BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032616
Article Type:	Protocol
Date Submitted by the Author:	27-Jun-2019
Complete List of Authors:	Luigjes, Yvonne; Helen Dowling Institute, ; Julius Center for Health Sciences and Primary Care, van der Lee, Marije; Helen Dowling Instituut, Scientific Research de Wit, Niek; University Medical Center Utrecht, Julius Center for Primary Care Helsper, Charles; University Medical Centre Utrecht, 1Julius Centre for Health Sciences and Primary Care
Keywords:	fear of cancer recurrence, PRIMARY CARE, psycho-oncology, mental health worker

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

Yvonne L Luigjes-Huizer

Scientific Research Department, Helen Dowling Instituut, Bilthoven, The Netherlands and Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands

y.l.huizer@umcutrecht.nl

Marije L van der Lee

Scientific Research Department, Helen Dowling Instituut, Bilthoven, The Netherlands

mvanderlee@hdi.nl

Niek J de Wit

Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands

n.j.dewit@umcutrecht.nl

Charles W Helsper

Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands

c.w.helsper-2@umcutrecht.nl

Corresponding author: Yvonne Luigjes yluigjes@hdi.nl

Word count: 3746 words

Abstract

Introduction: Many successfully treated cancer patients suffer from fear of cancer recurrence (FCR), affecting their quality of life and their physical, emotional, cognitive and social functioning. Effective psychological interventions for FCR exist, but are not widely available, as they are offered by specialised psycho-oncology professionals and institutes. Concurrently, the role of primary care in cancer and survivorship care is increasing. Therefore, there could be a role for general practitioners (GP) and mental health workers (MHW) working in primary care in supporting patients with FCR. In the current study the effectiveness of a primary care delivered FCR intervention will be evaluated.

Methods and analysis: A two-armed cluster-randomised trial will be conducted. The primary outcome will be FCR severity; secondary outcomes will be FCR-related distress, healthcare uptake and healthcare costs. Primary care practices in the Netherlands will be invited to participate in the study. Participating practices will be stratified by size and socio-economic status and randomly placed in the intervention or the control arm. In the control arm, practices will provide care as usual. In the intervention arm, practices will offer the cognitive behavioural FCR intervention that is being studied, which consists of an intake with the GP and five sessions with the MHW. 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 by invitation letter from their GPs. Participating patients fill out questionnaires at baseline, after three months and after twelve months. Data on healthcare use is collected from their electronic health records (EHR).

Ethics and dissemination: The Medical Research Ethics Committee Utrecht provided approval for the study. Results will be dispersed through peer-reviewed publications and scientific presentations.

Trial registration: NL7573 in the Netherlands Trial Register on 25-02-2019.

Keywords: fear of cancer recurrence, primary care, psycho oncology, mental health worker

Strengths and limitations of this study

- A robust, pragmatic trial design will be implemented in general practices, reflecting daily care.

- Quantitative and qualitative data are combined to provide comprehensive results.
- The intervention and trial were designed in close cooperation with patients and healthcare workers.
- A cluster randomised design, randomising at practice level, was required, since practitioners who have been trained on the intervention are unlikely to be able to provide usual care in the same way as before training.
- Patients are actively invited to participate in the study, making them less representative of the patients who currently seek care for FCR.

Introduction

Advances in the medical field have caused the number of cancer survivors to rise steadily in the past decades (1). With an increasing number of survivors, there is also an increasing need for survivorship care (2). A systematic review showed that fatigue, depression and anxiety are commonly reported in the ten years after primary cancer treatment (3). Fear of cancer recurrence (FCR) is a more prevalent concern than any physical issue (2). In a study about unmet needs after breast cancer, FCR was the most reported need in all age groups (38.2%), despite a relatively good prognosis (4).

FCR has been defined as “fear, worry, or concern relating to the possibility that cancer will come back or progress” (5). A review by Simard (2013) found that an average of 73% of cancer survivors experience FCR, 49% experience a moderate to high level of FCR and 7% experience a high level of FCR (6). FCR is a multidimensional construct, as demonstrated by the subscales of the Fear of Cancer Recurrence Inventory (FCRI): triggers, severity, psychological distress, coping strategies, functioning impairments, insight and reassurance (7). In a 2-day colloquium with a group of experts and patient advocates, five preliminary categories of potential characteristics of clinical FCR were identified using the Delphi method. These are: preoccupation with cancer return or progression, unhelpful coping

strategies, impairments in daily functioning, great level of distress and limited ability to make plans (5).

Many studies have explored factors that correlate with FCR development, with mixed results. The evidence for correlations between FCR and age, gender and physical symptoms is strongest, whereby younger patients, female patients and patients with more symptoms experience more FCR (6). In contrast, social support, optimism, having detailed information and being conscientious correlate with having less FCR (6,9,10). FCR can persist for many years after the end of cancer treatment (6,11). There are also triggers that can temporarily increase FCR. These include: medical appointments, having unexplainable symptoms, hearing about cancer in the media or hearing about the death of a fellow patient (12).

The impact of FCR varies. Having some FCR can be protective, since it may lead to treatment compliance and healthy lifestyle adaptations. However, severe FCR can significantly decrease quality of life (13). Maladaptive coping styles include overuse of primary care for common acute symptoms, but also avoidance of social and healthcare appointments. On average, healthcare uptake is increased for people with high FCR (15). Cancer survivors with high consultation rates due to seeking reassurance can inadvertently augment their fears and cause unnecessary healthcare costs (14). Yet, people who respond to their fear by avoiding healthcare, risk delayed diagnosis of cancer recurrence.

A Danish study found that patients tended to discuss social or psychological aspects of cancer, including fear of relapse, more with family and friends than with their GP, because they did not think it was the GP's mandate to address the concerns (18). In a Dutch study, 75% of patients' physical problems after having received a cancer diagnosis were discussed with GPs, compared to only one third of emotional and social problems (17). When the need for psychosocial care is recognised, this has a positive effect on quality of life, appreciation of care and communication with care providers (19). Therefore, it seems of added value if GPs assess the presence of FCR when patients come in for consultations, and refer to additional care when needed (20).

Treating FCR is different from treating other anxiety disorders, because most treatments for anxiety are based on the presumption that patients incorrectly perceive something as a threat. Yet, in the case of FCR, the fear is not irrational, since the threat is actual and significant (21). Currently, there are different treatment options for FCR, which can be applied in a stepped care approach. The first level involves psycho-education, normalisation and self-management. Next, cognitive behavioural therapy, therapies focusing on acceptance (22) and pharmacological treatment (23) can be applied. In recent years, several trials have shown the effectiveness of new FCR interventions (24,25), including mindfulness programs (26–28), psychoeducation (29), cognitive behavioural therapy interventions (30–32) and a gratitude intervention (33). Specialised psychological care for cancer is provided in hospitals and institutes for psycho-oncology.

Unfortunately, travel distance, limited energy of ex-cancer patients and waiting lists for specialised centres counteract accessibility (34). Also, most cancer survivors do not require intensive specialised psychotherapy, but rather accessible psychological care. Online treatment may be a suitable alternative. In addition to being easily accessible, it also allows patients to obtain care at moments when they feel fit enough and for a duration that they can manage. However, a review on self-guided online interventions specifically for cancer patients with psychological distress concludes that evidence for the effectiveness of completely self-guided interventions is lacking, and that some level of therapist involvement ('blended care') can help encourage engagement and promote adherence (36).

Concurrently, cancer care and survivorship care are increasingly being provided in primary care, because of patient preference, increasing numbers of cancer patients and rising healthcare costs (1). Primary care is comprehensive, longitudinal and integrated, provided by teams of different professionals (1), increasingly including mental health professionals (37). Primary care providers know their patients and their social and medical history and generally have a longstanding relation with the patient (38,39). Patients view primary care staff as trusted professionals (40) and prefer coming to primary care rather than specialised care for anxiety issues, because of both practical reasons and stigma (41). General practitioners want to provide psychosocial support to cancer patients and feel

they are well-positioned (42,43), but they face capacity challenges (44,45) and report a need for training on cancer survivorship (46,47), in particular on treating psychological problems (44). Involving and training auxiliary staff, such as primary care MHWs, in survivorship care, may help to overcome both capacity challenges and the need for improved expertise in primary care (47).

Aim

The BLANKET study was designed to assess the effectiveness of a primary care delivered, blended care intervention for fear of cancer recurrence, in reducing patients' severity of FCR, compared to usual care. The target group for this intervention is patients with moderate FCR, who want FCR support.

We hypothesise that

1. the current FCR intervention will reduce FCR severity,
2. the current FCR intervention will reduce FCR related distress,
3. healthcare consumption of patients who have received the current FCR intervention will be reduced.
4. the primary care FCR intervention will be considered desirable and of added value by patients and practitioners.

The primary outcome is FCR severity. Secondary outcomes are FCR-related distress, FCR-related healthcare use, FCR-related health costs, and satisfaction of patients and practitioners with support provided by trained MHWs and GPs.

Methods

Study design

The BLANKET study is a two-armed cluster randomised clinical trial, in which the general practice is the unit of randomisation.

Study procedure

Participating practices will identify all of their patients who have successfully completed curative cancer treatment between three months and ten years ago, and will send them an invitation letter

by mail. Patients are asked to participate if they desire support for FCR. After providing informed consent, patients are asked to fill out an online baseline questionnaire. Patients also fill out questionnaires after 3 months and after 12 months. At the end of the first questionnaire, they are urged to make an appointment with their GP about support for FCR. During this consultation, the GPs in the intervention group refer the patients to the MHW for the intervention, while GPs in the control group provide usual care.

Eligibility

Clusters of collaborating GPs and MHWs in the Netherlands who are willing to receive training and to implement it will be recruited. In the Dutch setting, almost all general practices employ mental health workers (MHW, in Dutch: POH-GGZ), who support the general practitioner in providing care for patients' psychological, psychosomatic and psychosocial issues (48).

Patients are eligible if they: (1) are registered at a general practice that is participating in the study, (2) are 18 years or older, (3) have finished successful curative cancer treatment between 3 months and 10 years ago, (4) desire support for FCR, and (5) have sufficient Dutch reading and writing skills to receive the intervention and complete the questionnaires. If patients have a cancer recurrence during the study, no more data will be collected.

