PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol of the BLANKET-trial: a cluster randomised controlled trial on the (cost-) effectiveness of a primary care intervention for fear of cancer recurrence in cancer survivors
AUTHORS	Luigjes, Yvonne; van der Lee, Marije; de Wit, Niek; Helsper, Charles

VERSION 1 – REVIEW

REVIEWER	Phyllis Butow CeMPED/ PoCoG, University of Sydney, Australia
REVIEW RETURNED	22-Jul-2019

GENERAL COMMENTS	This is an interesting protocol for a cluster randomised controlled trial of a blended intervention for fear of cancer recurrence (FCR) delivered by general practices. Given the high prevalence of FCR, an intervention which is scalable, such as this one, is desirable. Participants will be cancer survivors seen at participating GP practices, who received care for their cancer 3 months to 10 years previously, and who desire help for their FCR. Exclusion criteria (apart from inability to speak Dutch) are not provided and should be considered. Eg co-morbid psychiatric conditions. Since eligibility criteria is based on desire for help, FCR levels in participants may vary from low to high. It may not be cost-effective for those with low FCR to receive this fairly intensive intervention. The authors might consider an additional screen using the FCRI, with only those scoring over a pre-specified cut-off, perhaps supplemented by an independent assessment by the GP, eligible for inclusion. It is not clear what the likely uptake of this intervention will be within the GP setting. As noted, many patients prefer to discuss their FCR with oncology specialists. The sample size calculated from a power analysis, taking into account likely clustering within MHWs and drop-out, is n=244 participants. Given that randomization is at the level of GP practice, we need to know how many clusters are required, and minimum recruitment per cluster, for sufficient power in the analysis. Presumably if GPs but not MHWs (or vice versa) agree to participate in the study, the practice will not be eligible to join the study. The intervention (delivered at the practice level) appears to involve one intake visit with any participating GP from the practice, + five contacts with a mental health worker (MHW) from that practice, and some online modules. The GPs and MHWs from intervention sites will be trained prior to the study. The actual intervention, focusing on normalisation, psychoeducation and self-management, is not well described in the protocol. The reference given for the intervention is a protocol, thus there do not appear to be any data, pilot or otherwise, supporting its efficacy. This is concerning, given the size of the proposed study. The online modules are not described at all, and in fact it is not really clear whether they are included in this

	intervention. Participants in control practices will receive an intake visit with the GP where “usual care” will be delivered, whatever that is (although, as acknowledged by the authors, this visit in itself may not be usual care and GPs and patients will be primed to focus on FCR). Control participants may or may not be referred to the MHW, as per usual care; if they are referred they will receive usual care from the MHW. The study plans to document “usual care” as little is currently known about what this comprises, although as noted, this will be “primed usual care”. The hypotheses for the study refer to “the current intervention” which is confusing terminology. A strength of the study is plans to look at effect modifiers (if efficacy is demonstrated), including 15 patient factors, 3 practice factors and 2 MHW practices. It is not clear that the study is powered, however, to examine all these modifiers. Another strength is a planned cost analysis, and qualitative interviews with both survivors and staff to examine acceptability and value of the intervention.

REVIEWER	Tania Estapé FEFOC Foundation, Barcelona, Spain
REVIEW RETURNED	30-Jul-2019

GENERAL COMMENTS	Is difficult to review a protocol, and to analyze as it was a complete research. However it seems to address a good field very fashion in Psychooncology and a well done project. I think they must review the parts where I point "no" in the checklist in order to improve it.

REVIEWER	Ben Smith Ingham Institute for Applied Medical Research and UNSW, Australia
REVIEW RETURNED	09-Aug-2019

GENERAL COMMENTS	Thanks for the opportunity to review this protocol for an interesting and important trial of delivering FCR care in primary care. Abstract You state that ‘Patients who have finished successful curative treatment for cancer between 3 months and 10 years ago and desire support for FCR will be invited to participate in the study’ but you won’t know if they desire support until they respond to the invitation letter, so I would suggest dropping the ‘and desire support for FCR’ bit. A little more info regarding what the focus/components of the intervention are would be useful Strengths and limitations Combining quantitative and qualitative data is presented as a strength, but no qualitative methods are mentioned in the abstract Intro In paragraph outlining factors associated with FCR, probably worth noting that while relatively consistent associations between FCR and demographic factors such as age and gender have been noted, in general psychological factors (e.g. metacognitive beliefs) have been found to be more closely related to FCR. See below for details:

