PEER REVIEW HISTORY

This paper was submitted to the GUT but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open where it was re-reviewed and accepted.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Using physician-linked mailed invitations in an organized colorectal cancer screening program: effectiveness and factors associated with response.
AUTHORS	Tinmouth, Jill; Baxter, Nancy; Paszat, Lawrence; Rabeneck, Linda; Sutradhar, Rinku; Yun, Lingsong

VERSION 1 - REVIEW

REVIEWER	Hoff, Geir INSTITUTE FOR POPULATION-BASED CANCER RE
REVIEW RETURNED	14-Jun-2013

GENERAL COMMENTS	The authors address an important topic relevant to on-going and imminent screening programmes. Short of randomized trial design, they adequately present weaknesses and strengths of their study design.

REVIEWER	Halloran, Stephen Royal Surrey County Hospital, Clinical Biochemistry
REVIEW RETURNED	17-Jun-2013

GENERAL COMMENTS	"The paper is well written and describes studies related to the important topic of CRC screening uptake. The manuscript describes two related studies, 'factors associated with response to mailed invitation' (Study 1) and an 'evaluation of the effectiveness of mailed invitations' (Study 2). Unfortunately the authors assumes the reader has a reasonably detailed knowledge of the Ontario healthcare system and particularly of what they describe as the 'regular' mode of CRC screening. Having read the text several times I still do not have an adequate understanding of the 'physician-linked invitation'. What exactly was written in the invitation letter, how/if it avoided invitations going to patients recently diagnosed with CRC yet 'endorsed' by the family physician, what proportion of those made a timely visit to the physician and, what proportion of those completed the test. The observations made about factors that appear to influence uptake are pertinent and

	important but if they are to be replicated then we need more details, possibly with inclusion of the letter used in the study. I am even more unclear about the second study because even though the authors have gone to great pains to ensure comparability of the intervention cohort 'physician-linked invitation' for which they provide substantial data, they do not describe how the control group get to have their FOBT. Whilst mailing and physician-involvement are elements of the pilot cohort I cannot see where the manuscript explains how or whether the family physician is involved at all with the control cohort or whether the programme is just available but not publicized. Clearly, the interpretation of the impact of the pilot needs to be interpreted with a thorough understanding of the details of how the pilot and control CRC screening were conducted. The authors have all of the necessary data, the study is important and valuable and they need to be requested to rewrite the manuscript for an international audience that, having been convinced by the effectiveness of the intervention, might wish to adopt this element of the programme. It would also be helpful if we knew what FOBT kit was being used, how many faecal samples needed to be collected, what physician incentives were utilized in the programme (some information is given), what promotional material was used, whether it was necessary to have documented participant consent and whether reminders were used or any other form of publicity. Whilst the tables providing detailed comparative data are interesting they could be reduced in content to that which is more pertinent to the conclusion, their comprehensive nature is more appropriate to a report rather then a paper. I would be happy, if invited, to review a resubmitted and revised manuscript. Some minor points; • Several papers are cited but the authors do not then summarize the results of the studies or relate the results to their own (Page 17 Lines 32-41) • The 'English Bowel Cancer Screening Programme (BCSP)' is officially the 'NHS Bowel Cancer Screening Programme (BCSP) in England and although the first phase of rollout was to those 60-69 years the programme is now close to completing the second phase to 70-74 year and has commenced the third phase of the programme, flexisigmoidoscopy to all 55 year olds. s

	• The author may be aware of the difficulty that Hewitson et al (ref No 38) had in gaining GP involvement without financial incentives, this is probably pertinent and the authors might consider citing that in the discussion."

