PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted re-operation for recurrent colorectal cancer.</th>
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<tr>
<td>AUTHORS</td>
<td>Treasure, Tom; Monson, Kathryn; Fiorentino, Francesca; Russell, Christopher</td>
</tr>
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</table>

VERSION 1 - REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Dirk Grünhagen</th>
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<td>Erasmus MC Cancer Institute</td>
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<td></td>
<td>Rotterdam, the Netherlands</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>14-Nov-2013</td>
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GENERAL COMMENTS

This is a quite unusual paper on a trial performed 2 decades ago about the value of second-look surgery prompted by a raise in CEA level. The results of the trial were negative, and although this might have been counter-intuitive in that day and age, at present this result will not cause a raise of the eyebrow. Having said that, the results of the trial are not the reason for publishing now. I have read the present manuscript as a reflective paper on the way new therapies/operations are implemented in practice, because of intuition rather than because of scientific proof.

The authors have done a great job in retrieving the data from the trial. The methods are well-explained so that in my opinion, there is little doubt about the scientific quality of the original trial. The methods section is however too extensive, and should be shortened. In its present form, the methods section distracts from the message of the paper and could give the impression that the original trial is to be judged by the outcome itself.

The results section is to the point and the figures and tables are accurate. Dukes' classification is replaced by TNM classification in most countries.

The discussion section is the most interesting section and explains well how the outcome of the trial should be interpreted in the present day and age.

In conclusion, the present manuscript gives the reader an interesting insight in the (lack of) scientific evidence for today's surgical practice. The same holds true e.g. for the ubiquitous use of chemotherapy in the preoperative setting of colorectal liver metastases. The manuscript stresses the importance of evidence from randomized trials rather than presumed benefit. Editing the methods section would in my opinion improve the strength of the paper.
The following are major concerns I have about this manuscript:
1. Many portions of the text are identical to a previous manuscript, which was reportedly not written by the current authors.
2. Details of the introduction and methods are confusing and need to be streamlined for easy reading.
3. Differential ascertainment of the primary outcome was not explained.
4. There are figures presented as part of the manuscript that were not generated by the authors using the data they restored and it is unclear whether including them in the manuscript is appropriate.

I congratulate the authors on their conscientious efforts to restore an important trial and to transparently communicate its findings, along with the data and related documents, to the public. Following are my comments, categorized as major and minor. The manuscript is hard to read now with repetition of ideas and ordered in a way that is not easy to follow. I'm happy to re-review the manuscript after at least all the major comments are addressed.

**Major comments:**

1. I'd like to see a box or table clearly outlining what items about the trial were restored by the current authors and who previously held custody for each item, including the old draft manuscript.

2. The text in the current manuscript seems in many places identical to the text in the old manuscript. The authors of the current manuscript have been transparent about the origin of the text and have provided the original manuscript. I strongly suggest that the authors not use the same text as in the old, original manuscript for a few reasons. First, the current authors did not write the old, original manuscript and consequently, it is difficult to understand how they can vouch for its contents. Second, the current authors have restored the trial data and documents to gain sufficient understanding to write a scientific description of the trial's conduct and findings. So they are in a position to write their own description based on their understanding of what they restored about the trial. Finally, it seems imperative that if text from the old, original manuscript must be used then individuals who wrote that text must at least be co-authors on the current manuscript. I realize it means re-writing a good portion of the current manuscript but that seems to be the most appropriate option to avoid potential criticisms of identical text being re-used across manuscripts by different authors.

3. The scientific description about the trial is now accompanied by a poorly focused introduction and discussion sections. The description about why the trial was important at the time it was done, is helpful to understand the past context. What is missing is a more clearly articulated note in the introduction on whether and why the current clinical context should be informed by this trial, and a note in the discussion section on how the trial's findings, now that they are published in a detailed manuscript, should inform ongoing clinical practice and future research.

4. I would suggest that the methods section be structured as follows - methods for restoring the clinical trial data/documents (include...
This description should be followed by what the authors found from the restored data/documents about the methods used to design and conduct the trial. This description should be based on the authors' understanding from the restored trial data/documents.

5. The one patient for whom you were unable to resolve the date of birth (one out of 1447) - was this patient randomized? Please mention it in the manuscript.

6. The description under 'Statistical Analysis' is not helpful - please explain what exploratory and confirmatory analyses were done and how was testing done for statistical significance performed for each objective.

7. Figure 2 seems to be a reproduction from a previous paper. Please ensure and mention that you have the appropriate permissions to republish it in this manuscript.