	Smith, A. B., Sharpe, L., Thewes, B., Turner, J., Gilchrist, J., Fardell, J. E., . . . the ConquerFear Authorship, G. (2018). Medical, demographic and psychological correlates of fear of cancer recurrence (FCR) morbidity in breast, colorectal and melanoma cancer survivors with probable clinically significant FCR seeking psychological treatment through the ConquerFear study. Supportive Care in Cancer, 26(12), 4207-4216. doi:10.1007/s00520-018-4294-y Clearly I'm biased, having been involved in the trial, but I feel that it's worth mentioning ConquerFear among the efficacious FCR interventions listed, particularly as this demonstrates the efficacy of a treatment approach based more on metacognitive therapy rather than traditional CBT: Butow, P. N., Turner, J., Gilchrist, J., Sharpe, L., Smith, A. B., Fardell, J. E., . . . Thewes, B. (2017). Randomized Trial of ConquerFear: A Novel, Theoretically Based Psychosocial Intervention for Fear of Cancer Recurrence. Journal of Clinical Oncology, 35(36), 4066-4077. doi:10.1200/JCO.2017.73.1257 Line 108: Suggest adding typically after 'Specialised psychological care for cancer is' While proposed characteristics of clinical FCR are mentioned, there is limited discussion of FCR existing on a spectrum from normal to clinical. Perhaps this could be provided in the context of justifying the statement that 'most cancer survivors do not require intensive specialized psychotherapy, but rather accessible psychological care'. Line 114: The 'review on self-guided online interventions specifically for cancer patients' mentioned is actually a review of self-guided interventions generally and most of the interventions were not delivered online, please correct. Aims Given the study is testing a blended care intervention, perhaps more discussion of the SWORD study, which also evaluated a blended care approach to treating FCR would be appropriate. 133: You state that 'The target group for this intervention is patients with moderate FCR' but you don't give a definition of what you mean by moderate FCR, nor do you say how you plan to identify these patients, as opposed to patients with severe or low FCR. Please clarify. Eligibility It is probably self-evident, but it might be worth explicitly stating that only general practices in which the GP and MHW are able to participate will be included in the study, unless I have misunderstood and this is not a requirement? Study procedures Is CAREST a publicly available intervention? Is there any chance that patients from control practices will use the intervention, albeit without therapist support? 186: I think 'inclusion speed' should probably be 'inclusion rate' Intervention

	The abstract mentions that the intervention comprises an 'intake with the GP and five sessions with the MHW', but in the intervention section it is unclear whether GPs and MHWs will deliver the same intervention, or different components of the intervention (and what those components are). The CAREST intervention referenced is a self-guided intervention. Please explain how the intervention has been modified for guided delivery. In the limitations you discuss the fact that inviting patients to take part in the trial of a FCR intervention may 'activate patients', making them less representative of patients currently seeking care for FCR. Isn't there also a risk that asking GP responses regarding their 'usual care' for FCR may be also biased by the fact that GPs who agree to participate in the study are more likely to have an interest in and perhaps provide better care for FCR than usual care more generally? Primary outcome Can you please explain the rationale behind the primary outcome being the difference in FCR severity between the two groups at a single time point (i.e. 3 months), rather than the difference in the change in FCR severity from baseline to 3 months between the two groups? Data Collection Can you please explicitly state that the three FCRI subscales you are using are the severity, psychological distress and coping strategies subscales? 238: Expand EHR here instead of a couple of lines later. How will GP visits specifically related to FCR be ascertained and differentiated from cancer-related visits? For instance, patients are often told to report to their Dr if they have symptoms that maybe indicative of recurrence. How will you differentiate people who are simply following those instructions, versus being hyper-vigilant due to FCR? 255: I'm confused by the sentence 'Additional information about data collection, data management, monitoring and dissemination of results can be found in the study protocol.' Isn't this the study protocol? 265: close brackets after number of patients per MHW Sample size calculation Can a little more detail be provided regarding a mean difference of 3, with a standard deviation of 7, representing a 'relevant difference', so that readers can understand without having to refer to the FCRI-NL validation paper. Also, what is the rationale for assuming dropout rates of 12%? Statistical analysis There are many different comparisons of healthcare utlisation and costs mentioned. While I understand that these are secondary outcomes, I think it would strengthen your protocol to state a priori if there are particular comparisons that are of greater interest/importance.