REVIEWER	*The reviewer wished to be anonymous*
REVIEW RETURNED	18-Jun-2013

GENERAL COMMENTS	The main aim of this study was to identify patient and physician factors associated with response to mailed physician-linked invitations for colorectal cancer (CRC) screening. The problem is that participation was very low (22%). The uptake of the screening test was too low to expect a significant reduction in CRC mortality. Randomized trial suggested that participation has to lie over 50% to obtain a significant mortality reduction. The main conclusion from this study is that sending physician-linked mail invitations is not an effective strategy. Other invitation stratégies must be considered. In this context the identification of patient and physician factors associated to participation to CRC screening is of little interest. Although you conclude on the effectiveness of the screening programme there is no data in this paper to support this conclusion. A slightly higher participation than in a matched control group does not mean "effectiveness of mailed invitations".

REVIEWER	Senore, Carlo CPO Piemonte and San Giovanni Battista University Hospital, Turin
REVIEW RETURNED	24-Jun-2013

GENERAL COMMENTS	The paper reports the results of an interesting analysis of a pilot screening project. The interest is related both to the methodology adopted for assessing the impact of an intervention and to the results. Although the study was not designed as a randomized trial the authors can get valid and informative results by using propensity scores calculated at the individual level to identify a matched control cohort. Also the analysis of the determinants of participation taking into account clustering by physician is appropriate. I have, however, some concerns about the interpretation of the results. As far as I can understand the approach using physican-linked invitations does not seem novel: personal invitation letters signed (i.e. with the printed signature) by the GP have already been adopted in several pilots in Europe and are currently used in the context of organized screening programs in Italy, and probably also in several programs in France and Spain, based on previous experience with breast cancer screening. So the present study confirms (not really demonstrates) that this approach is feasible in the context of population based programs. The finding of a higher response rate among patients of female physicians is interesting and novel in the context of CRC screening (some indication already existed in the context of breast cancer screening, as it could be expected). It might be related to a higher

	involvement of female practitioners in promoting preventive interventions, emerging from previous studies on smoking cessation, for example. There are significant difference in the impact of the intervention by type of practice, the authors do not comment on this issue, but it deserves, in my opinion some comment, as this can represent a specific and novel contribution of this study. Indeed aspects related to the organization of practice are rarely investigated, as most studies have been focused on the type of invitation. I do not know in detail how the practice are actually organized, but if the practices adopting an interprofessional team model are basing their preventive activities on the collaboration with other health professionals (such as nurses), this would represent a useful indication on a possible way to enhance the impact of physician linked invitation for screening

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Comments to the Author
The authors address an important topic relevant to on-going and imminent screening programmes. Short of randomized trial design, they adequately present weaknesses and strengths of their study design.

Response: None as no suggestions made.

Reviewer: 2
Comments to the Author
The paper is well written and describes studies related to the important topic of CRC screening uptake.

The manuscript describe two related studies, factors associated with response to mailed invitation (Study 1) and evaluate the effectiveness of mailed invitations (Study 2). Unfortunately the authors assume the reader has a reasonably detailed knowledge of the Ontario healthcare system and particularly of what they describe as the 'regular' mode of CRC screening. Having read the text several times I still do not have an adequate understanding of the 'physician-linked invitation'. What exactly was written in the invitation letter, how/if it avoided invitations going to patients recently diagnosed with CRC yet 'endorsed' by the family physician, what proportion of those made a timely visit to the physician and what proportion of those completed the test. The observations made about factors that appear to influence uptake are pertinent and important but if they are to be replicated then we need more details, possibly with inclusion of the letter used in the study. I am even more unclear about the second study because even though the authors have gone to great pains to ensure comparability of the intervention cohort 'physician-linked invitation', for which they provide substantial data, they do not describe how the control group get to have their FOBT. Whilst mailing and physician-involvement are elements of the pilot cohort I cannot see where the manuscript explains how whether the family physician is involved at all with the control cohort or whether the programme is just available but not publicized. Clearly, the interpretation of the impact of the pilot needs to be interpreted with a thorough understanding of the details of how pilot and control CRC screening were conducted.