8. Figure 7 - I would refrain from showing this figure because the authors did not generate it using the data they restored.

9. Explain why mortality was ascertained on 06/01/2010 for patients in the "Aggressive" arm and on 08/09/2011 for patients in the "Conventional" arm. What is the impact of this differential ascertainment of the outcome on your findings?

10. Explain any details on ethical approval that may have been obtained for this trial.

Minor comments:

1. Explain the acronym 'CEA' the first time it is used in the manuscript.

2. The detailed discussion about the Wangensteen approach is good to read but it is distracting - see item 3 under major comments. Is the Wangensteen approach even still used in its original proposed form?

3. The second paragraph under resolution of data problems (lines 381 to 386) - is unclear - the terms, "Prime server" and "Universe" are unfamiliar to me and possibly for other readers of your manuscript - please add a note to explain.

4. Are there any data on the skill of surgeons participating in the study? If yes then describe them in the manuscript. If no then mention it as a limitation in the manuscript.

5. Figure 5 - to the extent possible, follow the CONSORT statement recommended items for this flowchart. For example, it is unclear how "eligible" is different from "met CEA criteria Randomised". My understanding of the terminology - 'eligible' means the patient meets criteria to be randomized to one of the interventions in the trial.

6. Figure 5 - what does "Blind" mean in the first box in the last row?

7. Figure 6 - if 1235 patients were eligible to be followed with CEA monitoring then why does Figure 6 show only 1230 patients under
the registered but not randomized category?

8. Figure 6 - explain the acronym "ONS" in the legend for this figure.

9. Last paragraph in Results - lines 494 to 497 - “The analysis presented to the British Oncological Association in 1994 showed that at 3, 6 and 12 months the CEA versus clinical detection rates for recurrence were 88% vs 18%, 95% vs 44% and 97% vs 70% at a year." - what are your findings based on the restored data? If none then state that you were unable to do this analysis based on the restored data. Information presented at the British Oncological Association probably has an abstract (if yes then cite) with this information and repeating them here without an actual analysis using the restored data is not helpful and should be avoided.

10. Discussion - line 508 - "The answer is that detecting and acting on CEA elevation did not reduce mortality." -- Qualify this sentence with information on the specific modality used to "act" on CEA elevation and the time-frame in which the trial was conducted.

REVIEWER
Susan Dutton
Oxford Clinical Trials Research Unit and Centre for Statistics in Medicine, University of Oxford

REVIEW RETURNED
25-Nov-2013

GENERAL COMMENTS
This is a well written paper extracting data from a previous trial and updating the analysis. It shows that surgical randomised trials can and should be undertaken.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Dirk Grünhagen
Institution and Country Erasmus MC Cancer Institute
Rotterdam, the Netherlands
Please state any competing interests or state 'None declared': None declared

This is a quite unusual paper on a trial performed 2 decades ago about the value of second-look surgery prompted by a raise in CEA level. The results of the trial were negative, and although this might have been counter-intuitive in that day and age, at present this result will not cause a raise of the eyebrow. Having said that, the results of the trial are not the reason for publishing now. I have read the present manuscript as a reflective paper on the way new therapies/operations are implemented in practice, because of intuition rather than because of scientific proof.

The authors have done a great job in retrieving the data from the trial. The methods are well-explained so that in my opinion, there is little doubt about the scientific quality of the original trial. The methods section is however too extensive, and should be shortened. In its present form, the methods section distracts from the message of the paper and could give the impression that the original trial is to be judged by the outcome itself.

The methods could be shortened and indeed for a present day paper it would be. We have reduced some redundancy and repetition. However, as RIAT authors, we have respected the authors’ analysis of the reasons for doing the study[2] in the introduction, and the methods and results as they wrote them up in the manuscript.[1] The full original methods section as written in 1994 is available and could be a web extra.

We have had to add the methods we used to restore the data to an analysable form. [Lines 402-62]
The results section is to the point and the figures and tables are accurate. Dukes' classification is replaced by TNM classification in most countries.

We used Duke's classification as recorded at the time. We did not translate that into TNM as no conclusion relies on that difference. Colorectal surgeons can see stage mix in Table 1 and draw their own conclusions about applicability to today's practice.

The discussion section is the most interesting section and explains well how the outcome of the trial should be interpreted in the present day and age.