Recruitment

The aim is to include 244 patients during 1,5 years. Patients are recruited using an invitation letter sent by patients' own GPs. All of the patients of participating practices, who are 18 years or older and have finished curative cancer treatment between 3 months and 10 years ago will receive the letter. To spread the workload for the practitioners, invitation will be done in rounds, starting with patients who most recently finished curative cancer treatment. In the invitation letter, patients who desire support for FCR are asked to participate in the study. Patients who are willing to participate, provide written informed consent to the researcher.

Randomisation

Randomisation is done at practice level. GPs and MHWs will know in which group they have been placed. Patients will not. Clusters are formed, in which all GPs and MHWs working in the same building are grouped together, to decrease the risk of contamination. Minimisation is applied for size of the practice and the socio-economic status (SES) of the neighbourhood they are located in, to ensure balance between study arms (patients and professionals). For practice size, there are three categories: small (1-3 GPs), middle-sized (4-6 GPs) or large (7 GPs or more). For SES, the list of disadvantaged areas by postal code made by the Dutch government for general practices is used. Practices will be assigned to the intervention or the control group, using the number generator at Research Randomizer (randomizer.org). An external data manager will generate the numbers. Practices are randomised in two blocks. The inclusion speed from the first block will help to confirm how many more practices are needed for the second block.

Intervention

GPs and MHWs in the intervention group will provide an intervention specifically designed for FCR, which focuses on normalisation, psychoeducation and self-management (49). This intervention was developed at the Helen Dowling Institute based on cognitive behavioural therapy, clinical experience and input from patients, and is currently being used by specialised psychologists for blended treatment. The intervention is available online, and includes five contact moments with the MHW. GPs and MHWs in the intervention group will receive training on the implementation of the intervention at the beginning of the study. GPs and MHWs in the control group will provide usual care.

Usual care

Patients in the control group receive usual care. In the literature, little is known about the usual care that GPs provide for fear of cancer recurrence. Therefore, usual care will be mapped in this study, in relation to the severity of FCR.

Outcomes

Participants will provide data using online self-report questionnaires hosted by ResearchOnline.com. Participants will receive an invitational e-mail with a link to complete the questionnaires online.

These links will be sent at baseline (T0), after three months, once the intervention in the intervention group is completed (T1), and one year after the baseline (T2). Participants who do not respond receive reminders. If participants prefer to fill out the questionnaires on paper, this will be arranged. If patients do not fill out the questionnaires, they are sent reminders.

Primary outcome

The primary outcome is the severity of fear of cancer recurrence after 3 months, comparing the FCR intervention with usual care. To measure this, the severity scale (SF) of the Dutch version of the Fear of Cancer Recurrence Inventory (FCRI-NL) will be used.

Secondary outcomes

The secondary outcomes are the development from baseline to T1 to T2 of severity of fear of cancer recurrence, FCR-related distress, FCR-related healthcare use and FCR-related health costs; and the desirability and added value of the intervention.

Covariates

If the intervention is found to be effective, relations between the outcomes and the following variables will be explored, to identify groups of patients for whom the intervention might be more or less effective.

At the patient level: age, gender, level of education, coping style, severity of anxiety and depression, somatic complaints, severity of FCR at the start of the study, FCR related distress at the start of the study, psychiatric history, previous health care use, additional care used by patients (e.g. alternative care), time since the cancer diagnosis, time since the end of the curative cancer treatment, cancer type.

At the practice level: general practice size and SES status of practice.

At the MHW level: number of years of work experience and educational background of the MHW.

Data collection

The Dutch version of the fear of cancer recurrence inventory (FCRI-NL) will be used to measure FCR severity, distress and coping. It contains 43 items, measuring seven subscales. The FCRI was

translated into Dutch and validated by van Helmondt, van der Lee & de Vries (50). While for the FCRI, it is recommended to use the total score of all subscales to obtain a score for FCR (7), this multi-dimensional structure was not replicated in the validation of the FCRI-NL. Instead, the individual subscales provide important information and are recommended to be used separately (50).

The 4DKL will be used to provide data on general distress, depression, anxiety and somatic complaints. The 4DKL is a 50-item questionnaire that measures four dimensions: distress, depression, anxiety and somatic complaints. The list is already used in some GP practices and is therefore practically applicable.

Patients will also be surveyed about their educational level, current daily activity (e.g. work), reasons for participating in the study, additional care used that is not in the EHR including alternative care, and other factors that they think might have influenced their FCR.

In order to collect data on patients' cancer type, treatment and healthcare use, data will be obtained from patients' electronic health records (EHR). Data will be collected on number of GP visits related to cancer, FCR and neither, number of sessions with MHW and number of referrals for physical care and for psychological care. At baseline, data on healthcare use per year since the end of curative cancer treatment will also be obtained, to exploratively compare usual care in our control group with usual care in the years prior to the study. FCR-related health costs will be calculated based on the healthcare use.

The desirability and added value of the intervention will be evaluated using custom-made, non-validated questionnaires and semi-structured interviews with a selection of patients and practitioners at T1. The interviews will explore which aspects of the support are effective, unnecessary, practical or pleasant and why. They will also explore whether the GP and MHW are considered to be the right practitioners to provide this type of care and what changes with regard to FCR are most desirable and sought after. Varied groups will be purposively sampled. For patients, in terms of age, time since diagnosis, severity of FCR at T0, and severity of FCR at T1; for practitioners in terms of professional background and years of work experience.

Additional information about data collection, data management, monitoring and dissemination of results can be found in the study protocol.

Sample size calculation

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. These numbers were based on the FCRI-NL validation study by van Helmondt et al. (2017) (50). Using an alpha of 0.05 and beta of 0.8, we calculated a required sample size of 86 participants in both groups for sufficient power. Because multiple patients are treated by the same MHW, there might be a cluster effect. Based on an average of 15 inclusions per MHW and an intraclass correlation coefficient (ICC) of 0.01, an inflation factor of 1.14 has been applied. This leads to a group size of 98 patients per arm. Because the clusters (number of patients per MHW will probably not all have the same size, an inflation factor of 10% is applied, leading to a group size of 108. We also assume a dropout of 12% of patients. That is why we aim to include 122 patients in each group.

Statistical analysis

The primary outcome will be expressed as difference in the mean (with 95% CI and p-value) of the severity scale of the FCRI-NL scale between intervention and control group at T1.

This will be analysed with a linear mixed model. A random intercept will be included to correct for inclusion per MHW. We will include residual covariances in order to correct for repeated measurement in each patient.

The analyses will be conducted in two steps. First, an analysis will be performed with time, treatment and a time by treatment interaction. Second, a correction for baseline measurement of the outcome will be added to the first model.

The validity of the models will be assessed with residual analyses (51).

A similar approach will be used to analyse secondary outcomes and covariates. Where applicable, a generalised linear model will be used to analyse dichotomous and count outcomes (for binomial and Poisson distributions respectively).

Healthcare utilisation is analysed using multilevel analyses. The number of visits to the GP between T1 and T2 is compared between the intervention group and the control group. Shifts in type of visits – physical vs. psychological – will also be explored. The healthcare uptake in the control group between T1 and T2 will also be compared to the period before the baseline measurement to assess whether healthcare uptake has changed since participating in the study.

The costs of healthcare are compared between the control group and the intervention group for the period between T0-T1, T1-T2 and T0-T2. Healthcare costs are calculated based on healthcare utilisation, according to the method of the *Guidelines for carrying out economic evaluations in health care* (52).

For the outcomes for which the intervention is found to be effective, the effect of the covariates on the outcomes will be explored.

First, intention to treat (ITT) analyses will be done. Then, per-protocol analyses will be carried out to estimate the effectiveness of the intervention if executed per protocol. During the analyses, the assessor will be blinded about the groups.

The validity of study results may be challenged by missing values, either at baseline or missing outcomes at follow-up. Multiple imputation will be used to address missing values at baseline for relevant variables. For missing outcomes, correction for relevant prognostic factors will be considered to ensure the validity of the results (53).

Patient and practitioner satisfaction are measured qualitatively. Semi-structured interviews are held. These are transcribed and then coded. Important themes will be identified, using the data as the starting point.

Patient and public involvement

When developing the online intervention, patient provided input on the desired content and the appearance of the online intervention, e.g. their preference for texts to be short. Once the intervention was developed, patients used it and shared their experiences, and the intervention was further adapted based on this, e.g. adding reminder e-mails.

When developing the study, patients provided input on the general idea. They also provided feedback on the recruitment process and in particular on the invitation letter to patients. Based on their input, the study and the letter were adapted.

Discussion

With an increased number of cancer survivors, there is an increased need for survivorship care. Provision of psychological care for FCR in primary care may improve access and reduce the pressure on specialised institutions. In the current study, the effectiveness of a primary care delivered FCR intervention will be compared to usual care. An evaluation of healthcare consumption and costs is included in the study to assess whether this can also decrease healthcare uptake and costs of healthcare. To our knowledge, this is the first trial assessing the effectiveness of an FCR intervention implemented in primary care. In addition, it is one of few implementation studies on FCR interventions.

Heterogeneity of usual care

Furthermore, we have chosen to compare this intervention with usual care. Since no clear guidelines are available for general practices for FCR, usual care may be quite diverse. Yet, since we want to know whether this intervention is more effective than what is currently being offered, we chose to compare with usual care, despite its heterogeneity, and to register usual care during the study.

Recruitment

Because prior research shows that patients often do not mention FCR to their GP, we chose to actively invite patients who desire support for FCR to participate in the study. The disadvantage of this choice is that we are activating our participants, making them less representative of the patients who currently seek care for FCR. We made this choice, because we want to know whether this intervention can help patients with FCR if they choose to seek care.

Usual care

We recognise that the usual care measured in this study might not fully reflect actual usual care, since we have activated the patient population and made the general practices more aware of this

issue. To assess the effect of this activation, we compare the healthcare use in the control group with retrospective healthcare use.

Randomisation level

We chose to randomise practices and not patients to prevent contamination. Practitioners who have been trained will have increased knowledge and awareness, and will no longer be able to provide usual care the way they did before training. Also, patients at the same practice might discuss the intervention they receive with one another and notice the differences. Patients are unaware of the randomisation, to prevent patients in the control group from being disappointed and less motivated if they know that they are not receiving the intervention that is being studied.

