PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Improving the Wellbeing of Men by Evaluating and Addressing the Gastrointestinal Late Effects of Radical Treatment for Prostate Cancer (EAGLE): study protocol for a mixed-method implementation project
AUTHORS	Taylor, Sophia; Demeyin, Weyinmi Demeyin; Muls, Ann; Ferguson, Catherine; Farnell, Damian; Cohen, David; Andreyev, Jervoise; Green, John; Smith, Lesley; Ahmedzai, Sam; Pickett, Sara; Nelson, Annmarie; Staffurth, John

VERSION 1 - REVIEW

REVIEWER	Professor Hitendra RH Patel Pelvic Centre University Hospital North Norway Arctic University of Tromso Norway
REVIEW RETURNED	16-Mar-2016

GENERAL COMMENTS	The study objective is relevant and current.

REVIEWER	Tim Showalter, MD, MPH University of Virginia School of Medicine, USA
REVIEW RETURNED	28-Mar-2016

GENERAL COMMENTS	The protocol is very clearly written and includes enough information to understand the overall approach. I believe the topic is presented with adequate background information for readers to understand the context and the intervention. I think the project is exciting and I believe the intervention is promising. Note that the limitations of the study are not presented adequately. I think this is a great study, but I will suggest some limitations: From a study design perspective, one might make a statement about limitation of the anticipated sample size to identify an effect of the intervention. In addition, selection approach could be mentioned, since there is very little evidence that any specific intervention improves proctitis symptoms. My own personal opinion is that using early signs of acute proctitis as a selection criteria might improve the chance of seeing an effect of an intervention, since acute toxicity is the strongest predictor of late toxicity. Since only 20% of patients develop late rectal toxicity, any study that includes the whole group of prostate patients (with 20% event rate) is not likely to observe significant impact for an intervention that is ultimately aimed at just 20% of the cohort. In other words, an enriched patient sample would be more likely to show an effect. Lastly, the investigators should

	mention that there is some chance the intervention might not help. In some areas, the clinical experience with managing proctitis may be among the radiation oncologists, not the GI specialists, since they see more of this. And, most medical interventions have been shown in previous clinical studies to have minimal or no benefit, so there is some chance that this program may not have a real impact. On the other hand, there may be some real secondary gains in terms of laying the groundwork for future efforts at testing candidate strategies for preventing or treating late GI toxicity after RT.

REVIEWER	Liam Bourke Sheffield Hallam University Receive research funding from CRUK and the NIHR Receive honorarium for research lectures from Sanofi
REVIEW RETURNED	21-Apr-2016

GENERAL COMMENTS	I really struggled to understand what is happening in this protocol. In places it covers specifics of what is going to be carried out e.g. the section describing the QoL outcomes is clear and helpful. However, in other places its extremely vague and meandering. For instance the introduction reads like a mini-review. The section on study design doesn't really tell me much about the study design, either. Other sections highlight intended cost-effectiveness analysis but surely this cant be done outside of an RCT? You can look at implementation in an RCT, it just requires cluster randomisation rather than patient level randomisation. The manuscript contains sentences such as "Mixed-methods data collection and analysis will be carried out, and research results will be documented for use in publications." This just looks very odd. Its too effort intensive to read this and try to join the dots to join the dots regarding what's proposed. The subject matter is important and Im sure the team have some good ideas but they need to put these across in a clearer more concise fashion.