In conclusion, the present manuscript gives the reader an interesting insight in the (lack of) scientific evidence for today's surgical practice. The same holds true e.g. for the ubiquitous use of chemotherapy in the preoperative setting of colorectal liver metastases. The manuscript stresses the importance of evidence from randomized trials rather than presumed benefit. Editing the methods section would in my opinion improve the strength of the paper.

Reviewer Name: Swaroop Vedula
Institution and Country: Johns Hopkins University, USA
Please state any competing interests or state 'None declared': None declared.
We are grateful to Dr Vedula for a meticulous critique of the manuscript which has resulted in a number of clarifications.

The following are major concerns I have about this manuscript:
1. Many portions of the text are identical to a previous manuscript, which was reportedly not written by the current authors.
   That is as intended and is indicated in the introduction and is with their knowledge, agreement and acknowledgment. We have now added a statement at the beginning of the methods section to clarify this.

2. Details of the introduction and methods are confusing and need to be streamlined for easy reading.
   What is here, is a faithful record of a trial that was abandoned twenty years ago. We have reconfigured some of the text but are keen to include the previously unpublished original detail that illustrates the quality of the trial design and its conduct.

3. Differential ascertainment of the primary outcome was not explained.
   The primary outcome was death which was obtained from national records without any differentiation on our part. We have checked and there is no error. However the retrieval of the death dates was made blind to which arm of the trial the patients were in and it was misleading to provide the first and last death dates separately. We have simplified the writing by using the first and last date of death of the randomised patients which is a more correct way to provide that information. We are grateful for the comment which has helped us.

4. There are figures presented as part of the manuscript that were not generated by the authors using the data they restored and it is unclear whether including them in the manuscript is appropriate.
   Figure 7 was the original authors' analysis of lead time gain with CEA monitoring. We accept the reviewer's point and we will not use it. We have simply stated the results of their analysis as in the 1994 manuscript.
   I congratulate the authors on their conscientious efforts to restore an important trial and to transparently communicate its findings, along with the data and related documents, to the public. Following are my comments, categorized as major and minor. The manuscript is hard to read now with repetition of ideas and ordered in a way that is not easy to follow. I'm happy to re-review the manuscript after at least all the major comments are addressed.
   Thank you. It had already had the benefit of BMJ editors' comments and a reconfiguration based on that. We are ready to accept further suggestions if necessary.

Major comments:
1. I'd like to see a box or table clearly outlining what items about the trial were restored by the current authors and who previously held custody for each item, including the old draft manuscript.
The custodians are named. We can attempt to provide such a table if the Editor requires it but there are limitations to the usefulness of such an exercise from records as far back as 30 years for a trial abandoned 20 years ago. It should also be noted that although we can vouch for the data we have used we cannot always be sure of exactly who did what when. That was part of the difficult we encountered in getting this far.

2. The text in the current manuscript seems in many places identical to the text in the old manuscript. The authors of the current manuscript have been transparent about the origin of the text and have provided the original manuscript. I strongly suggest that the authors not use the same text as in the old, original manuscript for a few reasons. First, the current authors did not write the old, original manuscript and consequently, it is difficult to understand how they can vouch for its contents. Any vouching would indeed have to rest with the people who wrote it in 1994 and had run the trial since 1982. Hence we attribute it to them and use their words other than where we needed to edit for reasons of cultural nuances and the like. We have interviewed both of these authors and they accept our restoration as valid.

Second, the current authors have restored the trial data and documents to gain sufficient understanding to write a scientific description of the trial's conduct and findings. So they are in a position to write their own description based on their understanding of what they restored about the trial.

We are able to add our own interpretation of the meaning of the results. That is done more completely in another paper which is an analysis to be published in BMJ of the significance of these data in current practice.

Finally, it seems imperative that if text from the old, original manuscript must be used then individuals who wrote that text must at least be co-authors on the current manuscript. I realize it means re-writing a good portion of the current manuscript but that seems to be the most appropriate option to avoid potential criticisms of identical text being re-used across manuscripts by different authors.

The Editors have suggested that we attribute sections of the old manuscript as necessary, rather than re-write for the sake of it, as this can inadvertently introduce ambiguities when attempting to rephrase text.

3. The scientific description about the trial is now accompanied by a poorly focused introduction and discussion sections. The description about why the trial was important at the time it was done, is helpful to understand the past context. What is missing is a more clearly articulated note in the introduction on whether and why the current clinical context should be informed by this trial, and a note in the discussion section on how the trial's findings, now that they are published in a detailed manuscript, should inform ongoing clinical practice and future research.