Trial status

Invitation of primary care practices has started in October 2018. The first patient was included on April 15, 2019. Final results are expected in 2020.

Declarations

1. Ethics approval and consent to participate: The Medical Research Ethics Committee Utrecht (METC Utrecht) has reviewed the study in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and other applicable Dutch and European regulations. Based on the requirements of the WMO, the METC Utrecht has issued an approval of the above-mentioned study. Any protocol amendments will be communicated to all relevant parties. Written consent is obtained from study participants.
2. Author contributions: All authors participated in the design of the study. YL wrote the draft manuscript. ML, CH and NW improved the manuscript. All authors read and approved the final manuscript.
3. Funding: This work was supported by the Dutch Cancer Society (KWF) grant number 10936. KWF is not involved in study design, collection, management, analysis, and interpretation of data, writing of the report, the decision to submit the report for publication, nor does it have authority over the publications.
4. Competing interests: The authors declare that they have no competing interests.
5. Sponsor: Helen Dowling Institute, Professor Bronkhorstlaan 20, 3723 MB Bilthoven
6. Acknowledgements: Not applicable.

References

1. Rubin G, Berendsen A, Crawford SM, Dommett R, Earle C, Emery J, et al. The expanding role of primary care in cancer control. Lancet Oncol. 2015;16(12):1231–72.
2. Ness S, Kokal J, Fee-Schroeder K, Novotny P, Satele D, Barton D. Concerns Across the Survivorship Trajectory: Results From a Survey of Cancer Survivors. Oncol Nurs Forum. 2013;40(1):35–42.
3. Harrington CB, Hansen JA, Moskowitz M, Todd BL, Feuerstein M. It's Not over When it's Over: Long-Term Symptoms in Cancer Survivors—A Systematic Review. Int J Psychiatry Med [Internet]. 2010;40(2):163–81. Available from: http://journals.sagepub.com/doi/10.2190/PM.40.2.c
4. Brennan ME, Butow P, Spillane AJ, Boyle F. Patient-reported quality of life, unmet needs and care coordination outcomes: Moving toward targeted breast cancer survivorship care planning. Asia Pac J Clin Oncol. 2016;12(2):e323–31.
5. Lebel S, Ozakinci G, Humphris G, Mutsaers B, Thewes B, Prins J, et al. From normal response to clinical problem: definition and clinical features of fear of cancer recurrence. Support Care Cancer [Internet]. 2016;24(8):3265–8. Available from: http://dx.doi.org/10.1007/s00520-016-3272-5
6. Simard S, Thewes B, Humphris G, Dixon M, Hayden C, Mireskandari S, et al. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. J Cancer Surviv. 2013;7:300–22.
7. Simard S, Savard J. Fear of Cancer Recurrence Inventory: Development and initial validation of a multidimensional measure of fear of cancer recurrence. Support Care Cancer. 2009;17(3):241–51.
8. Mutsaers B, Jones G, Rutkowski N, Tomei C, Séguin Leclair C, Petricone-Westwood D, et al. When fear of cancer recurrence becomes a clinical issue: a qualitative analysis of features associated with clinical fear of cancer recurrence. Support Care Cancer [Internet]. 2016;24(10):4207–18. Available from: http://dx.doi.org/10.1007/s00520-016-3248-5
9. Hedman C, Strang P, Djärv T, Widberg I, Lundgren CI. Anxiety and Fear of Recurrence Despite a Good Prognosis: An Interview Study with Differentiated Thyroid Cancer Patients. Thyroid [Internet]. 2017;27(11):1417–23. Available from: http://online.liebertpub.com/doi/10.1089/thy.2017.0346
10. Liao KYH, Yeung NCY, Wong CCY, Warmoth K, Lu Q. Fear of cancer recurrence and physical well-being among Chinese cancer survivors: the role of conscientiousness, positive reappraisal and hopelessness. Support Care Cancer. 2017;25(4):1141–9.
11. Simard S, Savard J, Ivers H. Fear of cancer recurrence: Specific profiles and nature of intrusive thoughts.

J Cancer Surviv. 2010;

12. 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):633–9.

13. Simonelli LE, Siegel SD, Duffy NM. Fear of cancer recurrence: a theoretical review and its relevance for clinical presentation and management. Psychooncology. 2017;26(10):1444–54.

14. Butow P, Sharpe L, Thewes B, Turner J, Gilchrist J, Beith J. Fear of Cancer Recurrence: A Practical Guide for Clinicians. Oncol J. 2018;32(1):32–8.

15. Champagne A, Ivers H, Savard J. Utilization of Health Care Services in Cancer Patients with Elevated Fear of Cancer Recurrence. Psychooncology [Internet]. 2018;(March):1–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29719072%0Ahttp://doi.wiley.com/10.1002/pon.4748

16. Heins MJ, Korevaar JC, Rijken PM, Schellevis FG. For which health problems do cancer survivors visit their General Practitioner? Eur J Cancer [Internet]. 2013;49(1):211–8. Available from: http://dx.doi.org/10.1016/j.ejca.2012.07.011

17. NIVEL. Afstemming van zorg tussen huisarts en specialist bij kanker kan beter [Internet]. 2013 [cited 2018 May 22]. Available from: https://www.nivel.nl/nl/nieuws/afstemming-van-zorg-tussen-huisarts-en-specialist-bij-kanker-kan-beter

18. Mikkelsen T, Sondergaard J, Sokolowski I, Jensen A, Olesen F. Cancer survivors' rehabilitation needs in a primary health care context. Fam Pract. 2009;26(3):221–30.

19. NHG. NHG-standpunt Oncologische zorg in de huisartsenpraktijk. 2014.

20. Fann JR, Ell K, Sharpe M. Integrating psychosocial care into cancer services. J Clin Oncol. 2012;30(11):1178–86.

21. Curran L, Sharpe L, Butow P. Anxiety in the context of cancer: A systematic review and development of an integrated model. Clin Psychol Rev [Internet]. 2017;56(June):40–54. Available from: http://dx.doi.org/10.1016/j.cpr.2017.06.003

22. Volker C, van der Lee M, Pet A. Angst voor terugkeer van kanker. GZ-Psychologie. 2011;3:30–8.

23. Cupit-Link M, Syrjala KL, Hashmi SK. Damocles' syndrome revisited: Update on the fear of cancer recurrence in the complex world of today's treatments and survivorship. Hematol Oncol Stem Cell Ther [Internet]. 2018; Available from: https://doi.org/10.1016/j.hemonc.2018.01.005

24. Chen D, Sun W, Liu N, Wang J, Zhao J, Zhang Y, et al. Fear of cancer recurrence: A systematic review of randomized, controlled trials. Oncol Nurs Forum. 2018;45(6):703–12.

25. Sharpe L, Thewes B, Butow P. Current directions in research and treatment of fear of cancer recurrence. Curr Opin Support Palliat Care. 2017;11(3):191–6.

26. Crane-Okada R, Kiger H, Sugerman F, Uman GC, Shapiro SL, Wyman-McGinty W, et al. Mindful movement program for older breast cancer survivors: A pilot study. Cancer Nurs. 2012;35(4):1–13.

27. Lengacher CA, Shelton MM, Reich RR, Barta MK, Johnson-Mallard V, Moscoso MS, et al. Mindfulness based stress reduction (MBSR(BC)) in breast cancer: Evaluating fear of recurrence (FOR) as a mediator of psychological and physical symptoms in a randomized control trial (RCT). J Behav Med. 2014;37(2):185–95.

28. Lengacher CA, Reich RR, Paterson CL, Ramesar S, Park JY, Alinat C, et al. Examination of broad symptom improvement resulting from mindfulness-based stress reduction in breast cancer survivors: A randomized controlled trial. J Clin Oncol. 2016;34(24):2827–34.

29. 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;

30. Dodds SE, Pace TWW, Bell ML, Fiero M, Negi LT, Raison CL, et al. Feasibility of Cognitively-Based Compassion Training (CBCT) for breast cancer survivors: a randomized, wait list controlled pilot study. Support Care Cancer. 2015;23(12):3599–608.

31. Lichtenthal WG, Corner GW, Slivjak ET, Roberts KE, Li Y, Breitbart W, et al. A pilot randomized controlled trial of cognitive bias modification to reduce fear of breast cancer recurrence. Cancer. 2017;123(8):1424–33.

32. Wal M, Thewes B, Gielissen M, Speckens A, Prins J, Van De Wal M, et al. Efficacy of blended cognitive behavior therapy for high fear of recurrence in breast, prostate, and colorectal cancer survivors: The SWORD study, a randomized controlled trial. J Clin Oncol [Internet]. 2017;35(19):2173–83. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85021649029&doi=10.1200%2FJCO.2016.70.5301&partnerID=40&md5=f159be668de252f5b14f60fe08799680%0Ahttp://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/658/CN-01395658/frame.html

33. Otto AK, Szczesny EC, Soriano EC, Laurenceau J, Siegel SD. Supplemental Material for Effects of a Randomized Gratitude Intervention on Death-Related Fear of Recurrence in Breast Cancer Survivors. Heal Psychol [Internet]. 2016;35(12):1320–8. Available from: http://supp.apa.org/psycarticles/supplemental/hea0000400/hea0000400_supp.html

34. Zernicke KA, Campbell TS, Speca M, Mccabe-Ruff K, Flowers S, Carlson LE. A randomized wait-list controlled trial of feasibility and efficacy of an online mindfulness-based cancer recovery program: The eTherapy for cancer applying mindfulness trial. Psychosom Med. 2014;76(4):257–67.

35. Carlbring P, Andersson G, Cuijpers P, Riper H, Hedman-Lagerlöf E. Internet-based vs. face-to-face cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and meta-analysis. Cogn Behav Ther [Internet]. 2018;47(1):1–18. Available from: http://doi.org/10.1080/16506073.2017.1401115

36. Ugalde A, Haynes K, Boltong A, White V, Krishnasamy M, Schofield P, et al. Self-guided interventions for managing psychological distress in people with cancer – A systematic review. Patient Educ Couns. 2017;100(5):846–57.

37. Elaine FH, Peter JB. On-site mental health workers delivering psychological therapy and psychosocial interventions to patients in primary care: effects on the professional practice of primary care providers. Cochrane Database Syst Rev. 2009;(1).

