PEER REVIEW HISTORY

This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open after one more subsequent round of revision.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Enhanced involvement of general practitioners in cancer rehabilitation: a randomised controlled trial
AUTHORS	Stinne Holm Bergholdt, Pia Veldt Larsen, Jakob Kragstrup, Jens Søndergaard and Dorte Gilså Hansen

VERSION 1 - REVIEW

REVIEWER	Knut Holtedahl

GENERAL COMMENTS	Exploring the GP's role in follow-up of cancer is important, and this study is large, seems well designed with a clearly defined research question and merits publication. The negative results do not ruin the interest of the study. The results are made more credible by consistent results in three other studies cited. However, the discussion could have focused more on the short follow-up period, which in this and other studies may be crucial to understand the results. Quality of life and psychological distress in a newly treated cancer patient is understandably related to that patient's post-treatment clinical condition and prospects of being cured, and this would be randomly distributed in a RCT like this. Intervention effects would probably seem less important and be diluted at this time in cancer patients' careers. Measures like the EORTC are designed for cancer patients and outcomes may be expected to change primarily when the clinical condition changes. If it will be possible to follow these patients for several years, intervention effects may appear when terminal care approaches, on condition that it can be shown that GPs from intervention practices actually follow their patients more closely. To understand the results better, I miss numbers for how many in the intervention group actually followed the encouragement and contacted their patients, and/or numbers for the proportion in each group who actually had consultations with their patients during the follow-up period. Common sense and clinical experience suggest that patients during the first months after treatment would want close surveillance of possible relapse but otherwise have as little as possible to do with health services, in

	order to resume their ordinary lives. Co-morbidity has been shown to be considerable in cancer patients and would need to be seen to after a period of intense focusing on cancer. If such elements are taken into consideration, the article makes an important contribution to a discussion about rational distribution of tasks and co-operation in cancer care. The randomization procedure is less clear than desirable and should be described better. I have consulted the Method article in Ref 23 without finding more details. It seems to me that the randomization was not a simple randomization but a cluster or block randomization with equal numbers of practices in each group? The final phrases in the “Sample size” part seem to refer to this but are difficult to understand. The statistical analysis seems to have been adapted to such a block randomization, but I am not sufficiently familiar with this. There was no Figure 3 (see p.6) in my manuscript. On p 9 it is said that a theoretical basis was established through review of papers etc.. Is this not rather an empirical basis, theory being rather absent in this methodology-centered tradition of medical research?

REVIEWER	Jon Emery

GENERAL COMMENTS	This paper reports a cluster RCT of an intervention aimed at improving the involvement of Danish GPs in rehabilitation care for adults who have recently completed cancer treatment. The role of general practice in follow-up of cancer patients has been well researched for certain cancers but few trials have explicitly aimed to improve uptake of rehabilitation services. The term ‘rehabilitation’ in this setting may be somewhat confusing to many readers of the BMJ and the paper really needs to explain further which types of services they include in their definition of rehabilitation (eg physiotherapy, psychology, social work etc). Importance New approaches to meeting the range of common unmet needs of cancer patients are needed which bridge the gap between hospital care and general practice. If the findings of this trial were more interesting, then this paper would be of importance to clinicians and policy makers. However, given the negative finding and relatively poor description of the intervention, the paper would be of limited