We have worked further on the introduction and discussion to try to focus them better.

With respect to current clinical context, it is a very fair comment but we have already been round that loop. I think that is very much what we did before and it presented difficulties in re-interpreting history. We followed the advice of BMJ editors to separate the 1982-1994 work and interpretation in 2014. What you see here is as far we can make it faithful to what was done in 1982-1994 and might have been published in 1994. You will note that the citations for the introduction are curtailed at 1980.

4. I would suggest that the methods section be structured as follows - methods for restoring the clinical trial data/documents (include table on what was restored, who previously held custody for each item), how custody was obtained for the data that were restored, and how the data was restored.

This description should be followed by what the authors found from the restored data/documents about the methods used to design and conduct the trial. This description should be based on the authors' understanding from the restored trial data/documents.

There is a limitation here in what we have been able to do. The manuscript ready for publication indicated what had been agreed and also indicated that the sticking point was post hoc subset analyses. It is a typical reason for clinicians and methodologists falling out and I believe it was the reason here. The trial protocol and manuscript gave detailed explanations of the trial method and conduct. Interviews with those originally involved with the study confirmed that these are faithful...
accounts of how the trial was run.
5. The one patient for whom you were unable to resolve the date of birth (one out of 1447) - was this patient randomized? Please mention it in the manuscript.
   No. That patient was not randomised. This has now been added to the manuscript.

6. The description under 'Statistical Analysis' is not helpful - please explain what exploratory and confirmatory analyses were done and how was testing done for statistical significance performed for each objective.
   No exploratory analyses were planned and none were done by us.

7. Figure 2 seems to be a reproduction from a previous paper. Please ensure and mention that you have the appropriate permissions to republish it in this manuscript.
   Of course – if the editors decide to use it.

8. Figure 7 - I would refrain from showing this figure because the authors did not generate it using the data they restored.
   We have omitted this figure.

9. Explain why mortality was ascertained on 06/01/2010 for patients in the "Aggressive" arm and on 08/09/2011 for patients in the "Conventional" arm. What is the impact of this differential ascertainment of the outcome on your findings?
   Certification of death was obtained from ONS on behalf of the RIAT restorative authors. The data were retrieved without knowledge of whether they were randomised and if so, which arm they were in. There was no differential ascertainment. The fact that the death sequence in the aggressive arm (17/10/1983 to 06/01/2010) started and finished earlier than in the conventional arm (19/09/1984 to 08/09/2011) is therefore a true finding (on average they died sooner than those in the control group) and is reflected in the statistical analysis. We have simplified that section which is now technically more correct.

10. Explain any details on ethical approval that may have been obtained for this trial.
   They are in the original protocol and that is available. They gave full consideration to ethical requirements of the time.

Minor comments:

1. Explain the acronym 'CEA' the first time it is used in the manuscript.
   It is now explained the first time we use it.

2. The detailed discussion about the Wangensteen approach is good to read but it is distracting - see item 3 under major comments. Is the Wangensteen approach even still used in its original proposed form?
   The expression is still used.[3] Rather than being distracting we think it sets the scene. It was the pressure the trial founders were under from American colleagues to do 'second-look' surgery. We are concerned about harm done by unavailing cancer surgery.[4] That too was a concern of Northover.[5] This inclusion is historically faithful to the context of the trial.

3. The second paragraph under resolution of data problems (lines 381 to 386) - is unclear - the terms, "Prime server" and "Universe" are unfamiliar to me and possibly for other readers of your manuscript - please add a note to explain.
   They are computer operating systems which were in a state of flux in the 1980s. We think putting them in quotation marks signifies that adequately.

4. Are there any data on the skill of surgeons participating in the study? If yes then describe them in the manuscript. If no then mention it as a limitation in the manuscript.
   No. This information wasn’t captured then. This was a pragmatic trial, which aimed to produce results generalisable to routine care.

5. Figure 5 - to the extent possible, follow the CONSORT statement recommended items for this flowchart. For example, it is unclear how "eligible" is different from "met CEA criteria Randomised". My understanding of the terminology - 'eligible' means the patient meets criteria to be randomized to one of the interventions in the trial.
The study had two phases. “All patients up to the age of 76 who had undergone a potentially curative resection for adenocarcinoma of the colon or rectum, who were fit and willing to adhere to the post-operative monitoring routine were eligible for the study.” These were the 1447. And then some met the very stringent CEA criteria to be randomised. These were the 216. We use the words they used and they are defined in the manuscript.