38. Del Giudice ME, Grunfeld E, Harvey BJ, Piliotis E, Verma S. Primary care physicians' views of routine follow-up care of cancer survivors. J Clin Oncol. 2009;27(20):3338–45.

39. Johansen ML, Holtedahl KA, Rudebeck CE. How does the thought of cancer arise in a general practice consultation? Interviews with GPs. Scand J Prim Health Care. 2012;30(3):135–40.

40. Mitchell AJ, Vahabzadeh A, Magruder K. Screening for distress and depression in cancer settings: 10 lessons from 40 years of primary-care research. Psychooncology. 2011;20(6):572–84.

41. Curran GM, Sullivan G, Mendel P, Craske MG, Sherbourne CD, Stein MB, et al. Implementation of the CALM intervention for anxiety disorders: A qualitative study. Implement Sci. 2012;7(1):1–11.

42. Lawrence RA, McLoone JK, Wakefield CE, Cohn RJ. Primary Care Physicians' Perspectives of Their Role in Cancer Care: A Systematic Review. J Gen Intern Med [Internet]. 2016;31(10):1222–36. Available from: http://dx.doi.org/10.1007/s11606-016-3746-7

43. Berrett-Abebe J, Cadet T, Vitello J, Maramaldi P. Developing content for an interprofessional training on

fear of cancer recurrence (FCR): Key informant interviews of healthcare professionals, researchers and cancer survivors. J Psychosoc Oncol [Internet]. 2018;0(0):1–15. Available from: https://doi.org/10.1080/07347332.2018.1443987

44. Berrett-Abebe J, Cadet T, Nekhlyudov L, Vitello J, Maramaldi P. Impact of an Interprofessional Primary Care Training on Fear of Cancer Recurrence on Clinicians' Knowledge, Self-Efficacy, Anticipated Practice Behaviors, and Attitudes Toward Survivorship Care. J Cancer Educ. 2018;1–7.

45. Fidjeland HL, Brekke M, Vistad I. Scandinavian Journal of Primary Health Care General practitioners' attitudes toward follow-up after cancer treatment: A cross-sectional questionnaire study. Scand J Prim Health Care [Internet]. 2015;334(4):223–32. Available from: http://www.tandfonline.com/action/journalInformation?journalCode=ipri20%0Ahttp://dx.doi.org/10.3109/02813432.2015.1118836

46. Nekhlyudov L, O'malley DM, Hudson S V. Integrating primary care providers in the care of cancer survivors: gaps in evidence and future opportunities. Lancet Oncol [Internet]. 2017;18(1):e30–8. Available from: http://dx.doi.org/10.1016/S1470-2045(16)30570-8

47. Adam R, Watson E. The role of primary care in supporting patients living with and beyond cancer. 2018;261–7. Available from: www.supportiveandpalliativecare.com

48. Landelijke verening POH-GGZ. Functie-en competentieprofiel POH-GGZ. 2014;17.

49. Helmondt SJ Van, Lee ML Van Der, Vries J De. Study protocol of the CAREST-trial : a randomised controlled trial on the (cost-) effectiveness of a CBT-based online self- help training for fear of cancer recurrence in women with curatively treated breast cancer. BMC Cancer [Internet]. 2016;1–11. Available from: http://dx.doi.org/10.1186/s12885-016-2562-0

50. van Helmondt SJ, van der Lee ML, de Vries J. Translation and validation of the Dutch version of the Fear of Cancer Recurrence Inventory (FCRI-NL). J Psychosom Res [Internet]. 2017;102(August):21–8. Available from: http://dx.doi.org/10.1016/j.jpsychores.2017.09.001

51. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. 2nd ed. Hoboken: John Wiley & sons; 2004.

52. Assessment MT. Verdiepingsmodule Kostenevaluatie. Available from: https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg

53. Groenwold RHH, Moons KGM, Vandenbroucke JP. Randomized trials with missing outcome data: How to analyze and what to report. Cmaj. 2014;186(15):1153–7.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed in protocol
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page, line 2-4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract, line 45

	2b	All items from the World Health Organization Trial Registration Data Set	Title page, line 2-4, 22 Abstract, line 32, 45, Introduction, line 130-143 Methods, line 158-167, 168-175, 176-187, 188-199, 207-214 Trial status, 342-344 Declarations, line 355
Protocol version	3	Date and version identifier	Footer
Funding	4	Sources and types of financial, material, and other support	Declarations, 355-358
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page, line 6-21
	5b	Name and contact information for the trial sponsor	Declarations, 360
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Declarations, 355-358

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Methods, 255-256
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction, 100-117, 130-143
	6b	Explanation for choice of comparators	Methods, 196-199 Discussion, 330-334
Objectives	7	Specific objectives or hypotheses	Introduction, 130-143
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Methods, 147-148
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Methods, 159-160
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Methods, 158-167

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Methods, 188-195
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n.a.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Methods, 193-195
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n.a.
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Methods, 207-256
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Methods, 149-157
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Methods, 257-267
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Methods, 169-171
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Methods, 176-187
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Methods, 176-187
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Methods, 177-178, 185
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Methods, 177-178, 255-256, 331-333
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n.a.
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Methods, 226-256
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Methods, 166-167, 206, 255-256

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Methods, 255-256
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Methods, 268-301
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Methods, 268-301
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Methods, 292-293, 296-297
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Methods, 255-256
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n.a.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Methods, 255-256
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Methods, 255-256
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Declarations 345-351

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Declarations, 350
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Methods, 174-175
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Methods, 255-256
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Declarations, 359
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Methods, 255-256
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Methods, 256-256
	31b	Authorship eligibility guidelines and any intended use of professional writers	Declarations, 352-354
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable

Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See attachment
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032616.R1
Article Type:	Protocol
Date Submitted by the Author:	06-Sep-2019
Complete List of Authors:	Luigjes, Yvonne; Helen Dowling Institute, ; Julius Center for Health Sciences and Primary Care, van der Lee, Marije; Helen Dowling Institute, Scientific Research de Wit, Niek; University Medical Center Utrecht, Julius Center for Primary Care Helsper, Charles; University Medical Centre Utrecht, 1Julius Centre for Health Sciences and Primary Care
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Mental health, Oncology
Keywords:	fear of cancer recurrence, PRIMARY CARE, psycho-oncology, mental health worker

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

Yvonne L Luigjes-Huizer

Scientific Research Department, Helen Dowling Instituut, Bilthoven, The Netherlands and Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands

y.l.huizer@umcutrecht.nl

Marije L van der Lee

Scientific Research Department, Helen Dowling Instituut, Bilthoven, The Netherlands

mvanderlee@hdi.nl

Niek J de Wit

Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands

n.j.dewit@umcutrecht.nl

Charles W Helsper

Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands

c.w.helsper-2@umcutrecht.nl

Corresponding author: Yvonne Luigjes yluigjes@hdi.nl

Word count: 3746 words

Abstract

Introduction: Many successfully treated cancer patients suffer from fear of cancer recurrence (FCR), affecting their quality of life and their physical, emotional, cognitive and social functioning. Effective psychological interventions for FCR exist, but are not widely available, as they are offered by specialised psycho-oncology professionals and institutes. Concurrently, the role of primary care in cancer and survivorship care is increasing. Therefore, there could be a role for general practitioners (GP) and mental health workers (MHW) working in primary care in supporting patients with FCR. In the current study the effectiveness of a primary care delivered FCR intervention will be evaluated.

Methods and analysis: A two-armed cluster-randomised trial will be conducted. The primary outcome will be FCR severity; secondary outcomes will be FCR-related distress, healthcare uptake and healthcare costs. Primary care practices in the Netherlands will be invited to participate in the study. Participating practices will be stratified by size and socio-economic status and randomly placed in the intervention or the control arm. In the control arm, practices will provide care as usual. In the intervention arm, practices will offer the cognitive behavioural FCR intervention that is being studied, which consists of an intake with the GP and five sessions with the MHW. Patients who have finished successful curative treatment for cancer between 3 months and 10 years ago will be invited to participate in the study by invitation letter from their GPs. Participating patients fill out questionnaires at baseline, after three months and after twelve months. Data on healthcare use is collected from their electronic health records (EHR). Qualitative interviews are held at T1 with patients and practitioners in the intervention group.

Ethics and dissemination: The Medical Research Ethics Committee Utrecht provided approval for the study. Results will be dispersed through peer-reviewed publications and scientific presentations.

Trial registration: NL7573 in the Netherlands Trial Register on 25-02-2019.

Keywords: fear of cancer recurrence, primary care, psycho oncology, mental health worker

Strengths and limitations of this study

- A robust, pragmatic trial design will be implemented in general practices, reflecting daily care.
- Quantitative and qualitative data are combined to provide comprehensive results.
- The intervention and trial were designed in close cooperation with patients and healthcare workers.
- A cluster randomised design, randomising at practice level, was required, since practitioners who have been trained on the intervention are unlikely to be able to provide usual care in the same way as before training.
- Patients are actively invited to participate in the study, making them less representative of the patients who currently seek care for FCR.

Introduction

Advances in the medical field have caused the number of cancer survivors to rise steadily in the past decades (1). With an increasing number of survivors, there is also an increasing need for survivorship care (2). A systematic review showed that fatigue, depression and anxiety are commonly reported in the ten years after primary cancer treatment (3). Fear of cancer recurrence (FCR) is a more prevalent concern than any physical issue (2). In a study about unmet needs after breast cancer, FCR was the most reported need in all age groups (38.2%), despite a relatively good prognosis (4).

FCR has been defined as “fear, worry, or concern relating to the possibility that cancer will come back or progress” (5). A review by Simard (2013) found that an average of 73% of cancer survivors experience FCR, 49% experience a moderate to high level of FCR and 7% experience a high level of FCR (6). FCR is a multidimensional construct, as demonstrated by the subscales of the Fear of Cancer Recurrence Inventory (FCRI): triggers, severity, psychological distress, coping strategies, functioning impairments, insight and reassurance (7). FCR exists on a scale from normal to clinical (8). In a 2-day colloquium with a group of experts and patient advocates, five preliminary categories of potential characteristics of clinical FCR were identified using the Delphi method. These are: preoccupation with

cancer return or progression, unhelpful coping strategies, impairments in daily functioning, great level of distress and limited ability to make plans (5).