	299: More detail regarding the approach taken to the qualitative analysis of patient/provider satisfaction with the intervention would be appreciated. 303: I assume patient should be patients. Discussion 317: It's stated that this is one of few 'implementation studies' on FCR interventions. Could you please offer further explanation of what qualifies this as an implementation study? It may also be worth citing some of the existing studies focused on implementation of FCR interventions: Cruickshank, S., Steel, E., Fenlon, D., Armes, J., Banks, E., & Humphris, G. (2019). Specialist breast cancer nurses' views on implementing a fear of cancer recurrence intervention in practice: a mixed methods study. Supportive Care in Cancer. doi:10.1007/s00520-019-04762-9 Butow, P., Williams, D., Thewes, B., Tesson, S., Sharpe, L., Smith, A. B., . . . Beith, J. (2019). A psychological intervention (ConquerFear) for treating fear of cancer recurrence: Views of study therapists regarding sustainability. Psychooncology, 28(3), 533-539. doi:10.1002/pon.4971 339: While participants may not be informed of their group allocation, presumably in some cases usual care will comprise no FCR-specific care, so they may figure it out. Perhaps it is worth asking patients which group they thought they had been allocated to at the end of the intervention period, so that expectancy effects can be controlled for.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Phyllis Butow
Institution and Country: CeMPED/ PoCoG, University of Sydney, Australia
Please state any competing interests or state 'None declared': None declared

This is an interesting protocol for a cluster randomised controlled trial of a blended intervention for fear of cancer recurrence (FCR) delivered by general practices. Given the high prevalence of FCR, an intervention which is scalable, such as this one, is desirable.
Thank you very much for the time taken to carefully read our manuscript. All your insightful input has really helped us to improve our article.

Participants will be cancer survivors seen at participating GP practices, who received care for their cancer 3 months to 10 years previously, and who desire help for their FCR. Exclusion criteria (apart from inability to speak Dutch) are not provided and should be considered. Eg co-morbid psychiatric conditions.
GPs select patients who can be sent the invitation letter for the study. GPs are asked not to invite vulnerable patients, who would be confused by the letter or unable to participate in the study (e.g. patients with dementia, schizophrenia, etc.).
We do not exclude anxiety or depression disorders, because we do not have reason to believe those disorders will limit the intervention's effectiveness. We do train MHWs to assess whether patients fit within the scope of their care, or need to be referred to psychological care.

Since eligibility criteria is based on desire for help, FCR levels in participants may vary from low to high. It may not be cost-effective for those with low FCR to receive this fairly intensive intervention. The authors might consider an additional screen using the FCRI, with only those scoring over a pre-

specified cut-off, perhaps supplemented by an independent assessment by the GP, eligible for inclusion.
We considered using a questionnaire to identify patients with FCR, but the cut-offs that have been established (e.g. for the FCRI) are to identify patients with clinical levels of FCR. This intervention could also be relevant for patients with non-clinical levels of FCR who are still limited by FCR in daily life.
If many patients with low FCR join the study, this could indeed lead to limitations in cost-effectiveness. We will then analyze for what level of FCR this intervention is cost-effective.

It is not clear what the likely uptake of this intervention will be within the GP setting. As noted, many patients prefer to discuss their FCR with oncology specialists.
It is true that the uptake is unknown. The GP is the first contact for care for these patients, since they are no longer under active care by their oncology specialist.

The sample size calculated from a power analysis, taking into account likely clustering within MHWs and drop-out, is n=244 participants. Given that randomization is at the level of GP practice, we need to know how many clusters are required, and minimum recruitment per cluster, for sufficient power in the analysis.
We have clustered at the level of MHW. We have estimated that approximately 15 patients per MHW will participate in the study. Since the clusters may not all have the same size, we applied an inflation factor of 10%. There is no minimum recruitment per cluster.

Presumably if GPs but not MHWs (or vice versa) agree to participate in the study, the practice will not be eligible to join the study.
This is correct. We have clarified this in the article.

The intervention (delivered at the practice level) appears to involve one intake visit with any participating GP from the practice, + five contacts with a mental health worker (MHW) from that practice, and some online modules. The GPs and MHWs from intervention sites will be trained prior to the study. The actual intervention, focusing on normalisation, psychoeducation and self-management, is not well described in the protocol. The reference given for the intervention is a protocol, thus there do not appear to be any data, pilot or otherwise, supporting its efficacy. This is concerning, given the size of the proposed study. The online modules are not described at all, and in fact it is not really clear whether they are included in this intervention.
Additional information about the intervention has been added to the article. The intervention was developed based on evidence and is currently being used in the daily practice of specialized psychologists. In the CAREST trial, it was tested if it could be effective as a self-guided intervention (effect article currently under review), but without any guidance, the uptake of the intervention was low and it was not effective. Patients also expressed a desire for guidance and support with the intervention. Therefore, we are now investigating whether the intervention is effective with support from a MHW.

Participants in control practices will receive an intake visit with the GP where “usual care” will be delivered, whatever that is (although, as acknowledged by the authors, this visit in itself may not be usual care and GPs and patients will be primed to focus on FCR). Control participants may or may not be referred to the MHW, as per usual care; if they are referred they will receive usual care from the MHW. The study plans to document “usual care” as little is currently known about what this comprises, although as noted, this will be “primed usual care”.

The hypotheses for the study refer to “the current intervention” which is confusing terminology.
We have replaced this with 'the FCR intervention' in all hypotheses.