6. Figure 5 - what does "Blind" mean in the first box in the last row?
It means that the result of CEA was withheld. ‘This centralised system was to ensure that all participating clinicians were kept blind as to the CEA results for all trial patients.’ [Lines 306-9]

7. Figure 6 - if 1235 patients were eligible to be followed with CEA monitoring then why does Figure 6 show only 1230 patients under the registered but not randomized category?
We are not able to fully resolve this discrepancy. The KM shows a difference in survival between participants who entered the trial but were not randomised (1230/1446) and those who were randomised (108+108). When we tally the specified exclusions they reduce the 1447 (as in the original study) to 1235 but we cannot determine the reason that 5 patients (0.4%) were not included in the non-randomised cohort. We include in our KM the 1230 patients who were in the dataset and who were not randomised.

8. Figure 6 - explain the acronym "ONS" in the legend for this figure.
Office for National Statistics. That has been inserted.

9. Last paragraph in Results - lines 494 to 497 - “The analysis presented to the British Oncological Association in 1994 showed that at 3, 6 and 12 months the CEA versus clinical detection rates for recurrence were 88% vs 18%, 95% vs 44% and 97% vs 70% at a year.” - what are your findings based on the restored data? If none then state that you were unable to do this analysis based on the restored data. Information presented at the British Oncological Association probably has an abstract (if yes then cite) with this information and repeating them here without an actual analysis using the restored data is not helpful and should be avoided.
We didn’t attempt to redo this analysis. This is now stated. The abstract is cited.[6]

10. Discussion - line 508 - “The answer is that detecting and acting on CEA elevation did not reduce mortality.” -- Qualify this sentence with information on the specific modality used to “act” on CEA elevation and the time-frame in which the trial was conducted.
We have changed that to ‘acting on CEA elevation by second-look surgery did not reduce mortality compared with patients in whom similar CEA elevation remained unknown’.

Reviewer Name   Susan Dutton
Institution and Country Oxford Clinical Trials Research Unit and Centre for Statistics in Medicine, University of Oxford
Please state any competing interests or state ‘None declared’: None declared

This is a well written paper extracting data from a previous trial and updating the analysis. It shows that surgical randomised trials can and should be undertaken.

We thank the reviewer for her comment.

Reference List


**VERSION 2 – REVIEW**

<table>
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<th>REVIEWER</th>
<th>Swaroop Vedula</th>
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<td>Johns Hopkins University, USA</td>
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<td>03-Mar-2014</td>
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</table>

**GENERAL COMMENTS**

I appreciate the authors’ careful consideration of the reviewers' comments and revisions to the manuscript. Below are my residual comments, because I still find the manuscript hard to read and follow.

1. Abstract: Capitalize the first words under each of the subheadings.

2. Spell out numbers at the beginning of sentence under the Setting subheading. Please also check for typos and copy-editing errors throughout the manuscript.

3. I suggest that the Abstract also include a statement that this was a work of restoration, and is being reported as a mix of original findings and the authors' own follow-up data collection on patient survival in 2011.

4. Abstract - what is the relative risk after counting the 25 additional patients who died by 2011?

5. Strengths and limitations - It is unclear to me how the third bullet in the list is a strength of this work. The strength of this work is availability of data from a long-shelved trial in a state sufficient to be adequately restored, and your follow-up of participants' survival status to compare long-term effects of the test and control interventions.

6. To make a better narration, I suggest that the authors first describe their own narration of the context (abandonment of the original trial and their access to the data) and methods for their restorative work.
(including their additional follow-up on survival status of the participants and their analyses with the 25-year follow-up data) and then describe the original trial. That is, to move to the beginning of the Introduction section the text that is now described at the end of this section. The readers should be presented with the context and reason for this restoration, methods for this restoration, and then the results of the restorative work. That way, the readers are explicitly informed upfront that most of the text in the manuscript is faithfully restored from the original, with some changes. The current structure doesn't reveal the restorative nature of this work until the reader reaches the end of the Introduction section. To the extent possible, I also suggest making a distinction in the text between the original draft text and the current authors' narration text perhaps, using a different text type (italics or indented paragraphs). Without such a distinction, it is harder to comprehend the manuscript as a restorative work.

7. Figure 5 and the legend for Figure 6 is all blacked out in the current submission - please verify.

8. I don't know what the standard is for citing unpublished work but I suggest that unpublished work in the form of letters should be included as an appendix to the paper.