Many studies have explored factors that correlate with FCR development, with mixed results. The evidence for correlations between FCR and age, gender and physical symptoms is strongest, whereby younger patients, female patients and patients with more symptoms experience more FCR (6). In contrast, social support, optimism, having detailed information and being conscientious correlate with having less FCR (6,9,10). Notably, associations between FCR and psychological factors (e.g. metacognitions) are generally stronger than associations between FCR and demographic factors (11). FCR can persist for many years after the end of cancer treatment (6,12). There are also triggers that can temporarily increase FCR. These include: medical appointments, having unexplainable symptoms, hearing about cancer in the media or hearing about the death of a fellow patient (13).

The impact of FCR varies. Having some FCR can be protective, since it may lead to treatment compliance and healthy lifestyle adaptations. However, severe FCR can significantly decrease quality of life (14). Maladaptive coping styles include overuse of primary care for common acute symptoms, but also avoidance of social and healthcare appointments. On average, healthcare uptake is increased for people with high FCR (15). Cancer survivors with high consultation rates due to seeking reassurance can inadvertently augment their fears and cause unnecessary healthcare costs (16). Yet, people who respond to their fear by avoiding healthcare, risk delayed diagnosis of cancer recurrence.

A Danish study found that patients tended to discuss social or psychological aspects of cancer, including fear of relapse, more with family and friends than with their GP, because they did not think it was the GP's mandate to address the concerns (17). In a Dutch study, 75% of patients' physical problems after having received a cancer diagnosis were discussed with GPs, compared to only one third of emotional and social problems (18). When the need for psychosocial care is recognised, this has a positive effect on quality of life, appreciation of care and communication with care providers (19). Therefore, it seems of added value if GPs assess the presence of FCR when patients come in for consultations, and refer to additional care when needed (20).

Treating FCR is different from treating other anxiety disorders, because most treatments for anxiety are based on the presumption that patients incorrectly perceive something as a threat. Yet, in the case of FCR, the fear is not irrational, since the threat is actual and significant (21). Currently, there are different treatment options for FCR, which can be applied in a stepped care approach. The first level involves psycho-education, normalisation and self-management. Next, cognitive behavioural therapy, therapies focusing on acceptance (22) and pharmacological treatment (23) can be applied. In recent years, several trials have shown the effectiveness of new FCR interventions (24,25), including mindfulness programs (26–28), psychoeducation (29), cognitive behavioural therapy interventions (30–32), an intervention based on metacognitive therapy (33) and a gratitude intervention (34). The SWORD study found that blended treatment using an online FCR program with five face-to-face and three online sessions with a specialized psychologist reduced FCR significantly more than usual care (32). Specialised psychological care for cancer is typically provided in hospitals and institutes for psycho-oncology.

Unfortunately, travel distance, limited energy of ex-cancer patients and waiting lists for specialised centres counteract accessibility (35). Also, most cancer survivors do not require intensive specialised psychotherapy, but rather accessible psychological care. Online treatment may be a suitable alternative. In addition to being easily accessible, it also allows patients to obtain care at moments when they feel fit enough and for a duration that they can manage. However, a review on the effectiveness of self-guided interventions among cancer patients with psychological distress concludes that evidence for the effectiveness of completely self-guided interventions is lacking, and that some level of therapist involvement ('blended care') can help encourage engagement and promote adherence (36).

Concurrently, cancer care and survivorship care are increasingly being provided in primary care, because of patient preference, increasing numbers of cancer patients and rising healthcare costs (1). Primary care is comprehensive, longitudinal and integrated, provided by teams of different professionals (1), increasingly including mental health professionals (37). Primary care providers know

their patients and their social and medical history and generally have a longstanding relation with the patient (38,39). Patients view primary care staff as trusted professionals (40) and prefer coming to primary care rather than specialised care for anxiety issues, because of both practical reasons and stigma (41). General practitioners want to provide psychosocial support to cancer patients and feel they are well-positioned (42,43), but they face capacity challenges (44,45) and report a need for training on cancer survivorship (46,47), in particular on treating psychological problems (44). Involving and training auxiliary staff, such as primary care MHWs, in survivorship care, may help to overcome both capacity challenges and the need for improved expertise in primary care (47).

Aim

The BLANKET study was designed to assess the effectiveness of a primary care delivered, blended care intervention for fear of cancer recurrence, in reducing patients' severity of FCR, compared to usual care. We aim to include patients with moderate FCR, who want FCR support.

We hypothesise that

1. the FCR intervention will reduce FCR severity,
2. the FCR intervention will reduce FCR related distress,
3. healthcare consumption of patients who have received the FCR intervention will be reduced.
4. the FCR intervention will be considered desirable and of added value by patients and practitioners.

The primary outcome is FCR severity. Secondary outcomes are FCR-related distress, FCR-related healthcare use, FCR-related health costs, and satisfaction of patients and practitioners with support provided by trained MHWs and GPs.

Methods

Study design

The BLANKET study is a two-armed cluster randomised clinical trial, in which the general practice is the unit of randomisation.

Study procedure

Participating practices will identify all of their patients who have successfully completed curative cancer treatment between three months and ten years ago, and will send them an invitation letter by mail. Patients are asked to participate if they desire support for FCR. After providing informed consent, patients are asked to fill out an online baseline questionnaire. Patients also fill out questionnaires after 3 months and after 12 months. At the end of the first questionnaire, they are urged to make an appointment with their GP about support for FCR. During this consultation, the GPs in the intervention group refer the patients to the MHW for the intervention, while GPs in the control group provide usual care.

Eligibility

Clusters of collaborating GPs and MHWs in the Netherlands who are willing to receive training and to implement it will be recruited. In the Dutch setting, almost all general practices employ mental health workers (MHW, in Dutch: POH-GGZ), who support the general practitioner in providing care for patients' psychological, psychosomatic and psychosocial issues (48). Both a GP and an MHW need to agree to participate for the practice to be eligible to join the study.

Patients are eligible if they: (1) are registered at a general practice that is participating in the study, (2) are 18 years or older, (3) have finished successful curative cancer treatment between 3 months and 10 years ago, (4) desire support for FCR, and (5) have sufficient Dutch reading and writing skills to receive the intervention and complete the questionnaires. If patients have a cancer recurrence during the study, no more data will be collected. GPs select patients who can be sent the invitation letter for the study. GPs are asked not to invite vulnerable patients (e.g. severe psychiatric morbidity), who would be confused by the letter or unable to participate in the study.

Recruitment

The aim is to include 244 patients during 1,5 years. Patients are recruited using an invitation letter sent by patients' own GPs. All of the patients of participating practices, who are 18 years or older and have finished curative cancer treatment between 3 months and 10 years ago will receive the letter.

To spread the workload for the practitioners, invitation will be done in rounds, starting with patients who most recently finished curative cancer treatment. In the invitation letter, patients who desire support for FCR are asked to participate in the study. Patients who are willing to participate, provide written informed consent to the researcher.

Randomisation

Randomisation is done at practice level. GPs and MHWs will know in which group they have been placed. Patients will not. Clusters are formed, in which all GPs and MHWs working in the same building are grouped together, to decrease the risk of contamination. Minimisation is applied for size of the practice and the socio-economic status (SES) of the neighbourhood they are located in, to ensure balance between study arms (patients and professionals). For practice size, there are three categories: small (1-3 GPs), middle-sized (4-6 GPs) or large (7 GPs or more). For SES, the list of disadvantaged areas by postal code made by the Dutch government for general practices is used. Practices will be assigned to the intervention or the control group, using the number generator at Research Randomizer (randomizer.org). An external data manager will generate the numbers. Practices are randomised in two blocks. The inclusion rate from the first block will help to confirm how many more practices are needed for the second block.

Intervention

GPs and MHWs in the intervention group will provide an intervention specifically designed for FCR, with online modules, which focus on normalisation, psychoeducation and self-management (49). The modules were developed at the Helen Dowling Institute based on cognitive behavioural therapy, clinical experience and input from patients, and are currently being used by specialised psychologists for blended treatment. The intervention consists of two CBT modules, which include psycho-education on FCR, and five optional modules on rumination, avoidance, relaxing, reassuring and undertaking activities. Optional modules can be used depending on the specific needs of the patients. 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. GPs and MHWs in the intervention group will receive

training on FCR and the implementation of the intervention, including roleplays with an actor. GPs and MHWs in the control group will provide usual care.

Usual care

Patients in the control group receive usual care. In the literature, little is known about the usual care that GPs provide for fear of cancer recurrence. Therefore, usual care will be mapped in this study, in relation to the severity of FCR.

Outcomes

Participants will provide data using online self-report questionnaires hosted by ResearchOnline.com. Participants will receive an invitational e-mail with a link to complete the questionnaires online. These links will be sent at baseline (T0), after three months, once the intervention in the intervention group is completed (T1), and one year after the baseline (T2). Participants who do not respond receive reminders. If participants prefer to fill out the questionnaires on paper, this will be arranged. If patients do not fill out the questionnaires, they are sent reminders.

Primary outcome

The primary outcome is the severity of fear of cancer recurrence after 3 months, comparing the FCR intervention with usual care. To measure this, the severity scale (SF) of the Dutch version of the Fear of Cancer Recurrence Inventory (FCRI-NL) will be used.

Secondary outcomes

The secondary outcomes are the development from baseline to T1 to T2 of severity of fear of cancer recurrence, FCR-related distress, FCR-related healthcare use and FCR-related health costs; and the desirability and added value of the intervention.

Covariates

If the intervention is found to be effective, relations between the outcomes and the following variables will be explored, to identify groups of patients for whom the intervention might be more or less effective.

At the patient level: age, gender, level of education, coping style, severity of anxiety and depression, somatic complaints, severity of FCR at the start of the study, FCR related distress at the start of the study, psychiatric history, previous health care use, additional care used by patients (e.g. alternative care), time since the cancer diagnosis, time since the end of the curative cancer treatment, cancer type.

At the practice level: general practice size and SES status of practice.

At the MHW level: number of years of work experience and educational background of the MHW.

Data collection

Patients will fill out the Dutch version of the fear of cancer recurrence inventory (FCRI-NL). It contains 43 items, measuring seven subscales. The severity, distress and coping subscales will be used to measure FCR severity, distress and coping. The FCRI was translated into Dutch and validated by van Helmondt, van der Lee & de Vries (50). While for the FCRI, it is recommended to use the total score of all subscales to obtain a score for FCR (7), this multi-dimensional structure was not replicated in the validation of the FCRI-NL. Instead, the individual subscales provide important information and are recommended to be used separately (50).