REVIEWER	Frances Drummond University College Cork
REVIEW RETURNED	30-Apr-2016

GENERAL COMMENTS	The authors describe a three-tiered intervention to (i) identify men with localised prostate cancer, who have bowel problem following treatment with radiotherapy (external beam and/or brachytherapy), (ii) refer men to a gastroenterological service, and (iii) investigation of and treatment for these post-treatment symptoms. This is a much needed intervention for prostate cancer survivors. However, some aspects are unclear and require clarity. Post-treatment acute and chronic symptoms ae a significant problem for many men which negatively affects their health-related quality of life. The authors report that 90% of men develop a permanent change in bowel habit from one review which is 9 years old. From the literature, this is certainly the upper limit and the authors should present a range regarding the proportion of men who experience bowel problems post-treatment and also the proportion with negative

	QOL post-radiotherapy, with more up to date references. In the aims, the authors describe that the aim of the intervention is to reduce the psychological and social impact of late GI effects. However, they do not describe how they will measure the psychological and social impact. Do they intend to use the anxiety/distress question in the EQ-5D-5L? That appears to be the only psychological measure included in the pack. The authors collect information from carers, however, it is not clear what the aim of this is and how they will use the information - the intervention appears to be specific to the patients. Within the study, the authors will also validate the Alert-B tool, but intend not to use the information if it conflicts with GSRS they will not use it. They don't include the Alert-B tool in the Cardiff center, why? How will the centralisation of referrals be managed, and from where? How will the authors deal with attrition from the study, e.g. through cancer recurrence through the course of the intervention, unacceptability of the intervention to some men, burden of the research ..in both statistical analysis and qualitative analysis? The authors will use both the QLQ-PR25 and EPIC-26; there is some overlap here? Again, QLQ-PR25 will not be used in Cardiff, why? Along with the EQ-5D-5L and ALERT-B it might be quite burdensome to the men? The authors state that they will use the Normalising Process Theory on pg 11. They do not refer to this in the data analysis section - will this form the basis of the framework analysis? In general I found the manuscript to be quite long, and it might benefit from some editing. I could not see Figure 2. The paragraphs describing interview data analysis appear to be reversed - please address. Minor: Some typos need to be addressed; pg 8, line 20, '67% reported using'

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Professor Hitendra RH Patel Institution and Country: Pelvic Centre, University Hospital North Norway, Arctic University of Tromso, Norway Competing Interests: None

The study objective is relevant and current.

*Thank you for Reviewer 1's comments.

Reviewer: 2
Reviewer Name: Tim Showalter, MD, MPH
Institution and Country: University of Virginia School of Medicine, USA Competing Interests: None declared

The protocol is very clearly written and includes enough information to understand the overall approach. I believe the topic is presented with adequate background information for readers to understand the context and the intervention. I think the project is exciting and I believe the intervention is promising.

Note that the limitations of the study are not presented adequately. I think this is a great study, but I will suggest some limitations: From a study design perspective, one might make a statement about limitation of the anticipated sample size to identify an effect of the intervention. In addition, selection approach could be mentioned, since there is very little evidence that any specific intervention improves proctitis symptoms. My own personal opinion is that using early signs of acute proctitis as a selection criteria might improve the chance of seeing an effect of an intervention, since acute toxicity is the strongest predictor of late toxicity. Since only 20% of patients develop late rectal toxicity, any study that includes the whole group of prostate patients (with 20% event rate) is not likely to observe significant impact for an intervention that is ultimately aimed at just 20% of the cohort. In other words, an enriched patient sample would be more likely to show an effect. Lastly, the investigators should mention that there is some chance the intervention might not help. In some areas, the clinical experience with managing proctitis may be among the radiation oncologists, not the GI specialists, since they see more of this. And, most medical interventions have been shown in previous clinical studies to have minimal or no benefit, so there is some chance that this program may not have a real impact. On the other hand, there may be some real secondary gains in terms of laying the groundwork for future efforts at testing candidate strategies for preventing or treating late GI toxicity after RT.

*Thank you for Reviewer 2's comments about the protocol paper. The late gastrointestinal effects of pelvic radiotherapy can have a significant impact on the quality of life of prostate cancer patients. Thank you for providing suggestions for the study limitations. A limitations statement has now been included after the abstract. The limitations statement includes the impact of the sample size and that the implementation of the intervention might not help. In terms of the intervention, the clinical investigation and treatment algorithm used in this study has been shown to be effective in the ORBIT study.