A strength of the study is plans to look at effect modifiers (if efficacy is demonstrated), including 15 patient factors, 3 practice factors and 2 MHW practices. It is not clear that the study is powered, however, to examine all these modifiers.
We agree that it is not clear whether the study will be powered to examine all these modifiers. We aim to explore these effect modifiers, since it is not feasible to power the study for all effect modifiers.

Another strength is a planned cost analysis, and qualitative interviews with both survivors and staff to examine acceptability and value of the intervention.

Reviewer: 3
Reviewer Name: Ben Smith
Institution and Country: Ingham Institute for Applied Medical Research and UNSW, Australia
Please state any competing interests or state 'None declared': None declared

Thanks for the opportunity to review this protocol for an interesting and important trial of delivering FCR care in primary care.
Thank you very much the time taken to accurately review our manuscript and for all your insightful input. This has really helped us to improve our paper.

Abstract
You state that 'Patients who have finished successful curative treatment for cancer between 3 months and 10 years ago and desire support for FCR will be invited to participate in the study' but you won't know if they desire support until they respond to the invitation letter, so I would suggest dropping the 'and desire support for FCR' bit.
We have removed 'and desire support for FCR' as suggested.

A little more info regarding what the focus/components of the intervention are would be useful.
In the abstract, we lack space to go into depth on the intervention, but we have added more information in the article.

Strengths and limitations
Combining quantitative and qualitative data is presented as a strength, but no qualitative methods are mentioned in the abstract
We have added this.

Intro
In paragraph outlining factors associated with FCR, probably worth noting that while relatively consistent associations between FCR and demographic factors such as age and gender have been noted, in general psychological factors (e.g. metacognitive beliefs) have been found to be more closely related to FCR. See below for details:
Thank you for this suggestion. We have added information on the relation between psychological factors and FCR.
Smith, A. B., Sharpe, L., Thewes, B., Turner, J., Gilchrist, J., Fardell, J. E., . . . the ConquerFear Authorship, G. (2018). Medical, demographic and psychological correlates of fear of cancer recurrence (FCR) morbidity in breast, colorectal and melanoma cancer survivors with probable clinically significant FCR seeking psychological treatment through the ConquerFear study. Supportive Care in Cancer, 26(12), 4207-4216. doi:10.1007/s00520-018-4294-y

Clearly I'm biased, having been involved in the trial, but I feel that it's worth mentioning ConquerFear among the efficacious FCR interventions listed, particularly as this demonstrates the efficacy of a treatment approach based more on metacognitive therapy rather than traditional CBT:
Butow, P. N., Turner, J., Gilchrist, J., Sharpe, L., Smith, A. B., Fardell, J. E., . . . Thewes, B. (2017). Randomized Trial of ConquerFear: A Novel, Theoretically Based Psychosocial Intervention for Fear of Cancer Recurrence. Journal of Clinical Oncology, 35(36), 4066-4077. doi:10.1200/JCO.2017.73.1257
Our apologies. ConquerFear was meant to have been included and has now been included.

Line 108: Suggest adding typically after 'Specialised psychological care for cancer is'
Thank you, we have added this.

While proposed characteristics of clinical FCR are mentioned, there is limited discussion of FCR existing on a spectrum from normal to clinical. Perhaps this could be provided in the context of justifying the statement that 'most cancer survivors do not require intensive specialized psychotherapy, but rather accessible psychological care'.
Thank you for this suggestion. We have added this at line 73, where the proposed characteristics are also mentioned.

Line 114: The ‘review on self-guided online interventions specifically for cancer patients’ mentioned is actually a review of self-guided interventions generally and most of the interventions were not delivered online, please correct.
We have removed online. We have rephrased the sentence to clarify that the interventions were tested among cancer patients, rather than designed for cancer patients.

Aims
Given the study is testing a blended care intervention, perhaps more discussion of the SWORD study, which also evaluated a blended care approach to treating FCR would be appropriate.
Thank you for this suggestion. We have added more information about the SWORD study.

133: You state that ‘The target group for this intervention is patients with moderate FCR’ but you don’t give a definition of what you mean by moderate FCR, nor do you say how you plan to identify these patients, as opposed to patients with severe or low FCR. Please clarify.
We have edited the sentence to 'We aim to include patients with moderate FCR, who want FCR support.' Under recruitment we further explain how we plan to identify patients.
We did consider using a questionnaire to identify patients with FCR, but the cut-offs that have been established (e.g. for the FCRI) are to identify patients with clinical levels of FCR. This intervention could also be relevant for patients with non-clinical levels of FCR who are still limited by FCR in daily life.

Eligibility
It is probably self-evident, but it might be worth explicitly stating that only general practices in which the GP and MHW are able to participate will be included in the study, unless I have misunderstood and this is not a requirement?
This is correct. We have clarified this in the article.

