

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Right Iliac Fossa Pain Treatment (RIFT) Study: Protocol for an international, multicentre, prospective observational study
AUTHORS	on behalf of the West Midlands Research Collaborative, The Right Iliac Fossa Pain Treatment ; Nepogodiev, Dmitri

VERSION 1 - REVIEW

REVIEWER	Kjetil Søreide Stavanger University Hospital, Norway I have previously done similar collaborative research with some of the investigators.
REVIEW RETURNED	20-May-2017

GENERAL COMMENTS	<p>This study protocol describes the RIFT study focusing on right iliac fossa pain, and subsequently on the diagnostic performance, management and outcomes of appendicitis care. The negative appendectomy rate and the accuracy of clinical risk scores are egged among the outcome measures. I have a few comments:</p> <ol style="list-style-type: none">1. The centre survey is essential as it will give info on the type of centres participating. However, crucial information from this survey will also influence to what degree the objectives of the data collection and study endpoints can be met, e.g. how data for Alvarado score, AIR score or utility/access to imaging studies are available and can influence such measures. This does not seem to be well discussed or taken as an upfront limitation in the protocol (although planned adjusted for in the analyses).2. Are there any "power calculation" in terms of the perceived outcomes and number needed to enrol for the study? Please give at least an estimate. If the negative appendectomy rate is believed to be at 20% this is unusually high, what if the real rate is 5%, will it influence period of data collection?3. How do you ensure a good quality definition of "appendicitis" and negative apps, are pathologists involved or trained to a similar description of this?4. References: ref 1 needs date of access and a link, if available. <p>Two recent updates on appendicitis should be referenced, as aspects of the diagnosis and management with relevance to the study protocol are discussed therein:</p> <ul style="list-style-type: none">-- Bhangu A, Søreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. <i>Lancet</i>. 2015 Sep 26;386(10000):1278-87.-- Baird DLH, Simillis C, Kontovounisios C, Rasheed S, Tekkis PP. Acute appendicitis. <i>BMJ</i>. 2017 Apr 19;357:j1703.
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REVIEWER	<i>Dr. Salomone Di Saverio MD PhD FACS FRCS Maggiore Hospital - AUSL Bologna, ITALY</i>
REVIEW RETURNED	23-May-2017

GENERAL COMMENTS	<p>A Landmark and eagerly awaited study planning an international multicentre collaborative study. Overall the Protocol is well written and the present paper is scientifically sound.</p> <p>I have some minor comments:</p> <ul style="list-style-type: none"> -The intended dates and duration of the study should be disclosed and included in the manuscript. - Should the Conclusions section section be deleted or this paragraph be incorporated within the Discussion? As far as I know, Study Protocol type of manuscript should not have a Conclusions or Results section - Please explain better the following sentence (pag.5): "Unlike laparoscopic surgery, open procedures typically commit the surgeon to proceed to appendectomy even if the appendix is found to be macroscopically normal once visualised. This study will test the hypothesis that, associated with increased take-up of laparoscopy, the negative appendectomy rate will have decreased since 2012." Do you really think tha increased uf laparoscopy have determined an lower rate of negative appendectomies? Is this due to the fact that in some countries if appendix is found to be macroscopically normal, the procedure is ended without an appendectomy? This is a strong matter of debate but to date in most countries and most surgeons still tale out the appendix at laparoscopy even if it is found to be of normal appearance at laparoscopy. Please discuss further this issue with a focus on the background and evidence from the literature and/or guidelines <p>Again this sentence needs better clarification (pag. 11): "By mapping real-life determine whether any increase in laparoscopy has been associated with a decrease in the rate of negative appendectomy." Are you sure the decrease of the negative appendectomy rate is due to the increase in laparoscopy or may be due more probably to a better diagnostics and larger use of CT scan in Emergency Departments (therefore leading to a higher sensitivity and specificity and higher diagnostic accuracy)??</p> <p>Another probable reason for the decrease of the rate of negative appendectoy could be the wide spreading use of Non Operative management with antibiotics of uncomplicated appendicitis. Initial treatment with antibiotics and expectant management of uncomplicated appendicitis / suspected appendicitis / RIF pain may definitely be associated with lower incidence of negative appendectomies since those patients with negative appies will definitely improve with simple expectant management!</p> <ul style="list-style-type: none"> - The authors also need to clearly explain the following sentence (pag 11): "research collaboratives have been targeted at either senior trainees or medical students, RIFT is the first study aimed at junior specialty trainees." What do you exactly mean by RIFT study "aiming" at junior surgical trainees?
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REVIEWER	Anne Ehlers University of Washington, USA
REVIEW RETURNED	07-Jun-2017