	interest. Scientific reliability The main aim of the trial is reasonably well defined. The authors chose to use a cluster randomised design although this decision is not that well justified. The intervention was aimed at both the patient and their individual GP and so I presume they chose to randomise at the practice level to avoid potential contamination between patients recruited into the trial from the same practice. However, the nature of the intervention meant it was relatively weak at the practitioner level and, in retrospect, a cluster design could possibly have been avoided. The paper does not report the study according to the revised CONSORT statement for cluster randomised trials. For example, there is no information provided about the practices and only limited data on the distribution of patients across practices. The intervention requires more detailed description including the number of patient interviews conducted by the rehabilitation coordinator and the nature of the checklist for unmet needs. Furthermore, there are no data provided about how well it was actually implemented, especially for example whether GPs even contacted their patient. I expect the negative finding of the trial was more likely to be due to its limited dose at the practitioner level but this is purely surmise because we have no process measures to determine the fidelity of this complex intervention. The primary outcome measure is a well validated measure relevant to all cancers and which covers the key domains of quality of life which one would have hoped might have been improved by a rehabilitation intervention. The sample size, even accounting for clustering (which is not well described) and for attrition, should have been adequate to identify an effect. The negative finding is therefore probably not due to an inappropriate outcome measure, contamination or an underpowered trial. The conclusions are reasonable although I think they could be more critical about the nature of the intervention as an explanation for the negative finding. References overall are satisfactory although they might want to mention the following relevant paper: Lewis, R.A., et al., Follow-up of cancer in primary care versus secondary care: systematic review. Br J Gen Pract, 2009. 59(564): p. e234-47.

The manuscript received a third review at the BMJ but the reviewer did not give permission for their comments to be published.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments...

Name: Knut Holtedahl

Position:

Exploring the GP's role in follow-up of cancer is important, and this study is large, seems well designed with a clearly defined research question and merits publication. The negative results do not ruin the interest of the study. The results are made more credible by consistent results in three other studies cited. However, the discussion could have focused more on the short follow-up period, which in this and other studies may be crucial to understand the results. Quality of life and psychological distress in a newly treated cancer patient is understandably related to that patient's post-treatment clinical condition and prospects of being cured, and this would be randomly distributed in a RCT like this. Intervention effects would probably seem less important and be diluted at this time in cancer patients' careers. Measures like the EORTC are designed for cancer patients and outcomes may be expected to change primarily when the clinical condition changes. If it will be possible to follow these patients for several years, intervention effects may appear when terminal care approaches, on condition that it can be shown that GPs from intervention practices actually follow their patients more closely. To understand the results better, I miss numbers for how many in the intervention group actually followed the encouragement and contacted their patients, and/or numbers for the proportion in each group who actually had consultations with their patients during the follow-up period. Common sense and clinical experience suggest that patients during the first months after treatment would want close surveillance of possible relapse but otherwise have as little as possible to do with health services, in order to resume their ordinary lives. Co-morbidity has been shown to be considerable in cancer patients and would need to be seen to after a period of intense focusing on cancer. If such elements are taken into consideration, the article makes an important contribution to a discussion about rational distribution of tasks and co-operation in cancer care.

The randomization procedure is less clear than desirable and should be described better. I have consulted the Method article in Ref 23 without finding more details. It seems to me that the randomization was not a simple randomization but a cluster or block randomization with equal numbers of practices in each group? The final phrases in the "Sample size" part seem to refer to this but are difficult to understand. The statistical analysis seems to have been adapted to such a block randomization, but I am not sufficiently familiar with this.

Comment [shb1]: We did not expect any effects of the intervention to appear after more than 14 months of follow-up and therefore did not discuss the possibility of a longer period of follow-up.

Comment [shb2]: Future studies will describe in more detail the proportion of patients contacted by their GP by looking further into and comparing answers from patient as well as GP questionnaires. P. 13.

Comment [shb3]: No data regarding comorbidity was collected but was regarded randomly distributed between groups. No corrections made.

Comment [shb4]: Additional description added on p. 8.

Comment [shb5]: The randomisation procedure is described in detail in the feasibility paper (reference 26): All general practices in Denmark were randomized prior to study start giving 164 and 159 practices in the intervention group and control group respectively. At time of inclusion, study patients were subsequently allocated according to the randomization of their GP.

Comment [shb6]: Rephrased at p. 9.

There was no Figure 3 (see p.6) in my manuscript.

Comment [shb7]: We apologise for this. The number of the reference to the Figure is changed to 2.

On p 9 it is said that a theoretical basis was established through review of papers etc.. Is this not rather an empirical basis, theory being rather absent in this methodology-centered tradition of medical research?