Study procedures
Is CAREST a publicly available intervention? Is there any chance that patients from control practices will use the intervention, albeit without therapist support?
The intervention is available as self-help on the website of the Helen Dowling Institute. Patients in the control group could find it there, but we do not expect this to be likely if they are already receiving care from the GP. Should they find and use it, we will consider this part of usual care.
We ask patients what care they have used that is not part of regular healthcare and if anything other than healthcare helped them cope with their FCR (e.g. conversations with friends, books, etc.).

186: I think ‘inclusion speed’ should probably be ‘inclusion rate’
We have changed this.

Intervention
The abstract mentions that the intervention comprises an ‘intake with the GP and five sessions with the MHW’, but in the intervention section it is unclear whether GPs and MHWs will deliver the same intervention, or different components of the intervention (and what those components are).
We have clarified this, stating "The GP's role is to assess the need for care during an intake. The MHW's role is to assign and discuss the modules with the patients during five contact moments."

The CAREST intervention referenced is a self-guided intervention. Please explain how the intervention has been modified for guided delivery.
While the intervention used in the CAREST trial is self-guided, it is provided on a platform designed to provide blended care (e.g. with options for linked therapists to read along and provide feedback) and is already being used for blended care by specialized therapists at the Helen Dowling Institute. Therefore, the online modules of the intervention did not need to be adapted for guided delivery. The MHWs will receive training on cancer and FCR, providing care for FCR and how to use the online modules.

In the limitations you discuss the fact that inviting patients to take part in the trial of a FCR intervention may ‘activate patients’, making them less representative of patients currently seeking care for FCR. Isn't there also a risk that asking GP responses regarding their ‘usual care’ for FCR may be also biased by the fact that GPs who agree to participate in the study are more likely to have an interest in and perhaps provide better care for FCR than usual care more generally?

This is indeed a risk. We therefore ask practitioners what training on FCR or related topics they have received outside of the study. We have clarified this in the discussion.

Primary outcome
Can you please explain the rationale behind the primary outcome being the difference in FCR severity between the two groups at a single time point (i.e. 3 months), rather than the difference in the change in FCR severity from baseline to 3 months between the two groups?
The baseline is expected to be the same for both groups. If this is indeed the case, then the difference between the two groups at T1 and the difference in the change from baseline to T1 will be the same. Should there be differences at baseline, we will correct for baseline differences.

Data Collection
Can you please explicitly state that the three FCRI subscales you are using are the severity, psychological distress and coping strategies subscales?
We have changed this.

238: Expand EHR here instead of a couple of lines later.
We have changed this.

How will GP visits specifically related to FCR be ascertained and differentiated from cancer-related visits? For instance, patients are often told to report to their Dr if they have symptoms that maybe indicative of recurrence. How will you differentiate people who are simply following those instructions, versus being hyper-vigilant due to FCR?
This is indeed a challenge. Since it can be difficult to distinguish, we measure visits that are FCR-related, cancer-related, and neither. FCR-related visits are only those in which FCR is mentioned specifically. If cancer-related visits are due to hyper-vigilance, we expect this number to decrease if the intervention decreases FCR. We have clarified this in the article.

255: I'm confused by the sentence 'Additional information about data collection, data management, monitoring and dissemination of results can be found in the study protocol.' Isn't this the study protocol?
We have clarified this by stating it can be found in the trial master file.

265: close brackets after number of patients per MHW
We have changed this.

Sample size calculation
Can a little more detail be provided regarding a mean difference of 3, with a standard deviation of 7, representing a 'relevant difference', so that readers can understand without having to refer to the FCRI-NL validation paper.
We have adjusted this in the paper, stating "When determining the required group size for finding a relevant difference between the groups, we used a difference in means of 3 and a standard deviation of 7 on the FCRI severity scale. The difference in means was based on expert opinion. The standard deviation was based on the FCRI-NL validation study by van Helmondt et al. (2017), which found an SD of 7 on the severity scale (47)."

Also, what is the rationale for assuming dropout rates of 12%?
We selected 12% based on clinical experience.

Statistical analysis
There are many different comparisons of healthcare utilization and costs mentioned. While I understand that these are secondary outcomes, I think it would strengthen your protocol to state a priori if there are particular comparisons that are of greater interest/importance.
We have changed this in the protocol, stating that T0-T2 is most important, because it combines the costs of the intervention with the costs of healthcare after the intervention, e.g. reduced costs as a result of reduced hyper-vigilance.

299: More detail regarding the approach taken to the qualitative analysis of patient/provider satisfaction with the intervention would be appreciated.