GENERAL COMMENTS	As I read this protocol, the study authors are trying to determine what leads to variation in rates of negative appendectomy across hospitals. I think that this is an important question, especially if their rates are truly greater than 20%. The methods of the study are not quite clear to me. For example, must patients undergo appendectomy in order to be included? It seems that they should. One cannot have a "negative appendectomy" if they are not operated on to begin with. I also think that the comparator groups are not well defined. Is it rate of negative appendectomy comparing laparoscopic to open, or comparing across centers? On a final note, I would caution the authors not to include too many analyses. Trying to tackle the issue of variation rates in addition to the effect of delayed treatment, usefulness of predictive scores, and pre-op management seem to be somewhat disparate and may dilute the ultimate results.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Kjetil Søreide

Institution and Country: Stavanger University Hospital, Norway

This study protocol describes the RIFT study focusing on right iliac fossa pain, and subsequently on the diagnostic performance, management and outcomes of appendicitis care. The negative appendectomy rate and the accuracy of clinical risk scores are egged among the outcome measures. I have a few comments:

1.1. The centre survey is essential as it will give info on the type of centres participating. However, crucial information from this survey will also influence to what degree the objectives of the data collection and study endpoints can be met, e.g. how data for Alvarado score, AIR score or utility/access to imaging studies are available and can influence such measures. This does not seem to be well discussed or taken as an upfront limitation in the protocol (although planned adjusted for in the analyses).

Thank you very much for your comments on our protocol. The authors agree that variation in centre-level access to imaging studies may exist, as described in our centre survey. This is a pragmatic study which represents a real-world snapshot of practice across 4 European countries, and not every centre will have equal access to investigations. We intend to describe this fully in the final manuscript, and as a result of this comment have detailed this limitation further in our discussion section of the protocol:

“A centre survey has been developed to determine details about participating centres resources and policies (Table 2). Due to the large number of centres involved in this study from different countries and health systems, it is anticipated that there may be variation in the resources available, such as CT scanning and review clinics. By asking for details of this resource variation in advance we aim to control for this in our statistical analysis.”

1.2. Are there any "power calculation "in terms of the perceived outcomes and number needed to

enrol for the study? Please give at least an estimate. If the negative appendectomy rate is believed to be at 20% this is unusually high, what if the real rate is 5%, will it influence period of data collection?

Precise sample size and power calculations in observational studies are challenging, for example GlobalSurg, however, this methodology has been proven effective in hypothesis testing across large cohort studies where precise predictions of patient numbers are difficult.

A sample of 1300 patients would allow for the detection of a significant difference (>5%) in the diagnostic performance of both the Alvarado and AIR appendicitis risk scores with 95% power. This is based on a negative appendectomy rate (NAR) of 20%, which we still believe to be a good estimate of the rate within the UK*, however, we accept that due to a variation in practice the negative appendectomy rate may be much lower in other countries.

If, however, the NAR is lower than previously reported in the UK, then a larger sample would be required to validate the risk scores. That estimated sample size, which is based on pilot studies, would require 6000 patients to power this observational study.

Given that there are many unknown variables in a study of this description, we aim to recruit above the minimum number of patients required to power a difference of 5% in score specificity. Therefore, the length of data collection for this study should not be affected.

*National Surgical Research Collaborative. Multicentre observational study of performance variation in provision and outcome of emergency appendectomy. *Br J Surg* 2013 ;100:1240–52

1.3. How do you ensure a good quality definition of "appendicitis" and negative apps, are pathologists involved or trained to a similar description of this?

Thank you for your comment on the definition of appendicitis. Prior to designing this study, we reviewed the literature regarding the definition of appendicitis and were unable to find a clear, agreed upon definition. The literature itself suggests that the pathological definition of appendicitis can be quite subjective, especially borderline cases of inflammation within the appendix that may have been caused by excess handling during its extraction.

Due to the nature of this study being a pragmatic observational study, we will not be able to provide all participating centres with a standardised definition of appendicitis for the pathologists to use. However, as part of our protocol and data collection proforma, a definition of simple and complex appendicitis will be available for use by the collaborators collecting data and we foresee that this will be used in conjunction with the histology reports. We believe that this stratification will be sufficient and although we accept that there may be some variation in histology reporting between pathologists, this is likely to be minimal as the histology reports used for this study will those used in clinical practice; and will, therefore, be acceptable.

1.4. References:

ref 1 needs date of access and a link, if available.

Two recent updates on appendicitis should be referenced, as aspects of the diagnosis and management with relevance to the study protocol are discussed therein:

-- Bhangu A, Søreide K, Di Saverio S, Assarsson JH, Drake FT. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *Lancet*. 2015 Sep 26;386(10000):1278-87.