*This study focuses on identifying the late effects of pelvic radiotherapy. Andreyev, a consultant gastroenterologist with a special interest in managing the late effects of pelvic radiotherapy, considers that acute symptoms tend to settle within three months (Andreyev 2005). The management of chronic symptoms that persist after this time has been the focus of Andreyev's work. Consequently this study focuses on identifying patients who have bowel symptoms at least six months after pelvic radiotherapy. Studies have also shown that up to 90% of patients report a change in bowel function with 50% experiencing a reduction in quality of life (Andreyev 2007).

Reviewer: 3
Reviewer Name: Liam Bourke
Institution and Country: Sheffield Hallam University Competing Interests: Receive research funding from CRUK and the NIHR; Receive honorarium for research lectures from Sanofi

I really struggled to understand what is happening in this protocol. In places it covers specifics of what is going to be carried out e.g. the section describing the QoL outcomes is clear and helpful.

However, in other places its extremely vague and meandering. For instance the introduction reads like a mini-review. The section on study design doesn't really tell me much about the study design, either. Other sections highlight intended cost-effectiveness analysis but surely this cant be done outside of an RCT? You can look at implementation in an RCT, it just requires cluster randomisation rather than patient level randomisation. The manuscript contains sentences such as "Mixed-methods data collection and analysis will be carried out, and research results will be documented for use in publications." This just looks very odd.

Its too effort intensive to read this and try to join the dots to join the dots regarding what's proposed. The subject matter is important and Im sure the team have some good ideas but they need to put these across in a clearer more concise fashion.

*Thank you for reviewer 3's comments. The protocol paper has been revised to try and make it easier to read. The introduction has been reduced in length and the section on study design has been revised for clarity. The study design section outlines a mixed methods implementation study that involves setting up and testing a new gastroenterology service in three UK centres.

*The study includes the analysis of health economic data and will compare the cost-effectiveness of those patients referred to the new gastroenterology service to those patients in a sub-group from the Cardiff site who receive standard care. This sub-group will act as a comparison group.

*The sentence "Mixed methods data collection and analysis" has been amended to "Outcomes will be measured via collection and analysis of both quantitative and qualitative data sets". The sentence on research results will be documented for use in publications has been removed.

*We hope that the changes made throughout the paper have made it easier to read and follow.

Reviewer: 4
Reviewer Name: Frances Drummond
Institution and Country: University College Cork, Ireland Competing Interests: No competing interest to declare

The authors describe a three-tiered intervention to (i) identify men with localised prostate cancer, who have bowel problem following treatment with radiotherapy (external beam and/or brachytherapy), (ii) refer men to a gastroenterological service, and (iii) investigation of and treatment for these post-treatment symptoms. This is a much needed intervention for prostate cancer survivors. However, some aspects are unclear and require clarity.

Post-treatment acute and chronic symptoms are a significant problem for many men which negatively affects their health-related quality of life. The authors report that 90% of men develop a permanent change in bowel habit from one review which is 9 years old. From the literature, this is certainly the upper limit and the authors should present a range regarding the proportion of men who experience bowel problems post-treatment and also the proportion with negative QOL post-radiotherapy, with more up to date references.

*Thank you for reviewer 4's comments. The 90% figure reported in the paper is for those patients who report a change in bowel function. These changes can range from very mild changes to around 20-40% who report a moderate to severe reduction in their quality of life. This area is under researched

so there is very little recent data available on the impact of radiotherapy treatment. However, a more recent study has been added that showed 35% of prostate patients report bowel urgency 15 years after radiotherapy.

In the aims, the authors describe that the aim of the intervention is to reduce the psychological and social impact of late GI effects. However, they do not describe how they will measure the psychological and social impact. Do they intend to use the anxiety/distress question in the EQ-5D-5L? That appears to be the only psychological measure included in the pack.

*The psychological and social impact of the new gastroenterology service will be measured by qualitative interviews and overall quality of life as measured by EQ-5D-5L. The following sentence has now been included in the paper- “In addition interviews with participants and support givers will provide an insight into the psychological and social impact of GI symptoms and the new GI service”.