We have added a few details. However, since the focus of this paper is the quantitative aspect, we have kept our discussion of the qualitative research short. We will provide more details in the article about the qualitative study. More details are also available in the trial master file, including interview guides.

303: I assume patient should be patients.
This has been changed.

Discussion
317: It's stated that this is one of few 'implementation studies' on FCR interventions. Could you please offer further explanation of what qualifies this as an implementation study? It may also be worth citing some of the existing studies focused on implementation of FCR interventions:
By implementation study, we meant studies investigating effectiveness in routine clinical practice. We have now changed this to 'pragmatic trials' instead of implementation studies, to better describe this.

Cruickshank, S., Steel, E., Fenlon, D., Armes, J., Banks, E., & Humphris, G. (2019). Specialist breast cancer nurses' views on implementing a fear of cancer recurrence intervention in practice: a mixed methods study. Supportive Care in Cancer. doi:10.1007/s00520-019-04762-9

Butow, P., Williams, D., Thewes, B., Tesson, S., Sharpe, L., Smith, A. B., . . . Beith, J. (2019). A psychological intervention (ConquerFear) for treating fear of cancer recurrence: Views of study therapists regarding sustainability. Psychooncology, 28(3), 533-539. doi:10.1002/pon.4971

339: While participants may not be informed of their group allocation, presumably in some cases usual care will comprise no FCR-specific care, so they may figure it out. Perhaps it is worth asking patients which group they thought they had been allocated to at the end of the intervention period, so that expectancy effects can be controlled for.
To prevent patients from finding out in which group they have been enrolled, patients only know that the study is about support for FCR in primary care. They do not know there is a specific intervention that is being tested or that there is an intervention group and a control group. This makes it unlikely for them to expect they were missing out on an intervention.

VERSION 2 – REVIEW

REVIEWER	Phyllis Butow University of Sydney School of Psychology, CeMPED/ PoCoG
REVIEW RETURNED	16-Sep-2019

GENERAL COMMENTS	The authors have addressed many of the previous reviewer comments, and the protocol is strengthened. However, I still have a few questions. 1) I feel that the authors have not adequately addressed their stated aim to evaluate the utility of this approach for people with moderate FCR, in the absence of screening. They have replied stating that the problem with measuring FCR is that the cut-offs that have been established (e.g. for the FCRI) are to identify patients with clinical levels of FCR, while this intervention could also be relevant for patients with non-clinical levels of FCR who are still limited by FCR in daily life. This does not address whether their intervention is suitable for people with high FCR. Perhaps a largely online approach reinforced by MHW contact is not enough for such patients. Should they be excluded? But in any case, even if the authors feel that it is worthwhile to include people at all levels of FCR (including high or severe FCR) in their intervention, since they are not measuring FCR to enable eligibility screening, I think they should take out the goal of addressing moderate FCR.

	2) I am still unconvinced regarding the evidence-base for their intervention. There do not appear to be any efficacy data to support it, nor is a clear theoretical basis for the intervention provided. The fact that it is in wide clinical use currently is not a sufficient rationale, as many unproven and ineffective therapies are used in routine practice. I think the authors need to more clearly link their intervention to an existing proven intervention (such as Sword), provide a clearer theoretical rationale for it, and/or acknowledge the lack of a supportive evidence base in the Limitations. 3) It is still not clear to me what the MHWs are actually going to do. The authors have said that the previous version of the online intervention was already supported, and MHWs will receive training. However, what will the training be in? How will the MHWs address and discuss each online module? I think there needs to be more clarity about this critical point, since it is at the core of the intervention. Otherwise, the protocol is reading well.

REVIEWER	Ben Smith Ingham Institute for Applied Medical Research and University of New South Wales, Australia
REVIEW RETURNED	23-Sep-2019

GENERAL COMMENTS	I think the authors have done a reasonable job of clarifying issues raised by the reviewers. Additional details have been provided regarding the intervention and methodological decisions are now better justified. While the study is not fully powered to analyse the impact of all the covariates listed on intervention efficacy, I will be interested to see whether factors such as baseline FCR are significant, given the focus of the intervention on those with moderate FCR. I think it would be useful adding a statement as to why patients were not screened for FCR prior to study entry, as was provided in the authors response.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Phyllis Butow
Institution and Country: University of Sydney School of Psychology, CeMPED/ PoCoG, Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below The authors have addressed many of the previous reviewer comments, and the protocol is strengthened. However, I still have a few questions.

1) I feel that the authors have not adequately addressed their stated aim to evaluate the utility of this approach for people with moderate FCR, in the absence of screening.
They have replied stating that the problem with measuring FCR is that the cut-offs that have been established (e.g. for the FCRI) are to identify patients with clinical levels of FCR, while this intervention could also be relevant for patients with non-clinical levels of FCR who are still limited by FCR in daily life. This does not address whether their intervention is suitable for people with high FCR. Perhaps a largely online approach reinforced by MHW contact is not enough for such patients. Should they be excluded? But in any case, even if the authors feel that it is worthwhile to include people at all levels of FCR (including high or severe FCR) in their intervention, since they are not measuring FCR to enable eligibility screening, I think they should take out the goal of addressing moderate FCR.