Comment [shb8]: One more reference added on p.4 to support this sentence (Kendall M et al).

Reviewer 3 Comments...

Name:Jon Emery

Position:

Originality

This paper reports a cluster RCT of an intervention aimed at improving the involvement of Danish GPs in rehabilitation care for adults who have recently completed cancer treatment. The role of general practice in follow-up of cancer patients has been well researched for certain cancers but few trials have explicitly aimed to improve uptake of rehabilitation services. The term 'rehabilitation' in this setting may be somewhat confusing to many readers of the BMJ and the paper really needs to explain further which types of services they include in their definition of rehabilitation (eg physiotherapy, psychology, social work etc).

Comment [shb9]: WHO definition added at p. 4.

Importance

New approaches to meeting the range of common unmet needs of cancer patients are needed which bridge the gap between hospital care and general practice. If the findings of this trial were more interesting, then this paper would be of importance to clinicians and policy makers. However, given the negative finding and relatively poor description of the intervention, the paper would be of limited interest.

Scientific reliability

The main aim of the trial is reasonably well defined. The authors chose to use a cluster randomised design although this decision is not that well justified.

Comment [shb10]: Elaborated on p. 8.

The intervention was aimed at both the patient and their individual GP and so I presume they chose to randomise at the practice level to avoid potential contamination between patients recruited into the trial from the same practice. However, the nature of the intervention meant it was relatively weak at the practitioner level and, in retrospect, a cluster design could possibly have been avoided. The paper does not report the study according to the revised CONSORT statement for cluster randomised trials. For example, there is no information provided about the practices and only limited data on the distribution of patients across practices.

Comment [shb11]: The extended version of the CONSORT statement of cluster randomised trials is uploaded as a supplementary file.

The intervention requires more detailed description including the number of patient interviews conducted by the rehabilitation coordinator and the nature of the checklist for unmet needs. Furthermore, there are no data provided about how well it was actually implemented, especially for example whether GPs even contacted their patient. I expect the negative finding of the trial was

Comment [shb12]: Described in detail in Hansen et al., ref. number 26.

Comment [shb13]: The nature of the checklist appears from Figure 2.

Comment [shb14]: Those data were included in the GP-questionnaire. We are working on another paper, aiming to describe the GP behavior in detail.

more likely to be due to its limited dose at the practitioner level but this is purely surmise because we have no process measures to determine the fidelity of this complex intervention.
The primary outcome measure is a well validated measure relevant to all cancers and which covers the key domains of quality of life which one would have hoped might have been improved by a rehabilitation intervention. The sample size, even accounting for clustering (which is not well described) and for attrition, should have been adequate to identify an effect. The negative finding is therefore probably not due to an inappropriate outcome measure, contamination or an underpowered trial.
The conclusions are reasonable although I think they could be more critical about the nature of the intervention as an explanation for the negative finding.
References overall are satisfactory although they might want to mention the following relevant paper:
Lewis, R.A., et al., Follow-up of cancer in primary care versus secondary care: systematic review. Br J Gen Pract, 2009. 59(564): p. e234-47.

Comment [shb15]: Very important comment and paper which is now reference number 38.

VERSION 2 – REVIEW

REVIEWER	Knut Holtedahl Professor Institute of Community Medicine University of Tromsø Norway I declare I have no conflicts of interest
REVIEW RETURNED	19/01/2012

THE STUDY	The authors say they have uploaded the CONSORT statement as a supplementary file. The information in the article seems sufficient.
GENERAL COMMENTS	I still think that the statement on p. 9 about a theoretical basis is somewhat pretentious. The authors have added a reference, but I think that if they have a real theoretical basis it should be explained with two-three more sentences in the article. If not, the phrase could be modified. It seems that there is no Figure 3, and the authors say they have corrected this. But I think they have made the correction on the wrong page - there is still a reference to an unknown Fig 3. Since this is an open referee process, please write my name correctly also in Ref 36