-- Baird DLH, Simillis C, Kontovounisios C, Rasheed S, Tekkis PP. Acute appendicitis. *BMJ*. 2017 Apr

19;357;j1703.

Thank you for these relevant suggestions. We have now included these as references 2 and 8. And the link has been added to reference 1.

Reviewer: 2

Reviewer Name: Dr. Salomone Di Saverio MD PhD FACS FRCS

Institution and Country: Maggiore Hospital - AUSL Bologna, ITALY

A Landmark and eagerly awaited study planning an international multicentre collaborative study. Overall the Protocol is well written and the present paper is scientifically sound.

I have some minor comments:

2.1. The intended dates and duration of the study should be disclosed and included in the manuscript.

Thank you very much for your comments. This study will require centres to collect data over distinct 2-week intervals between February and August 2017. However, not all centres will be completing the data collection at the same time. This has been rephrased within the text as follows:

“Consecutive patients presenting within two-week long data collection periods will be included. Centres will be invited to participate in up to 4 data collection periods between February and August 2017.”

“Each centre will be able to submit data from up to 4 study periods between February and August 2017.”

2.2 Should the Conclusions section section be deleted or this paragraph be incorporated within the Discussion? As far as I know, Study Protocol type of manuscript should not have a Conclusions or Results section

We have removed this heading and reworded the paragraph as follows:

“In summary, the RIFT study is a protocol-driven, international, multicentre prospective observational study using a ‘snap-shot’ methodology, in line with the UK surgical research collaborative model. The study aims to describe the current variation in investigation and management of right iliac fossa pain in several European countries, aligned to contemporaneous specialty guidelines.”

2.3 Please explain better the following sentence (pag.5): "Unlike laparoscopic surgery, open procedures typically commit the surgeon to proceed to appendectomy even if the appendix is found to be macroscopically normal once visualised. This study will test the hypothesis that, associated with increased take-up of laparoscopy, the negative appendectomy rate will have decreased since 2012." Do you really think that increased use of laparoscopy have determined a lower rate of negative appendectomies? Is this due to the fact that in some countries if appendix is found to be macroscopically normal, the procedure is ended without an appendectomy? This is a strong matter of debate but to date in most countries and most surgeons still take out the appendix at laparoscopy even if it is found to be of normal appearance at laparoscopy. Please discuss further this issue with a focus on the background and evidence from the literature and/or guidelines

Thank you for your comment. That statement was based on current UK practice where there is much debate within the general surgical community regarding this issue. Some UK general surgeons prefer to leave macroscopically normal appendix in situ during a diagnostic laparoscopy whereas others

prefer to remove all appendix's from patients with suspicion of appendicitis. The hypothesis that an increase in the laparoscopy rate will reduce the negative appendectomy rate has been proposed previously by Baird et al. Baird DLH, Simillis C, Kontovounisios C, Rasheed S, Tekkis PP. Acute appendicitis. BMJ. 2017 Apr 19;357:j1703.

We agree that this is still a contentious issue and there are risks and benefits with either approach. The data collection form developed for this study will be able to capture this variation in current practice, however, this was not a specific aim of this study.

2.4 Again this sentence needs better clarification (pag. 11): "By mapping real-life determine whether any increase in laparoscopy has been associated with a decrease in the rate of negative appendectomy."

Are you sure the decrease of the negative appendectomy rate is due to the increase in laparoscopy or may be due more probably to a better diagnostics and larger use of CT scan in Emergency Departments (therefore leading to a higher sensitivity and specificity and higher diagnostic accuracy)??

We agree that the increase in CT scanning may also have reduced the negative rate and have amended the paragraph as follows:

"RIFT will indicate whether any increased use of modern technologies, including CT scanning and laparoscopy, have been associated with a decrease in the rate of negative appendectomy."

2.5 Another probable reason for the decrease of the rate of negative appendectomy could be the wide spreading use of Non Operative management with antibiotics of uncomplicated appendicitis. Initial treatment with antibiotics and expectant management of uncomplicated appendicitis / suspected appendicitis / RIF pain

may definitely be associated with lower incidence of negative appendectomies since those patients with negative appies will definitely improve with simple expectant management!

This is an insightful comment and reflects an increased research focus on this topic in randomised trials and meta-analyses (REF 1,2,3). We agree that NOM may have an effect on negative laparoscopy rates and we have captured planned non-operative management within our data collection form. As a result of this comment we will detail variation in non-operative management in our primary manuscript and adjust negative appendectomy rates for this important factor in our analyses. Non-inferiority of conservative management versus operative management of appendicitis has yet to be demonstrated in a randomised setting. We have a pre-planned explanatory sub-analysis of the effect of non-operative management on re-admission or eventual operative management which we hope will add to the evidence base for this contentious area. The following sentence has been added to the text:

"The non-operative group will also include those patients diagnosed as simple appendicitis and treated non-operatively and will require follow up to assess whether they then require a subsequent operation."

