achieved in daily medical practice.

Research should be reported transparently so that readers can follow what was planned, what was done, what was found, and what conclusions were drawn. The credibility of research depends on a

Reviewer 2: Styrud, Johan

Johan Styrud
Karolinska Institutet, General Surgery

The Study	Yes	No
Is the research question clearly defined?	✓	
Is the overall study design appropriate and adequate to answer the research question?		✓
Are the participants adequately described, their conditions defined, and the inclusion and exclusion criteria described?		✓
Are the patients representative of actual patients the evidence might affect?	✓	
Are the methods adequately described?	✓	
Is the main outcome measure clear?		✓
Are the abstract/summary/key messages/limitations accurate?	✓	
Are the statistical methods described?	✓	
Are they appropriate?	✓	
Is the standard of written English acceptable for publication?	✓	
Are the references up to date and relevant? (If not, please provide details of significant omissions below.)		✓
Do any supplemental documents e.g. a CONSORT checklist, contain information that should be better reported in the manuscript, or raise questions about the work?		✓

If you answered No to any of the above, please supply details below.

The level of this study has improved in this new version. However there are still a lot of problems left to be solved.
Side 2 Definition of "suspicion of acute appendicitis" is missing.
Side 2 Definition of "needing immediate surgery" is missing.
Side 3 The diagnostic accuracy of appendicitis is higher in newer studies than 70-85%.
The background side 4-8 is far too long.

RESULTS AND CONCLUSION (For articles reporting research findings only)	Yes	No
Do the results answer the research question?		✓
Are they credible?		✓
Are they well presented?	✓	
Are the interpretation and conclusions warranted by and sufficiently derived from/focused on the data?		✓
Are they discussed in the light of previous evidence?	✓	
Is the message clear?		✓

If you answered No to any of the above, please supply details below.

I would like to see the single-cohort study with result.
To make a paper on how the authors want to treat suspected appendicitis is not enough material for a paper, in my opinion.

REPORTING AND ETHICS	Yes	No
Is the article reported in line with the appropriate reporting statement or checklist (e.g. CONSORT)?	✓	
Are research ethics (e.g. consent, ethical approval) addressed appropriately?	✓	
Is the article free from any concerns about publication ethics (e.g. plagiarism, fabrication, redundant publication, undeclared conflicts of interest)?	✓	

If you answered No to any of the above, please supply details below or contact the editorial office.

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Authors Response to Decision Letter for (BMJ Open-2010-000006.R1)

The NOTA STUDY: Non Operative Treatment for Acute Appendicitis. Study on Efficacy and Safety of Antibiotic Treatment (Amoxicillin and Clavulanic Acid) in Patients With Right Sided Lower Abdominal Pain

Dear Editor,
Dear Dr. Catena,
Dear Prof. Styrud,

Thanks for your appreciation and your helpful suggestion.

Please find below the requested revisions and definitions:

- 1) Suspected acute appendicitis was defined as patient presenting with RIF pain AND absence of a definite alternative diagnosis, either of a GI disease (such as IBD, IBS, colitis etc.) or urinary tract disease (such as UTI, renal colic, UT stones etc.) or a OB-GY cause (pregnancy, PID, ovulation etc.)
- 2) Patients needing IMMEDIATE surgery were defined as those patients with diffuse peritonitis and/or signs of sepsis, as well as the patients with clinico-radiological (US or CT scan) evidence of an intra-abdominal collection/abscess.
- 3) with the diagnostic accuracy of acute appendicitis being as high as 71%-87% with combination of the modern preoperative investigations (Dig Surg. 1999; 16(1):39-44. Diagnostic accuracy in 2,351 patients undergoing appendectomy for suspected acute appendicitis: A retrospective study 1986-1993. Styrud J, Eriksson S, Segelman J, Granström L.), conservative treatment with antibiotics seems to represent a valid therapeutic approach for the cases of suspected or probable or proven acute appendicitis. Our study aims therefore to demonstrate that NOTA with Amoxicillin and Clavulanic Acid is still effective even in cases with probable/proven acute non perforated appendicitis and can still be chosen even when the diagnosis of a true acute acute appendicitis is highly probable.

All these comments have been added to the revised version of the manuscript.

Thanks in advance for your comments.

Kindest regards

SDS