The 4DKL will be used to provide data on general distress, depression, anxiety and somatic complaints. The 4DKL is a 50-item questionnaire that measures four dimensions: distress, depression, anxiety and somatic complaints. The list is already used in some GP practices and is therefore practically applicable.

Patients will also be surveyed about their educational level, current daily activity (e.g. work), reasons for participating in the study, additional care used that is not in the electronic health records (EHR) including alternative care, and other factors that they think might have influenced their FCR.

In order to collect data on patients' cancer type, treatment and healthcare use, data will be obtained from patients' EHR. Data will be collected on number of GP visits related to cancer, FCR and neither, number of sessions with MHW and number of referrals for physical care and for psychological care. GP visits will only be considered FCR-related if FCR is specifically mentioned. Some patients may not

mention FCR but have increased healthcare uptake due to hyper-vigilance. If that is the case, we expect the number of cancer-related visits to decrease if FCR decreases. At baseline, data on healthcare use per year since the end of curative cancer treatment will also be obtained, to exploratively compare usual care in our control group with usual care in the years prior to the study. FCR-related health costs will be calculated based on the healthcare use.

The desirability and added value of the intervention will be evaluated using custom-made, non-validated questionnaires and semi-structured interviews with a selection of patients and practitioners at T1. The interviews will explore which aspects of the support are effective, unnecessary, practical or pleasant and why. They will also explore whether the GP and MHW are considered to be the right practitioners to provide this type of care and what changes with regard to FCR are most desirable and sought after. Varied groups will be purposively sampled. For patients, in terms of age, time since diagnosis, severity of FCR at T0, and severity of FCR at T1; for practitioners in terms of professional background and years of work experience.

Additional information about data collection, data management, monitoring and dissemination of results can be found in the trial master file.

Sample size calculation

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 (50). Using an alpha of 0.05 and beta of 0.8, we calculated a required sample size of 86 participants in both groups for sufficient power. Because multiple patients are treated by the same MHW, there might be a cluster effect. Based on an average of 15 inclusions per MHW and an intraclass correlation coefficient (ICC) of 0.01, an inflation factor of 1.14 has been applied. This leads to a group size of 98 patients per arm. Because the clusters (number of patients per MHW) will probably not all have the

same size, an inflation factor of 10% is applied, leading to a group size of 108. We also assume a dropout of 12% of patients. That is why we aim to include 122 patients in each group.

Statistical analysis

The primary outcome will be expressed as difference in the mean (with 95% CI and p-value) of the severity scale of the FCRI-NL scale between intervention and control group at T1.

This will be analysed with a linear mixed model. A random intercept will be included to correct for inclusion per MHW. We will include residual covariances in order to correct for repeated measurement in each patient.

The analyses will be conducted in two steps. First, an analysis will be performed with time, treatment and a time by treatment interaction. Second, a correction for baseline measurement of the outcome will be added to the first model.

The validity of the models will be assessed with residual analyses (51).

A similar approach will be used to analyse secondary outcomes and covariates. Where applicable, a generalised linear model will be used to analyse dichotomous and count outcomes (for binomial and Poisson distributions respectively).

Healthcare utilisation is analysed using multilevel analyses. The number of visits to the GP between T1 and T2 is compared between the intervention group and the control group. Shifts in type of visits – physical vs. psychological – will also be explored. The healthcare uptake in the control group between T1 and T2 will also be compared to the period before the baseline measurement to assess whether healthcare uptake has changed since participating in the study.

The costs of healthcare are compared between the control group and the intervention group for the period between T0-T1, T1-T2 and T0-T2, whereby T0-T2 is most important since it combines the costs of the intervention and the potential change in costs in the 9 months after the intervention.

Healthcare costs are calculated based on healthcare utilisation, according to the method of the *Guidelines for carrying out economic evaluations in health care* (52).

For the outcomes for which the intervention is found to be effective, the effect of the covariates on the outcomes will be explored.

First, intention to treat (ITT) analyses will be done. Then, per-protocol analyses will be carried out to estimate the effectiveness of the intervention if executed per protocol. During the analyses, the assessor will be blinded about the groups.

The validity of study results may be challenged by missing values, either at baseline or missing outcomes at follow-up. Multiple imputation will be used to address missing values at baseline for relevant variables. For missing outcomes, correction for relevant prognostic factors will be considered to ensure the validity of the results (53).

The desirability and feasibility of the intervention according to patients and practitioners will be measured qualitatively. Semi-structured interviews will be held. These will be transcribed, and then coded by two independent researchers. Differences in coding will be discussed until consensus is reached. Important themes will be identified, using the data as the starting point.

Patient and public involvement

When developing the online intervention, patients provided input on the desired content and the appearance of the online intervention, e.g. their preference for texts to be short. Once the intervention was developed, patients used it and shared their experiences, and the intervention was further adapted based on this, e.g. adding reminder e-mails.

When developing the study, patients provided input on the general idea. They also provided feedback on the recruitment process and in particular on the invitation letter to patients. Based on their input, the study and the letter were adapted.

Discussion

With an increased number of cancer survivors, there is an increased need for survivorship care. Provision of psychological care for FCR in primary care may improve access and reduce the pressure on specialised institutions. In the current study, the effectiveness of a primary care delivered FCR intervention will be compared to usual care. An evaluation of healthcare consumption and costs is

included in the study to assess whether this can also decrease healthcare uptake and costs of healthcare. To our knowledge, this is the first trial assessing the effectiveness of an FCR intervention implemented in primary care. In addition, it is one of few pragmatic trials on FCR interventions.

Heterogeneity of usual care

Furthermore, we have chosen to compare this intervention with usual care. Since no clear guidelines are available for general practices for FCR, usual care may be quite diverse. Yet, since we want to know whether this intervention is more effective than what is currently being offered, we chose to compare with usual care, despite its heterogeneity, and to register usual care during the study.

Recruitment

Because prior research shows that patients often do not mention FCR to their GP, we chose to actively invite patients who desire support for FCR to participate in the study. The disadvantage of this choice is that we are activating our participants, making them less representative of the patients who currently seek care for FCR. We made this choice, because we want to know whether this intervention can help patients with FCR if they choose to seek care.

Usual care

We recognise that the usual care measured in this study might not fully reflect actual usual care, since we have activated the patient population and made the general practices more aware of this issue. To assess the effect of this activation, we compare the healthcare use in the control group with retrospective healthcare use. In addition, practices who agree to participate in the study might have increased interest and expertise in providing care for FCR. To assess this, we ask them about any education on FCR or related topics they have received.

Randomisation level

We chose to randomise practices and not patients to prevent contamination. Practitioners who have been trained will have increased knowledge and awareness, and will no longer be able to provide usual care the way they did before training. Also, patients at the same practice might discuss the intervention they receive with one another and notice the differences. Patients are unaware of the

randomisation, to prevent patients in the control group from being disappointed and less motivated if they know that they are not receiving the intervention that is being studied.

Trial status

Invitation of primary care practices has started in October 2018. The first patient was included on April 15, 2019. Final results are expected in 2020.

Declarations

1. Ethics approval and consent to participate: The Medical Research Ethics Committee Utrecht (METC Utrecht) has reviewed the study in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and other applicable Dutch and European regulations. Based on the requirements of the WMO, the METC Utrecht has issued an approval of the above-mentioned study. Any protocol amendments will be communicated to all relevant parties. Written consent is obtained from study participants.
2. Author contributions: All authors participated in the design of the study. YL wrote the draft manuscript. ML, CH and NW improved the manuscript. All authors read and approved the final manuscript.
3. Funding: This work was supported by the Dutch Cancer Society (KWF) grant number 10936. KWF is not involved in study design, collection, management, analysis, and interpretation of data, writing of the report, the decision to submit the report for publication, nor does it have authority over the publications.
4. Competing interests: The authors declare that they have no competing interests.
5. Sponsor: Helen Dowling Institute, Professor Bronkhorstlaan 20, 3723 MB Bilthoven
6. Acknowledgements: Not applicable.

References

1. Rubin G, Berendsen A, Crawford SM, Dommett R, Earle C, Emery J, et al. The expanding role of primary care in cancer control. Lancet Oncol. 2015;16(12):1231–72.
2. Ness S, Kokal J, Fee-Schroeder K, Novotny P, Satele D, Barton D. Concerns Across the Survivorship Trajectory: Results From a Survey of Cancer Survivors. Oncol Nurs Forum. 2013;40(1):35–42.
3. Harrington CB, Hansen JA, Moskowitz M, Todd BL, Feuerstein M. It's Not over When it's Over: Long-Term Symptoms in Cancer Survivors—A Systematic Review. Int J Psychiatry Med [Internet]. 2010;40(2):163–81. Available from: http://journals.sagepub.com/doi/10.2190/PM.40.2.c
4. Brennan ME, Butow P, Spillane AJ, Boyle F. Patient-reported quality of life, unmet needs and care coordination outcomes: Moving toward targeted breast cancer survivorship care planning. Asia Pac J Clin Oncol. 2016;12(2):e323–31.
5. Lebel S, Ozakinci G, Humphris G, Mutsaers B, Thewes B, Prins J, et al. From normal response to clinical problem: definition and clinical features of fear of cancer recurrence. Support Care Cancer [Internet]. 2016;24(8):3265–8. Available from: http://dx.doi.org/10.1007/s00520-016-3272-5
6. Simard S, Thewes B, Humphris G, Dixon M, Hayden C, Mireskandari S, et al. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. J Cancer Surviv. 2013;7:300–22.
7. Simard S, Savard J. Fear of Cancer Recurrence Inventory: Development and initial validation of a multidimensional measure of fear of cancer recurrence. Support Care Cancer. 2009;17(3):241–51.
8. Simard S, Savard J. Screening and comorbidity of clinical levels of fear of cancer recurrence. J Cancer Surviv. 2015;9(3):481–91.
9. Hedman C, Strang P, Djärv T, Widberg I, Lundgren CI. Anxiety and Fear of Recurrence Despite a Good Prognosis: An Interview Study with Differentiated Thyroid Cancer Patients. Thyroid [Internet]. 2017;27(11):1417–23. Available from: http://online.liebertpub.com/doi/10.1089/thy.2017.0346
10. Liao KYH, Yeung NCY, Wong CCY, Warmoth K, Lu Q. Fear of cancer recurrence and physical well-being among Chinese cancer survivors: the role of conscientiousness, positive reappraisal and hopelessness. Support Care Cancer. 2017;25(4):1141–9.
11. Smith A Ben, Sharpe L, Thewes B, Turner J, Gilchrist J, Fardell JE, et al. 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. 2018;4207–16.