2.6 The authors also need to clearly explain the following sentence (pag 11): "research collaboratives have been targeted at either senior trainees or medical students, RIFT is the first study aimed at junior specialty trainees." What do you exactly mean by RIFT study "aiming" at junior surgical trainees?

Thank you for your comment on junior speciality trainees. This term is widely used within the UK but

we understand may not have an equivalent in other healthcare systems. We use this term to describe post-graduate doctors who are within 1-3 years of surgical training. Junior surgical trainees were targeted to participate in the data capture in this study both to increase engagement within this group and for practical reasons: these doctors will be best placed to detect RIF pain through surgical clerking which will facilitate data collection.

For clarity, we have amended this term within the protocol to to "junior speciality trainees (recent graduates)".

Reviewer: 3

Reviewer Name: Anne Ehlers

Institution and Country: University of Washington, USA

3.1 As I read this protocol, the study authors are trying to determine what leads to variation in rates of negative appendectomy across hospitals. I think that this is an important question, especially if their rates are truly greater than 20%. The methods of the study are not quite clear to me. For example, must patients undergo appendectomy in order to be included? It seems that they should. One cannot have a "negative appendectomy" if they are not operated on to begin with.

Thank you very much for your comments. The primary aim of this study is to look at the variation of negative appendectomy rates between centres. The UK has previously been found to have a high normal rate of 20%, which is thought to be because in the UK, patients with RIF pain are not routinely CT scanned prior to a diagnostic laparoscopy.

The secondary aim of this paper is to validate the appendicitis risk scores in all patients with undifferentiated RIF pain. For this aim we will need to include follow up of the patients not operated on.

For analysis and publication purposes, the negative appendectomy rate will only be based on those who have had an operation.

To clarify our methodology and aims, the methods section of the protocol has been updated as follows:

"The group who undergo an operation will be followed up to determine the negative appendectomy rate, and the non-operative group will be followed up to allow for the validation of the AIR and Alvarado scores low risk prediction for this group. The non-operative group will also include those patients diagnosed as simple appendicitis and treated non-operatively and will require follow up to assess whether they then require a subsequent operation. "

3.2. I also think that the comparator groups are not well defined. Is it rate of negative appendectomy comparing laparoscopic to open, or comparing across centers?

Thank you for this comment. We agree that this wording could be more clear. The primary aim is to compare the negative appendectomy rate between centres. However, the variation in the negative appendectomy rate between centres we expect is partially explained because of the variation in local practice. One aspect of that variation will be whether the local surgeons prefer to perform open appendectomies as, particularly in the UK, an open appendectomy is more likely to result in the appendix being removed, even if macroscopically normal, and therefore, a higher normal appendectomy rate. Another aspect of the variation between centres will be due to the local use of CT scanning, which we will capture as part of the data collection and centre survey.

The aim of the paper is to compare the negative appendectomy rate between centres (as stated below), however, we will also capture the variation between open and laparoscopic procedures, but

this is not the primary aim of the study.

“(1) variation in the negative appendectomy and laparoscopy rates across participating centres and countries;”

3.3. On a final note, I would caution the authors not to include too many analyses. Trying to tackle the issue of variation rates in addition to the effect of delayed treatment, usefulness of predictive scores, and pre-op management seem to be somewhat disparate and may dilute the ultimate results.

Thank you for this advice. We believe that the aims of assessing variation in the negative appendectomy rate and validating the risk scores are linked because if the scores can be shown to be clinically specific enough to reduce unnecessary operations, then this may lead to a reduction in the negative appendectomy rate in the UK, if these scores can be more widely adopted. We have rationalised our statistical analysis protocol and plan to focus on variation in the negative appendectomy rates and validation of the appendicitis risk scores. The following secondary aims and analysis have been removed:

“(3) variation in management of RIF pain for patients with low-, medium- and high-risk of appendicitis, from both adult and paediatric populations; (4) delay to presentation and delay to surgery with relation to rates of complex appendicitis.”

“A similar multilevel model will be used to assess the association between delay to surgery and complex appendicitis.”

VERSION 2 – REVIEW

REVIEWER	Kjetil Søreide Stavanger University Hospital, Stavanger, Norway
REVIEW RETURNED	07-Jul-2017

GENERAL COMMENTS	no further comments my side
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REVIEWER	Dr Salomone Di Saverio MD FACS FRCS Maggiore Hospital "CA Pizzardi", AUSL Bologna, Italy
REVIEW RETURNED	04-Jul-2017

GENERAL COMMENTS	I am happy with the revisions done by the authors. Best wishes for this study.
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