Response: A copy of the physician linked invitation is now included as a figure (Fig 1) in order to give the reader an accurate understanding of the invitation. As noted on p9 (paragraph 2), we used the administrative data to ensure that the letters went only to persons due for screening who did not have a history of CRC – these databases included the physician/laboratory billing database (OHIP) to identify prior endoscopy or FOBT and the Ontario Cancer Registry to identify persons who had a history of CRC. As we cannot determine the reason (ie screening or otherwise) for visits to the family physician from the administrative data, we did not report on these visits, however, we did report the proportions of persons who completed a test within 6 months of the invitation (see p14 (paragraph 2) and p15 (paragraph 1)) in the Pilot and in the

control group. The control group was screened according to “usual care” – this is described p6 (paragraph 2) – there were no centralized invitations at the time of our study, instead the program relied on the family physician to promote screening. As noted on p8 (paragraph 2), these physicians were incented financially to do CRC screening.

The authors have all of the necessary data, the study is important and valuable and they need to be requested to rewrite the manuscript for an international audience that, having been convinced by the effectiveness of the intervention, might wish to adopt this element of the programme. It would also be helpful if we knew what FOBT kit was being used, how many faecal samples needed to be collected, what physician incentives were utilized in the programme (some information is given), what promotional material was used, whether it was necessary to have documented participant consent and whether reminders were used or any other form of publicity.

Response: Details about the FOBT itself including the type of kit, dietary restrictions, number of samples are now reported p6 (paragraph 2). The letter used is included in Figure 1. The other materials used, such as the brochure, could be provided in an appendix, should this be desired.

Whilst the tables providing detailed comparative data are interesting they could be reduced in content to that which is more pertinent to the conclusion, their comprehensive nature is more appropriate to a report rather then a paper.

Response: The tables have not been revised as we felt that the data would be of interest to some readers and that the space constraints pertinent to a print journal such as GUT would be less relevant to an online only journal such as BMJ Open. However, should it be desirable to reduce the tables nonetheless, this is easily done. Alternatively, some tables (such as Table 3) might be appropriate for an appendix.

I would be happy, if invited, to review a resubmitted and revised manuscript.

Some minor points;

- Several papers are cited but the authors do not then summarise the results of the studies or relate the results to their own (Page 17 Lines 32-41)

Response: The discussion has been revised with this comment in mind (p15 (paragraph 3) & p16 (paragraph 2)).

- The ‘English Bowel Cancer Screening Programme (BCSP)’ is officially the ‘NHS Bowel…..(BCSP) in England and although the first phase of rollout was to 60-69 year olds the programme is now close to completing the second phase of 70-74 and has commenced the third phase of flexisigmoidoscopy to all 55 year olds.

Response: The name of the programme has been corrected, see p16 (paragraph 2).

- The author may be aware of the difficulty that Hewitson et al (ref No 38) had in gaining GP involvement without financial incentives, this is probably pertinent and the authors might consider citing that in the discussion.

Response: We did not include this point for space reasons. The Ontario programme already employs financial incentives as noted p8 (paragraph 2).

Reviewer: 3
Comments to the Author
The main aim of this study was to identify patient and physician factors associated with response to mailed physician-linked invitations for colorectal cancer (CRC) screening. The problem is that participation was very low (22%). The uptake of the screening test was too low to expect a significant reduction in CRC mortality. Randomized trial suggested that participation has to lie over 50% to obtain a significant mortality reduction. The main conclusion from this study is that sending physician-linked mail invitations is not an effective strategy. Other invitation stratégies must be considered. In

this context the identification of patient and physician factors associated to participation to CRC screening is of little interest.
Although you conclude on the effectiveness of the screening programme there is no data in this paper to support this conclusion. A slightly higher participation than in a matched control group does not mean "effectiveness of mailed invitations".