12. Simard S, Savard J, Ivers H. Fear of cancer recurrence: Specific profiles and nature of intrusive thoughts. J Cancer Surviv. 2010;

13. 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):633–9.

14. Simonelli LE, Siegel SD, Duffy NM. Fear of cancer recurrence: a theoretical review and its relevance for clinical presentation and management. Psychooncology. 2017;26(10):1444–54.

15. Champagne A, Ivers H, Savard J. Utilization of Health Care Services in Cancer Patients with Elevated Fear of Cancer Recurrence. Psychooncology [Internet]. 2018;(March):1–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29719072%0Ahttp://doi.wiley.com/10.1002/pon.4748

16. Butow P, Sharpe L, Thewes B, Turner J, Gilchrist J, Beith J. Fear of Cancer Recurrence: A Practical Guide for Clinicians. Oncol J. 2018;32(1):32–8.

17. Mikkelsen T, Sondergaard J, Sokolowski I, Jensen A, Olesen F. Cancer survivors' rehabilitation needs in a primary health care context. Fam Pract. 2009;26(3):221–30.

18. NIVEL. Afstemming van zorg tussen huisarts en specialist bij kanker kan beter [Internet]. 2013 [cited 2018 May 22]. Available from: https://www.nivel.nl/nl/nieuws/afstemming-van-zorg-tussen-huisarts-en-specialist-bij-kanker-kan-beter

19. NHG. NHG-standpunt Oncologische zorg in de huisartsenpraktijk. 2014.

20. Fann JR, Ell K, Sharpe M. Integrating psychosocial care into cancer services. J Clin Oncol. 2012;30(11):1178–86.

21. Curran L, Sharpe L, Butow P. Anxiety in the context of cancer: A systematic review and development of an integrated model. Clin Psychol Rev [Internet]. 2017;56(June):40–54. Available from: http://dx.doi.org/10.1016/j.cpr.2017.06.003

22. Volker C, van der Lee M, Pet A. Angst voor terugkeer van kanker. GZ-Psychologie. 2011;3:30–8.

23. Cupit-Link M, Syrjala KL, Hashmi SK. Damocles' syndrome revisited: Update on the fear of cancer recurrence in the complex world of today's treatments and survivorship. Hematol Oncol Stem Cell Ther [Internet]. 2018; Available from: https://doi.org/10.1016/j.hemonc.2018.01.005

24. Chen D, Sun W, Liu N, Wang J, Zhao J, Zhang Y, et al. Fear of cancer recurrence: A systematic review of

randomized, controlled trials. Oncol Nurs Forum. 2018;45(6):703–12.

25. Sharpe L, Thewes B, Butow P. Current directions in research and treatment of fear of cancer recurrence. Curr Opin Support Palliat Care. 2017;11(3):191–6.

26. Crane-Okada R, Kiger H, Sugerman F, Uman GC, Shapiro SL, Wyman-McGinty W, et al. Mindful movement program for older breast cancer survivors: A pilot study. Cancer Nurs. 2012;35(4):1–13.

27. Lengacher CA, Shelton MM, Reich RR, Barta MK, Johnson-Mallard V, Moscoso MS, et al. Mindfulness based stress reduction (MBSR(BC)) in breast cancer: Evaluating fear of recurrence (FOR) as a mediator of psychological and physical symptoms in a randomized control trial (RCT). J Behav Med. 2014;37(2):185–95.

28. Lengacher CA, Reich RR, Paterson CL, Ramesar S, Park JY, Alinat C, et al. Examination of broad symptom improvement resulting from mindfulness-based stress reduction in breast cancer survivors: A randomized controlled trial. J Clin Oncol. 2016;34(24):2827–34.

29. 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;

30. Dodds SE, Pace TWW, Bell ML, Fiero M, Negi LT, Raison CL, et al. Feasibility of Cognitively-Based Compassion Training (CBCT) for breast cancer survivors: a randomized, wait list controlled pilot study. Support Care Cancer. 2015;23(12):3599–608.

31. Lichtenthal WG, Corner GW, Slivjak ET, Roberts KE, Li Y, Breitbart W, et al. A pilot randomized controlled trial of cognitive bias modification to reduce fear of breast cancer recurrence. Cancer. 2017;123(8):1424–33.

32. van de Wal M, Thewes B, Gielissen M, Speckens A, Prins J. Efficacy of blended cognitive behavior therapy for high fear of recurrence in breast, prostate, and colorectal cancer survivors: The SWORD study, a randomized controlled trial. J Clin Oncol [Internet]. 2017;35(19):2173–83. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85021649029&doi=10.1200%2FJCO.2016.70.5301&partnerID=40&md5=f159be668de252f5b14f60fe08799680%0Ahttp://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/658/CN-01395658/frame.html

33. Butow P, Turner J, Gilchrist J, Sharpe L, Smith A Ben, Fardell JE, et al. Randomized trial of ConquerFear:

A novel, theoretically based psychosocial intervention for fear of cancer recurrence. J Clin Oncol. 2017;35(36):4066–77.

34. Otto AK, Szczesny EC, Soriano EC, Laurenceau J, Siegel SD. Supplemental Material for Effects of a Randomized Gratitude Intervention on Death-Related Fear of Recurrence in Breast Cancer Survivors. Heal Psychol [Internet]. 2016;35(12):1320–8. Available from: http://supp.apa.org/psycarticles/supplemental/hea0000400/hea0000400_supp.html

35. Zernicke KA, Campbell TS, Speca M, Mccabe-Ruff K, Flowers S, Carlson LE. A randomized wait-list controlled trial of feasibility and efficacy of an online mindfulness-based cancer recovery program: The eTherapy for cancer applying mindfulness trial. Psychosom Med. 2014;76(4):257–67.

36. Ugalde A, Haynes K, Boltong A, White V, Krishnasamy M, Schofield P, et al. Self-guided interventions for managing psychological distress in people with cancer – A systematic review. Patient Educ Couns. 2017;100(5):846–57.

37. Elaine FH, Peter JB. On-site mental health workers delivering psychological therapy and psychosocial interventions to patients in primary care: effects on the professional practice of primary care providers. Cochrane Database Syst Rev. 2009;(1).

38. Del Giudice ME, Grunfeld E, Harvey BJ, Piliotis E, Verma S. Primary care physicians' views of routine follow-up care of cancer survivors. J Clin Oncol. 2009;27(20):3338–45.

39. Johansen ML, Holtedahl KA, Rudebeck CE. How does the thought of cancer arise in a general practice consultation? Interviews with GPs. Scand J Prim Health Care. 2012;30(3):135–40.

40. Mitchell AJ, Vahabzadeh A, Magruder K. Screening for distress and depression in cancer settings: 10 lessons from 40 years of primary-care research. Psychooncology. 2011;20(6):572–84.

41. Curran GM, Sullivan G, Mendel P, Craske MG, Sherbourne CD, Stein MB, et al. Implementation of the CALM intervention for anxiety disorders: A qualitative study. Implement Sci. 2012;7(1):1–11.

42. Lawrence RA, McLoone JK, Wakefield CE, Cohn RJ. Primary Care Physicians' Perspectives of Their Role in Cancer Care: A Systematic Review. J Gen Intern Med [Internet]. 2016;31(10):1222–36. Available from: http://dx.doi.org/10.1007/s11606-016-3746-7

43. Berrett-Abebe J, Cadet T, Vitello J, Maramaldi P. Developing content for an interprofessional training on fear of cancer recurrence (FCR): Key informant interviews of healthcare professionals, researchers and cancer survivors. J Psychosoc Oncol [Internet]. 2018;0(0):1–15. Available from:

https://doi.org/10.1080/07347332.2018.1443987

44. Berrett-Abebe J, Cadet T, Nekhlyudov L, Vitello J, Maramaldi P. Impact of an Interprofessional Primary Care Training on Fear of Cancer Recurrence on Clinicians' Knowledge, Self-Efficacy, Anticipated Practice Behaviors, and Attitudes Toward Survivorship Care. J Cancer Educ. 2018;1–7.

45. Fidjeland HL, Brekke M, Vistad I. Scandinavian Journal of Primary Health Care General practitioners' attitudes toward follow-up after cancer treatment: A cross-sectional questionnaire study. Scand J Prim Health Care [Internet]. 2015;334(4):223–32. Available from: http://www.tandfonline.com/action/journalInformation?journalCode=ipri20%0Ahttp://dx.doi.org/10.3109/02813432.2015.1118836

46. Nekhlyudov L, O'malley DM, Hudson S V. Integrating primary care providers in the care of cancer survivors: gaps in evidence and future opportunities. Lancet Oncol [Internet]. 2017;18(1):e30–8. Available from: http://dx.doi.org/10.1016/S1470-2045(16)30570-8

47. Adam R, Watson E. The role of primary care in supporting patients living with and beyond cancer. 2018;261–7. Available from: www.supportiveandpalliativecare.com

48. Landelijke verening POH-GGZ. Functie-en competentieprofiel POH-GGZ. 2014;17.

49. Helmondt SJ Van, Lee ML Van Der, Vries J De. Study protocol of the CAREST-trial : a randomised controlled trial on the (cost-) effectiveness of a CBT-based online self- help training for fear of cancer recurrence in women with curatively treated breast cancer. BMC Cancer [Internet]. 2016;1–11. Available from: http://dx.doi.org/10.1186/s12885-016-2562-0

50. van Helmondt SJ, van der Lee ML, de Vries J. Translation and validation of the Dutch version of the Fear of Cancer Recurrence Inventory (FCRI-NL). J Psychosom Res [Internet]. 2017;102(August):21–8. Available from: http://dx.doi.org/10.1016/j.jpsychores.2017.09.001

51. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. 2nd ed. Hoboken: John Wiley & sons; 2004.