The authors collect information from carers, however, it is not clear what the aim of this is and how they will use the information - the intervention appears to be specific to the patients.

*As part of the EAGLE study we aim to interview carers/support givers. The gastrointestinal symptoms can impact on work and social function therefore indirectly affecting those close to the patient. We hope that these interviews will help to evaluate the effectiveness of the new service from the carer/support giver’s perspective and identify any barriers to setting up or running the new service.

Within the study, the authors will also validate the Alert-B tool, but intend not to use the information if it conflicts with GSRS they will not use it. They don't include the Alert-B tool in the Cardiff center, why?

*In terms of the ALERT-B tool, it will be used to screen patients for eligibility for referral to the new gastroenterology service. The ALERT-B tool will be used in all sites including Cardiff and the Cardiff comparison sub-group. Apologies for the confusion over which information is used if the responses to ALERT-B and GSRS are conflicting. It is only the results of the ALERT-B tool that will be considered by healthcare professionals. The GSRS tool is just being collected as part of the validation of ALERT-B. The following sentence has been added to the manuscript- “The ALERT-B tool will be reviewed with the patient by the Clinical Nurse Specialist (CNS), research nurse, research radiographer or doctor.”

How will the centralisation of referrals be managed, and from where?
*Referrals to the new service will be centralised locally to try and streamline the referral process. This will result in referrals being made to a named healthcare professional. The following sentence has been added to the paper- “A streamlined referral pathway to a named healthcare professionals in the new multi-disciplinary PRD service in each centre will be established for EAGLE study participants who are identified with late GI effects of pelvic radiotherapy”.

How will the authors deal with attrition from the study, e.g. through cancer recurrence through the course of the intervention, unacceptability of the intervention to some men, burden of the research ..in both statistical analysis and qualitative analysis?

*A section on attrition has now been added to the data analysis section. In terms of attrition in the qualitative data set all effort will be made to ensure participants are retained throughout the study. The importance of qualitative interviews will be stressed and the time and place of interviews will be fitted in around the participant.

The authors will use both the QLQ-PR25 and EPIC-26; there is some overlap here? Again, QLQ-

PR25 will not be used in Cardiff, why? Along with the EQ-5D-5L and ALERT-B it might be quite burdensome to the men?

*The following sentence has been added to the manuscript- “Both prostate questionnaires were requested by the funder, Prostate Cancer UK (PCUK), to collect data as part of a series of global projects”.

The authors state that they will use the Normalising Process Theory on pg 11. They do not refer to this in the data analysis section - will this form the basis of the framework analysis?

*The matrix for the Framework Analysis will be developed from a deductive approach using Normalisation Process Theory, further supported by an overall inductive analysis of spontaneously arising themes during interviews. This section on Normalisation Process Theory has been added to the data analysis section.

In general I found the manuscript to be quite long, and it might benefit from some editing.

*The manuscript has been revised and reduced in length.

I could not see Figure 2.

*I apologise that you were not able to see Figure 2. I will ensure that this is uploaded with the revised manuscript.

The paragraphs describing interview data analysis appear to be reversed - please address.

*The order of the paragraphs describing the interview data has now been corrected.

Minor:
Some typos need to be addressed; pg 8, line 20, '67% reported using'

*The typo on line 20 page 8 has been removed.

VERSION 2 – REVIEW

REVIEWER	Tim Showalter, MD, MPH University of Virginia School of Medicine, USA
REVIEW RETURNED	16-May-2016

GENERAL COMMENTS	I think the revisions are appropriate.

REVIEWER	Frances Drummond University College Cork, Cork, Ireland
REVIEW RETURNED	06-Jun-2016

GENERAL COMMENTS	Where was this reference within the manuscript? I did not see this added to the text.... This area is under researched so there is very little recent data available on the impact of radiotherapy treatment. However, a more recent study has been added that showed 35% of prostate patients report bowel urgency 15 years after radiotherapy.