Thank you again for your helpful feedback. This has helped us to further clarify what we are trying to convey. We did not mean to say that only people with moderate FCR were to be included in our study. We meant to describe the population for whom our intervention is expected to be most suitable (people with moderate FCR). Since this phrase caused confusion, we have taken it out.

Regarding whether patients with high FCR should be excluded, we have chosen not to exclude these patients, because we expect that this intervention will be relevant for most FCR patients who seek care at their GP practice. Yet, there could indeed be patients that need to be referred to more advanced psychological care. Therefore, the health care providers in the study are trained to assess and refer patients to specialized psychological care when needed.

Under eligibility we have now detailed our target group:
"Since this is a pragmatic real world trial, we include all patients who want care for FCR at their GP practice. We chose not to screen for level of FCR as an inclusion criterion, because this would not reflect daily practice. This intervention could also be relevant for patients with non-clinical levels of FCR who are still limited by FCR in daily life. We will train the MHW to refer patients who require specialized psychological care."

2) I am still unconvinced regarding the evidence-base for their intervention. There do not appear to be any efficacy data to support it, nor is a clear theoretical basis for the intervention provided. The fact that it is in wide clinical use currently is not a sufficient rationale, as many unproven and ineffective therapies are used in routine practice. I think the authors need to more clearly link their intervention to an existing proven intervention (such as Sword), provide a clearer theoretical rationale for it, and/or acknowledge the lack of a supportive evidence base in the Limitations.
We understand that the reviewer is still concerned about the evidence-base for our intervention, and thank you for the opportunity to provide more explication about the theoretical basis of our intervention.
Before doing that we'd like to explain that we already gained funding for our proposal, which was thoroughly reviewed by the Dutch Cancer association. They support the proposed intervention and consider the plausibility of its effectiveness acceptable.
From a practical viewpoint, we have already gained ethical approval and have started training the mental health care workers and the recruitment of patients. So even if at this point there would be new evidence for other effective interventions, our intervention cannot easily be changed. Having said that, we do hope to provide you with more confidence about the sound theoretical rationale of our intervention.
Actually our intervention was developed earlier than SWORD was. I was in touch with the researcher of that project (Marieke Gielissen) at that time. They decided to build their own online intervention as it was intended to be a rather intensive blended intervention to be used within the hospital setting, whereas we developed our intervention to be a very accessible self-help intervention, that is also understandable for patients with a low level of education. Both interventions were based on Lee-Jones' theoretical model and both follow the principles of cognitive behavioral therapy.
We did an RCT, to investigate whether our intervention would be effective as self-help, without any guidance. That trial is about to be published, and was already presented at IPOS: there was no difference in slopes compared to Care as usual. We also evaluated the self-help qualitatively, manuscript in preparation, presented at IPOS in Dublin: Patients told us they appreciated the program, but they needed guidance. It was too hard for most of them to log in alone, or they said they needed reminders. The small number of patients who did complete the program, did experience a decrease in FCR.
So the next step following from our previous study was to have easily accessible low cost guidance. Since there is currently a transition for oncological care to move from the hospital setting to primary care, Mental Health Care Workers working in general practices seem the ideal persons to give this guidance.
What might help to know as background information is that the Helen Dowling Institute is a scientific mental health care institute specialized in Psycho-Oncology, very well known to all participating general practitioners and MHWs in our study. They know they can always refer patients if they suspect patients fulfill criteria for a DSM classified disorder. But we also know that FCR ranges on a continuum from normal to pathological anxiety and that we need easily accessible help for patients who suffer from FCR, but not to the extent that it warrants a DSM disorder. Accessible care can also prevent the development of psychiatric disorders. So this is the purpose of the current study.