> **Response:** We acknowledge the reviewer's point that a high screening participation rate is needed to impact CRC mortality. It is important to point out that the study population comprised those who either were due for screening OR had never been screened. Thus, it is reasonable to expect that the benefits seen in this study would be "additive", that is, would increase screening over the baseline rate in Ontario (at the time of the study just under 30% of Ontarians were up to date with FOBT). Therefore the 15% incremental benefit we have reported would be of considerable benefit as it would bring Ontario very close to the 50% described in the FOBT RCTs. Furthermore, most studies of interventions to increase patient participation in CRC screening report modest benefits (see systematic review by Brouwers M et al, https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=80349), similar to our study. As a result, it is likely that in order to achieve the thresholds needed to reduce CRC-related mortality, it is likely that multiple strategies will be needed to increase participation in screening. Our study is important as it demonstrates the effectiveness of one such possible strategy, although clearly others will also be needed.

Reviewer: 4
Comments to the Author

The paper reports the results of an interesting analysis of a pilot screening project. The interest is related both to the methodology adopted for assessing the impact of an intervention and to the results.
Although the study was not designed as a randomized trial the authors can get valid and informative results by using propensity scores calculated at the individual level to identify a matched control cohort. Also the analysis of the determinants of participation taking into account clustering by physician is appropriate.
I have, however, some concerns about the interpretation of the results.
As far as I can understand the approach using physican-linked invitations does not seem novel: personal invitation letters signed (i.e. with the printed signature) by the GP have already been adopted in several pilots in Europe and are currently used in the context of organized screening programs in Italy, and probably also in several programs in France and Spain, based on previous experience with breast cancer screening. So the present study confirms (not really demonstrates) that this approach is feasible in the context of population based programs.

> **Response:** We agree that physician linked invitations have been adopted in some organized screening programs in Europe however, there are many jurisdictions (some in the same country where adoption has occurred, but in a different jurisdiction) where they have not been adopted. This variation is likely due to the significant challenges in implementing such invitations in a centralized fashion. Furthermore, there is very little published literature describing the implementation of or the benefits of physician linked invitations in organized CRC screening programs. For this reason, we believe that our study, which demonstrates the feasibility (but also discusses the challenges, p17 (paragraph 2) as well as the benefits of physician linked invitations in an organized CRC screening program, is of considerable interest and is arguably, novel.

The finding of a higher response rate among patients of female physicians is interesting and novel in the context of CRC screening (some indication already existed in the context of breast cancer screening, as it could be expected). It might be related to a higher involvement of female practitioners in promoting preventive interventions, emerging from previous studies on smoking cessation, for example.

> **Response:** We agree this is novel – we will be interested to see if these findings are replicated elsewhere.

There are significant difference in the impact of the intervention by type of practice, the authors do not comment on this issue, but it deserves, in my opinion some comment, as this can represent a specific

and novel contribution of this study. Indeed aspects related to the organization of practice are rarely investigated, as most studies have been focused on the type of invitation. I do not know in detail how the practice are actually organized, but if the practices adopting an interprofessional team model are basing their preventive activities on the collaboration with other health professionals (such as nurses), this would represent a useful indication on a possible way to enhance the impact of physician linked invitation for screening

Response: We agree – the finding that screening was better in the practices that adopted an interprofessional team model is clearly of interest.

VERSION 2 – REVIEW

REVIEWER	Stephen Halloran NHS Bowel Cancer Screening Programme Royal Surrey County Hospital University of Surrey
REVIEW RETURNED	10-Dec-2013