REVIEWER	Chris Hurt Senior Statistician Cardiff University UK

	No competing interests
REVIEW RETURNED	16/02/2012

THE STUDY	Confirm that randomisation was simple 1:1 randomisation. Numbers of patients in flow diagram at 6 months (figure 1) do not match numbers used for primary outcome (results section). I think this study was probably massively overpowered to detect a difference in 8 units on the primary endpoint. A conservative assumption about the intracluster correlation coefficient may have been more appropriate than recruiting from the same number of clusters as the number of individuals suggested by the unclustered sample size calculation.
RESULTS & CONCLUSIONS	Was there any contamination caused by patients changing GP during the study? The main criticism I have is the lack of any measure of GP activity associated with the intervention. Was the lack of success due to a failure of the intervention or a failure to engage GPs involvement with the intervention? This should be at least discussed in the weaknesses section.
REPORTING & ETHICS	What was the consent process?

VERSION 2 – AUTHOR RESPONSE

Reviewer: Knut Holtedahl
Professor
Institute of Community Medicine
University of Tromsø
Norway

I declare I have no conflicts of interest

I still think that the statement on p. 9 about a theoretical basis is somewhat pretentious. The authors have added a reference, but I think that if they have a real theoretical basis it should be explained with two-three more sentences in the article. If not, the phrase could be modified.
Answer: The phrase on p. 9 has been modified to “Before designing the intervention we reviewed papers, reports and textbooks about the problems faced by cancer patients and GPs with respect to individual rehabilitation and continuity across healthcare sectors (1-3;16-24;36)”.

It seems that there is no Figure 3, and the authors say they have corrected this. But I think they have made the correction on the wrong page - there is still a reference to an unknown Fig 3.
Answer: There is no figure 3, reference changed to figure 2 on p. 7.

Since this is an open referee process, please write my name correctly also in Ref 36
Answer: We apologise for the misspelling, has now been corrected.

Reviewer: Chris Hurt
Senior Statistician
Cardiff University
UK

No competing interests

Confirm that randomisation was simple 1:1 randomisation.
Answer: The randomisation was 1:1, numbers of practices in each group added on p. 8 to clarify this point.

Numbers of patients in flow diagram at 6 months (figure 1) do not match numbers used for primary outcome (results section).
Answer: The reason why the numbers in figure 1 and table 2 do not match is that we used complete case analyses. This information has been added on p. 9. Further, supplementary information about the percentage of missing data in the primary outcome has been added to the result section on p. 10.

I think this study was probably massively overpowered to detect a difference in 8 units on the primary endpoint. A conservative assumption about the intracluster correlation coefficient may have been more appropriate than recruiting from the same number of clusters as the number of individuals suggested by the unclustered sample size calculation.
Answer: We agree that the study may have been overpowered.

Was there any contamination caused by patients changing GP during the study?
Answer: A Danish study from 2003 (T Drachmann et.al in Ugeskrift for Laeger, 165/26, p. 2743-46, 2003) showed that cancer patients do not change their GP during the first year after diagnosis more often than the basic population (2.7 % per annum). Thus, we therefore expect the number of patients changing GP during follow up to be very small and have no reason to believe that this has influenced our results.

The main criticism I have is the lack of any measure of GP activity associated with the intervention. Was the lack of success due to a failure of the intervention or a failure to engage GPs involvement with the intervention? This should be at least discussed in the weaknesses section.
Answer: We agree that GP activity is a very interesting aspect of the explanation of the lack of effect of the intervention. As mentioned on p. 13-14, we plan to analyse data regarding GP activity and patient as well as GP satisfaction with the GPs contribution to the rehabilitation course. These results will follow in future publications. The aim of this study was to evaluate the effect of the intervention in a close to real life setting, and we therefore exclusively report the results of the primary outcome as intention to treat.

What was the consent process?
Answer: As stated during the submission process, the patients gave oral consent firstly to their GPs being informed as to their individual problems and needs and secondly to their GPs being encouraged to be proactive regarding the patients' rehabilitation. This information has now been added on p. 6-7.

Somewhere between a minor and major revision needed - see comments above.