Below is some additional information about the content of the intervention and the evidence for it. The online tailored self-help training is based on cognitive behavioral therapy. CBT is an evidence based intervention in psycho-oncology and for FCR (1-3).
There are 2 basic modules (psycho-education; basic principles of cognitive behavioral therapy) with exercises about recognizing helpful and unhelpful thoughts. After these basic modules patients can choose from the following five modules what is relevant for their situation: 1) How to stop rumination, evidence-based behavioral techniques to stop ruminating; 2) Avoidance, how to stop avoiding situations; 3) Relax, audio files with relaxation practices; and 4) Reassurance, how and when to seek reassurance; 5) Action, making an action plan about what one can do when fear of recurrence pops up. Each module consists of an informative part (texts, videos, audio files) and a practical part in which participants are motivated to do exercises or assignments in daily life.
The psycho-education explains about physiology of fear. Normalization of FCR helps patients to understand that fear is a normal reaction which can be helpful in some situations. As you know psycho-education is an effective intervention in psycho-oncology (4). Psycho-education is also focused on how many bodily symptoms (such as fatigue, new aches and pains, muscle tension, joint stiffness, feeling of weakness, indigestion, and other physical symptoms) can easily be misinterpreted as symptoms of recurrence (5). Anxiety itself also can cause several bodily symptoms (such as increased heart rate, shortness of breath, chest pressure, sweating, dry mouth, dizziness, feeling of weakness, muscle tension, and indigestion), which may increase other bodily symptoms and therefore reinforce FCR. Misinterpretation of bodily symptoms can lead to negative thinking, which causes somatic amplification. Because of this somatic amplification, patients focus even more on their bodily symptoms, leading to a negative emotional spiral. With psycho-education, patients gain more knowledge about their own bodily mechanisms of fear. This knowledge can help them to break the negative spiral.

3) It is still not clear to me what the MHWs are actually going to do. The authors have said that the previous version of the online intervention was already supported, and MHWs will receive training. However, what will the training be in? How will the MHWs address and discuss each online module? I think there needs to be more clarity about this critical point, since it is at the core of the intervention.
We have added more details about the training and the support by the MHW, to further clarify this. It now states:

> "GPs in the intervention group will receive a 1-hour online training. MHWs in the intervention group will receive two 2-hour training sessions by an experienced clinical psychologist, including role plays with an actor playing a patient. The trainings will be about FCR and how to provide the intervention. In between sessions the MHWs will practice using the online modules, both as a patient and as a practitioner. In providing the intervention, the GP's role is to assess the need for care during an intake and to refer to the MHW. The MHW's role is to assign and discuss the modules with the patients during five contact moments. During these moments, MHWs will openly listen to the patients' experiences, normalize fears, apply CBT and discuss what was gained from the modules. Any related questions and issues that came up will also be discussed."

Otherwise, the protocol is reading well.

1. Tauber NM, O'Toole MS, Dinkel A, Galica J, Humphris G, Lebel S, et al. Effect of Psychological Intervention on Fear of Cancer Recurrence: A Systematic Review and Meta-Analysis. J Clin Oncol [Internet]. 2019;JCO.19.00572. Available from: https://ascopubs.org/doi/10.1200/JCO.19.00572
2. Herschbach P, Book K, Dinkel A, Berg P, Waadt S, Duran G, Engst-Hastreiter U, Henrich G. Evaluation of two group therapies to reduce fear of progression in cancer patients. Support Care Cancer. 2010;18:471–9 PubMed .
3. Schroevers M, van der Lee ML, Pet A. Cognitive behavioural therapy [in Dutch: Cognitieve gedragstherapie]. In: de Haes J, van Weezel L, Sanderman R, editors. Psychological care in oncology [in Dutch: Psychologische patiëntenzorg in de oncologie]. Assen: Van Gorcum; 2009. p. 227–38.
4. Dieng M, Butow PN, Costa DSJ, Morton RL, Menzies SW, Mireskandari S, et al. Psychoeducational Intervention to Reduce Fear of Cancer Recurrence in People at High Risk of Developing Another Primary Melanoma: Results of a Randomized Controlled Trial. J Clin Oncol. 2016;

5. Gil KM, Mishel MH, Belyea M, Germino B, Porter LS, Carlton LaNey I, et al. Triggers of Uncertainty About Recurrence and Long-Term Treatment Side Effects in Older African American and Caucasian Breast Cancer Survivors. Oncol Nurs Forum. 2004;31(3):633 PubMed –9.

Reviewer: 3
Reviewer Name: Ben Smith
Institution and Country: Ingham Institute for Applied Medical Research and University of New South Wales, Australia Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below I think the authors have done a reasonable job of clarifying issues raised by the reviewers. Additional details have been provided regarding the intervention and methodological decisions are now better justified. While the study is not fully powered to analyse the impact of all the covariates listed on intervention efficacy, I will be interested to see whether factors such as baseline FCR are significant, given the focus of the intervention on those with moderate FCR. I think it would be useful adding a statement as to why patients were not screened for FCR prior to study entry, as was provided in the authors response.
Thank you for your feedback, and thank you for this suggestion. We have now added this in the manuscript: "Since this is a pragmatic real world trial, we include all patients who want care for FCR at their GP practice. We chose not to screen for level of FCR as an inclusion criterion, because this would not reflect daily practice. This intervention could also be relevant for patients with non-clinical levels of FCR who are still limited by FCR in daily life. We will train the MHW to refer patients who require specialized psychological care."