GENERAL COMMENTS	The abstract need some further information to enable to ready to properly understand the studies undertaken. The method cannot be replicated because we are not give the details of the correspondence for invitation or the packaging used and we do not know the financial details which might influence the motivation of the physicians to influence uptake. With more details the results can be presented more clearly for the general reader. Again, a little additional information will inform the reader and explain the impact that incentives and control group selection might have upon the observations made in the studies. General comments An interesting but complex combination of studies, each valuable but in need of further information to aid understanding (as described below). The authors might like to consider a simpler title for the paper – the 'two linked studies' does not enlighten the reader The authors should ensure that the past tense is used throughout the manuscript – for example, in the Abstract, second sentence 'The aims of this study were to….'. It is more acceptable to refer to individuals invited for screening as 'subjects' rather than 'patients'. Acronyms should be defined in full when first used. For example, 'FOBT' is used in the Abstract but not defined. The study structure is a little complex and it assumes some knowledge of the current screening process and the system of remuneration for physician participation /involvement in screening. It would help if the author made it clear that the link between the cohort studies is because the most of the subject in study 1 were used in study 2 and that a match control group were added to study 2. The method by which the control group was invited to be

	screened needs further explanation. The term linked is also used to indicate that the local physician (GP) provided the test kits to subjects following their receipt of an invitation letter that carried the physician's name. The study of two interventions, a FOBT invitation and a choice for FOBT or colonoscopy is an added complexity but is reasonably well explained. All of this detail needs to be made plain in the main text and captured in the abstract. Payment to the physician for this screening activity is clearly a potentially important factor that needs to be explained to the reader since it might significantly influence the viability of the proposed approach. The definition of uptake needs to be spelt out to avoid any ambiguity, for the FOBT group does it mean completion to a definitive positive or negative test outcome and colonoscopy if positive, a definitive FOBT result, receipt of a test kit, etc etc. Does the denominator include invitations that do not reach their destination (returned because possible delivery or address problems), what happens to those who opt out because of clinical or other family issues? Similar issues apply to those who choose colonoscopy. The invitations have used a range of exclusions; do they apply equally to the control group? Strengths and limitations of the study: (bullet point 1) it is not accurate to say that there aren't any reports of the effectiveness of physician-linked invitations in an organised screening programme? What about Hewitson et al, as mentioned later in text (Discussion, third paragraph)? It is fair to say that the paper describes an organised process in which the physician is significantly more involve… perhaps just qualify the observation? (Hewitson P, Ward AM, Heneghan C, Halloran SP, Mant D. Primary care endorsement letter and a patient leaflet to improve participation in colorectal cancer screening: results of a factorial randomised trial. Br J Cancer 2011;105(4):475-80. Epub 2011/08/11.) Introduction, third paragraph: the word 'operationalization' is not easy on the ear! Suggest rewording. The discussion rightly refers to studies in Italy, the UK and Australia; it is important to quote the baseline uptake for these studies so that the impact of the intervention can be put into perspective. This study is valuable but the reader needs to be made aware that the baseline uptake was very poor and that whilst a significant impact was seen through physician involvement it is still much lower than that seen in organised programmes in the three countries cited.

REVIEWER	Carlo Senore AOU Città della salute e della Scienza CPO Piemonte
REVIEW RETURNED	11-Dec-2013

GENERAL COMMENTS	The paper reports the results of an interesting analysis of a pilot screening project. The interest is related both to the methodology adopted for assessing the impact of an intervention and to the results. Although the study was not designed as a randomized trial the authors can get valid and informative results by using propensity scores calculated at the individual level to identify a matched control

	cohort. Also the analysis of the determinants of participation taking into account clustering by physician is appropriate. I would only suggest to rephrase the initial statement of the strengths list: in fact the impact of physician's linked invitation has already been described in previous papers, some of them also mentioned by the authors. The EU guidelines for quality assurance in CRC screening and diagnosis are indeed already recommending to preferably use invitation letters signed by the GP – I A recommendation). Also as some large scale organized population bases European screening program are already routinely using invitation letters signed by the subject's GP, the feasibility of such approach has already been documented. The present paper confirms both the effectiveness and the feasibility of such approach in a different jurisdiction; in addition it also documents the role of physician and patient related factors which influence the response rate

VERSION 2 – AUTHOR RESPONSE

Reviewer Name Stephen Halloran
Institution and Country NHS Bowel Cancer Screening Programme
Royal Surrey County Hospital
University of Surrey

The abstract need some further information to enable to ready to properly understand the studies undertaken.
The method cannot be replicated because we are not give the details of the correspondence for invitation or the packaging used and we do not know the financial details which might influence the motivation of the physicians to influence uptake.
With more details the results can be presented more clearly for the general reader.
Again, a little additional information will inform the reader and explain the impact that incentives and control group selection might have upon the observations made in the studies.
RESPONSE: Abstract reviewed as per reviewer's suggestions.