9. I don't see how the trial investigators originally planned to analyze the data to answer their research questions. This is not described in the current description of the Methods section. Was the Kaplan-Meier analysis pre-specified in the original trial protocol or was it an addition by the current authors? Please add analysis details from the original protocol to the Methods section.

10. The current authors' ascertainment of the dates of death for the participants not randomized in the trial should also be mentioned in the Methods section (that describes the methods for the restoration).

11. Would the authors also add a note in the manuscript that they obtained institutional ethics approval for collecting the follow-up survival data for the patients randomized and not randomized into the original trial?

---

**VERSION 2 – AUTHOR RESPONSE**

Reviewer Name  Swaroop Vedula  
Institution and Country Johns Hopkins University, USA  

Please state any competing interests or state 'None declared': No competing interests.  
I appreciate the authors' careful consideration of the reviewers' comments and revisions to the manuscript. Below are my residual comments, because I still find the manuscript hard to read and follow.

1. Abstract: Capitalize the first words under each of the subheadings.  
AR: I will do this in the manuscript but it may be a matter of house style.

2. Spell out numbers at the beginning of sentence under the Setting subheading.  
AR: I agree with this but again it might be a matter of house style eventually.
. Please also check for typos and copy-editing errors throughout the manuscript.

AR: Apologies. Entirely the fault of TT who has done all the typing for this completely unfunded project.

3. I suggest that the Abstract also include a statement that this was a work of restoration, and is being reported as a mix of original findings and the authors' own follow-up data collection on patient survival in 2011.

AR: done

4. Abstract - what is the relative risk after counting the 25 additional patients who died by 2011?

AR: We have not recalculated this. We have restored the 1994 trial.

5. Strengths and limitations - It is unclear to me how the third bullet in the list is a strength of this work. The strength of this work is availability of data from a long-shelved trial in a state sufficient to be adequately restored, and your follow-up of participants' survival status to compare long-term effects of the test and control interventions.

6. To make a better narration, I suggest that the authors first describe their own narration of the context (abandonment of the original trial and their access to the data) and methods for their restorative work (including their additional follow-up on survival status of the participants and their analyses with the 25-year follow-up data) and then describe the original trial. That is, to move to the beginning of the Introduction section the text that is now described at the end of this section. The readers should be presented with the context and reason for this restoration, methods for this restoration, and then the results of the restorative work. That way, the readers are explicitly informed upfront that most of the text in the manuscript is faithfully restored from the original, with some changes. The current structure doesn't reveal the restorative nature of this work until the reader reaches the end of the Introduction section. To the extent possible, I also suggest making a distinction in the text between the original draft text and the current authors' narration text perhaps, using a different text type (italics or indented paragraphs). Without such a distinction, it is harder to comprehend the manuscript as a restorative work.

7. Figure 5 and the legend for Figure 6 is all blacked out in the current submission - please verify.

8. I don't know what the standard is for citing unpublished work but I suggest that unpublished work in the form of letters should be included as an appendix to the paper.

AR: this is being done.

9. I don't see how the trial investigators originally planned to analyze the data to answer their research questions. This is not described in the current description of the Methods section. Was the Kaplan-Meier analysis pre-specified in the original trial protocol or was it an addition by the current authors? Please add analysis details from the original protocol to the Methods section.

AR: It was to be KM. We have put that in the manuscript (around) 255. It was done and we have a copy of the 1994 graph as given to TT by JMAN. At some point in the editorial process it was decided not to use that. We have given the analysis as performed by the trialists and updated the image with further data.
10. The current authors’ ascertainment of the dates of death for the participants not randomized in the trial should also be mentioned in the Methods section (that describes the methods for the restoration).

AR: done

11. Would the authors also add a note in the manuscript that they obtained institutional ethics approval for collecting the follow-up survival data for the patients randomized and not randomized into the original trial?

AR: Ethics approval is now done nationally in the UK. UCL CTC obtained permission to rerun the search for death certification and the restorative authors. We dealt only with anonymised data and the UCL CTC was punctilious about that and they had the necessary consents and permissions.

Reference List

Ref Type: Unpublished Work

McConkey, C. Chris McConkey e-mail 1st October 2009. 1-10-2009.
Ref Type: Unpublished Work

Ref Type: Unpublished Work

Ref Type: Unpublished Work
The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted reoperation for recurrent colorectal cancer

Tom Treasure, Kathryn Monson, Francesca Fiorentino and Christopher Russell

*BMJ Open* 2014 4:
doi: 10.1136/bmjopen-2013-004385

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