Physician-linked mailed invitation to be screened improves uptake in an organized colorectal cancer screening program: Two linked cohort studies.

Tinmouth et al

Referee's comments for BMJ (Manuscript ID bmjopen-2013-004494)

General comments

An interesting but complex combination of studies, each valuable but in need of further information to aid understanding (as described below).

The authors might like to consider a simpler title for the paper – the 'two linked studies' does not enlighten the reader
RESPONSE: Please see new title (title page)

The authors should ensure that the past tense is used throughout the manuscript – for example, in the Abstract, second sentence 'The aims of this study were to….'.

RESPONSE: Revised as per suggestion throughout.

It is more acceptable to refer to individuals invited for screening as ‘subjects’ rather than ‘patients’.
RESPONSE: Where possible, we have substituted the word “participant” for “patient” (we chose to use “participant” over “subject” as in certain contexts, it seemed to be more appropriate). However, to enhance clarity (e.g., when referring to the subjects in the context of their relationship with the primary care provider), we may have retained the word patient.

Acronyms should be defined in full when first used. For example, ‘FOBT’ is used in the Abstract but not defined.
RESPONSE: Revised as per suggestion throughout.

The study structure is a little complex and it assumes some knowledge of the current screening process and the system of remuneration for physician participation /involvement in screening. It would help if the author made it clear that the link between the cohort studies is because the most of the subject in study 1 were used in study 2 and that a match control group were added to study 2. The method by which the control group was invited to be screened needs further explanation. The term linked is also used to indicate that the local physician (GP) provided the test kits to subjects following their receipt of an invitation letter that carried the physician’s name. The study of two interventions, a FOBT invitation and a choice for FOBT or colonoscopy is an added complexity but is reasonably well explained. All of this detail needs to be made plain in the main text and captured in the abstract.
RESPONSE: An expanded explanation of the 2 studies and their relationship is described in the abstract and on p 7.

Payment to the physician for this screening activity is clearly a potentially important factor that needs to be explained to the reader since it might significantly influence the viability of the proposed approach. The definition of uptake needs to be spelt out to avoid any ambiguity, for the FOBT group does it mean completion to a definitive positive or negative test outcome and colonoscopy if positive, a definitive FOBT result, receipt of a test kit, etc etc. Does the denominator include invitations that do not reach their destination (returned because possible delivery or address problems), what happens to those who opt out because of clinical or other family issues? Similar issues apply to those who choose colonoscopy. The invitations have used a range of exclusions; do they apply equally to the control group?
RESPONSE: Further details regarding payment for screening activities are now included in the introduction (p 6) and in the methods (p10, under mailing). Further explanation regarding the definition of response (p11, paragraph 1) and the denominator (p10, paragraph 1) are now included. We applied the same inclusion/exclusion criteria to the Pilot participants and the controls and used the same administrative databases to do so (p13, paragraph 2).

Strengths and limitations of the study: (bullet point 1) it is not accurate to say that there aren’t any reports of the effectiveness of physician-linked invitations in an organised screening programme? What about Hewitson et al, as mentioned later in text (Discussion, third paragraph)? It is fair to say that the paper describes an organised process in which the physician is significantly more involve… perhaps just qualify the observation?

(Hewitson P, Ward AM, Heneghan C, Halloran SP, Mant D. Primary care endorsement letter and a patient leaflet to improve participation in colorectal cancer screening: results of a factorial randomised trial. Br J Cancer 2011;105(4):475-80. Epub 2011/08/11.)
RESPONSE: Revised as per reviewer suggestion (p 5)

Introduction, third paragraph: the word ‘operationalization’ is not easy on the ear! Suggest rewording.
RESPONSE: Revised as per reviewer suggestion (p 7 last paragraph)

The discussion rightly refers to studies in Italy, the UK and Australia; it is important to quote the baseline uptake for these studies so that the impact of the intervention can be put into perspective. This study is valuable but the reader needs to be made aware that the baseline uptake was very poor and that whilst a significant impact was seen through physician involvement it is still much lower than that seen in organised programmes in the three countries cited.
RESPONSE: Revised as per reviewer suggestion (p 18-19 new paragraph)

Reviewer Name Carlo Senore
Institution and Country AOU Città della salute e della Scienza
CPO Piemonte
Turin, Italy
Please state any competing interests or state 'None declared': None declared

The paper reports the results of an interesting analysis of a pilot screening project.
The interest is related both to the methodology adopted for assessing the impact of an intervention and to the results.
Although the study was not designed as a randomized trial the authors can get valid and informative results by using propensity scores calculated at the individual level to identify a matched control cohort. Also the analysis of the determinants of participation taking into account clustering by physician is appropriate.
I would only suggest to rephrase the initial statement of the strengths list: in fact the impact of physician's linked invitation has already been described in previous papers, some of them also mentioned by the authors. The EU guidelines for quality assurance in CRC screening and diagnosis are indeed already recommending to preferably use invitation letters signed by the GP – I A recommendation). Also as some large scale organized population bases European screening program are already routinely using invitation letters signed by the subject's GP, the feasibility of such approach has already been documented.
The present paper confirms both the effectiveness and the feasibility of such approach in a different jurisdiction; in addition it also documents the role of physician and patient related factors which influence the response rate
RESPONSE: Revised as per reviewer suggestion (p 5)

VERSION 3 - REVIEW

REVIEWER	Stephen P. Halloran NHS Bowel Cancer Screening Programme England
REVIEW RETURNED	14-Jan-2014

GENERAL COMMENTS	The authors should be thanked for having addressed most the of issues identified at the time of an earlier review. The statistic error in table 2 where the point estimate fall outside of the stated confidence interval still remains. I will leave it to the Editors to decide whether they wish to press for a reference to the Generalised Estimating Equation highlighted in my previous response. I would still like to see a comment that the use of dietary restriction (vit C) is now not thought necessary (reference to published meta-analysis)... only to let the reader know that restriction is not essential. The text manipulation has introduced a number of typographical

	errors which I think can be taken care of by the Editors.

REVIEWER	Carlo Senore AOU Città della Salute e della Scienza - CPO Piemonte Turin, Italy
REVIEW RETURNED	07-Jan-2014

GENERAL COMMENTS	The revised version of the paper has addressed appropriately the issues raised by the reviewers. The methods, results and limitations of the interesting analysis of a well conducted intervention are adequately described . The paper offers also clear context related information which is useful to the reader to compare the results with different jurisdictions.

VERSION 3 – AUTHOR RESPONSE

RESPONSE: Thank you for catching that error which occurred when formatting the paper. It is now corrected, please see Table 2.

I will leave it to the Editors to decide whether they wish to press for a reference to the Generalised Estimating Equation highlighted in my previous response.
RESPONSE: This has been added. Please see p. 13, top of page.

I would still like to see a comment that the use of dietary restriction (vit C) is now not thought necessary (reference to published meta-analysis)... only to let the reader know that restriction is not essential.
RESPONSE: This has been added to the introduction. Please see p.6, paragraph 2.

The text manipulation has introduced a number of typographical errors which I think can be taken care of by the Editors.
RESPONSE: We have attempted to carefully proof – read. Hopefully, errors have been identified and corrected.