52. Assessment MT. Verdiepingsmodule Kostenevaluatie. Available from: https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg

53. Groenwold RHH, Moons KGM, Vandenbroucke JP. Randomized trials with missing outcome data: How to analyze and what to report. Cmaj. 2014;186(15):1153–7.

526

527

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed in protocol
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page, line 2-4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract, line 45

	2b	All items from the World Health Organization Trial Registration Data Set	Title page, line 2-4, 22 Abstract, line 32, 45, Introduction, line 130-143 Methods, line 158-167, 168-175, 176-187, 188-199, 207-214 Trial status, 342-344 Declarations, line 355
Protocol version	3	Date and version identifier	Footer
Funding	4	Sources and types of financial, material, and other support	Declarations, 355-358
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page, line 6-21
	5b	Name and contact information for the trial sponsor	Declarations, 360
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Declarations, 355-358

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Methods, 255-256
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction, 100-117, 130-143
	6b	Explanation for choice of comparators	Methods, 196-199 Discussion, 330-334
Objectives	7	Specific objectives or hypotheses	Introduction, 130-143
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Methods, 147-148
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Methods, 159-160
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Methods, 158-167

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Methods, 188-195
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n.a.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Methods, 193-195
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n.a.
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Methods, 207-256
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Methods, 149-157
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Methods, 257-267
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Methods, 169-171
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Methods, 176-187
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Methods, 176-187
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Methods, 177-178, 185
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Methods, 177-178, 255-256, 331-333
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n.a.
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Methods, 226-256
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Methods, 166-167, 206, 255-256

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Methods, 255-256
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Methods, 268-301
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Methods, 268-301
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Methods, 292-293, 296-297
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Methods, 255-256
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n.a.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Methods, 255-256
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Methods, 255-256
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Declarations 345-351

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Declarations, 350
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Methods, 174-175
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Methods, 255-256
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Declarations, 359
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Methods, 255-256
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Methods, 256-256
	31b	Authorship eligibility guidelines and any intended use of professional writers	Declarations, 352-354
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable

Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See attachment
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032616.R2
Article Type:	Protocol
Date Submitted by the Author:	22-Oct-2019
Complete List of Authors:	Luigjes, Yvonne; Helen Dowling Institute, ; Julius Center for Health Sciences and Primary Care, van der Lee, Marije; Helen Dowling Institute, Scientific Research de Wit, Niek; University Medical Center Utrecht, Julius Center for Primary Care Helsper, Charles; University Medical Centre Utrecht, 1Julius Centre for Health Sciences and Primary Care
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Mental health, Oncology
Keywords:	fear of cancer recurrence, PRIMARY CARE, psycho-oncology, mental health worker

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

Yvonne L Luigjes-Huizer

Scientific Research Department, Helen Dowling Instituut, Bilthoven, The Netherlands and Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands

y.l.huizer@umcutrecht.nl

Marije L van der Lee

Scientific Research Department, Helen Dowling Instituut, Bilthoven, The Netherlands

mvanderlee@hdi.nl

Niek J de Wit

Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands

n.j.dewit@umcutrecht.nl

Charles W Helsper

Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands

c.w.helsper-2@umcutrecht.nl

Corresponding author: Yvonne Luigjes yluigjes@hdi.nl

Word count: 4000 words

Abstract

Introduction: Many successfully treated cancer patients suffer from fear of cancer recurrence (FCR), affecting their quality of life and their physical, emotional, cognitive and social functioning. Effective psychological interventions for FCR exist, but are not widely available, as they are typically offered by specialised psycho-oncology professionals and institutes. Concurrently, the role of primary care in cancer and survivorship care is increasing. Therefore, there could be a role for general practitioners (GP) and mental health workers (MHW) working in primary care in supporting patients with FCR. In the current study the effectiveness of a primary care delivered FCR intervention will be evaluated.

Methods and analysis: A two-armed cluster-randomised trial will be conducted. The primary outcome will be FCR severity; secondary outcomes will be FCR-related distress, healthcare uptake and healthcare costs. Primary care practices in the Netherlands will be invited to participate in the study. Participating practices will be stratified by size and socio-economic status and randized. In the control arm, practices will provide care as usual. In the intervention arm, practices will offer the cognitive behavioural FCR intervention that is being studied, which consists of an intake with the GP and five sessions with the MHW. Patients who have finished successful curative treatment for cancer between 3 months and 10 years ago will be invited to participate in the study by invitation letter from their GPs. Participating patients fill out questionnaires at baseline, after three months and after twelve months. Data on healthcare use is collected from their electronic health records (EHR). Qualitative interviews are held at T1 with patients and practitioners in the intervention group.

Ethics and dissemination: The Medical Research Ethics Committee Utrecht provided approval for the study. Results will be dispersed through peer-reviewed publications and scientific presentations.

Trial registration: NL7573 in the Netherlands Trial Register on 25-02-2019.

Keywords: fear of cancer recurrence, primary care, psycho oncology, mental health worker

Strengths and limitations of this study

- A robust, pragmatic trial design will be implemented in general practices, reflecting daily care.

- Quantitative and qualitative data are combined to provide comprehensive results.
- The intervention and trial were designed in close cooperation with patients and healthcare workers.
- A cluster randomised design, randomising at practice level, was required, since practitioners who have been trained on the intervention are unlikely to be able to provide usual care in the same way as before training.
- Patients are actively invited to participate in the study, making them less representative of the patients who currently seek care for FCR.

Introduction

Advances in the medical field have caused the number of cancer survivors to rise steadily in the past decades (1). With an increasing number of survivors, there is also an increasing need for survivorship care (2). A systematic review showed that fatigue, depression and anxiety are commonly reported in the ten years after primary cancer treatment (3). Fear of cancer recurrence (FCR) is a more prevalent concern than any physical issue (2). In a study about unmet needs after breast cancer, FCR was the most reported need in all age groups (38.2%), despite a relatively good prognosis (4).

FCR has been defined as “fear, worry, or concern relating to the possibility that cancer will come back or progress” (5). A review by Simard (2013) found that an average of 73% of cancer survivors experience FCR, 49% experience a moderate to high level of FCR and 7% experience a high level of FCR (6). FCR is a multidimensional construct, as demonstrated by the subscales of the Fear of Cancer Recurrence Inventory (FCRI): triggers, severity, psychological distress, coping strategies, functioning impairments, insight and reassurance (7). FCR exists on a scale from normal to clinical (8). In a 2-day colloquium with a group of experts and patient advocates, five preliminary categories of potential characteristics of clinical FCR were identified using the Delphi method. These are: preoccupation with

cancer return or progression, unhelpful coping strategies, impairments in daily functioning, great level of distress and limited ability to make plans (5).

Many studies have explored factors that correlate with FCR development, with mixed results. The evidence for correlations between FCR and age, gender and physical symptoms is strongest, whereby younger patients, female patients and patients with more symptoms experience more FCR (6). In contrast, social support, optimism, having detailed information and being conscientious correlate with having less FCR (6,9,10). Notably, associations between FCR and psychological factors (e.g. metacognitions) are generally stronger than associations between FCR and demographic factors (11). FCR can persist for many years after the end of cancer treatment (6,12). There are also triggers that can temporarily increase FCR, including: medical appointments, having unexplainable symptoms and hearing about cancer in the media (13).

The impact of FCR varies. Having some FCR can be protective, if it leads to treatment compliance and healthy lifestyle adaptations. However, severe FCR can significantly decrease quality of life (14). Maladaptive coping styles include overuse of primary care for common acute symptoms, which can inadvertently augment fears and cause unnecessary healthcare costs (15), but also avoidance of social and healthcare appointments, risking delayed diagnosis of cancer recurrence. On average, healthcare uptake is increased for people with high FCR (16).

A Danish study found that patients discussed social or psychological aspects of cancer, including FCR, more with family and friends than with their GP, because they thought it was not the GP's mandate to address these concerns (17). In a Dutch study, 75% of patients' physical problems after having received a cancer diagnosis were discussed with GPs, compared to only one third of emotional and social problems (18). When the need for psychosocial care is recognised, this positively affects quality of life, appreciation of care, and communication with care providers (19). Therefore, it seems of added value if GPs assess the presence of FCR and refer to additional care when needed (20).

Treating FCR is different from treating other anxiety disorders, because FCR is not irrational, since the threat is actual and significant (21). Currently, there are different treatment options for FCR, which can

be applied in a stepped care approach. The first level involves psycho-education, normalisation and self-management. Next, cognitive behavioural therapy (CBT), therapies focusing on acceptance (22) and pharmacological treatment (23) can be applied. In recent years, several trials have shown the effectiveness of new FCR interventions (24,25), including mindfulness programs (26–28), psychoeducation (29), cognitive behavioural therapy interventions (30–32), an intervention based on metacognitive therapy (33) and a gratitude intervention (34). The SWORD study found that blended treatment with a specialized psychologist and an online FCR program reduced FCR significantly more than usual care (32).

Specialised psychological care for cancer is typically provided in hospitals and specialized institutes. Unfortunately, travel distance, limited energy of ex-cancer patients and waiting lists counteract accessibility (35). Also, most cancer survivors do not require intensive specialised psychotherapy, but rather accessible psychological care. Online treatment is easily accessible, and allows patients to obtain care when they feel fit enough and for a manageable duration. However, evidence for the effectiveness of completely self-guided interventions among cancer patients with psychological distress is lacking. Some level of therapist involvement can help encourage engagement and promote adherence (36).

Concurrently, cancer care and survivorship care are increasingly being provided in primary care, because of patient preference, increasing numbers of cancer patients and rising healthcare costs (1). Primary care is comprehensive, longitudinal and integrated, provided by teams of different professionals (1), increasingly including mental health professionals (37). Primary care providers generally have a longstanding relation with the patient (38,39). Patients view primary care staff as trusted professionals (40) and prefer coming to primary care for anxiety issues, because of practical reasons and stigma (41). General practitioners want to provide psychosocial support to cancer patients and feel they are well-positioned (42,43), but they face capacity challenges (44,45) and report a need for training on cancer survivorship (46,47), in particular on treating psychological problems (44). Involving and training auxiliary staff, such as primary care MHWs, in survivorship care, may help to overcome both capacity challenges and the need for improved expertise in primary care (47).

Aim

The BLANKET study was designed to assess the effectiveness of a primary care delivered, blended care intervention for FCR, in reducing patients' severity of FCR, compared to usual care. Since this is a pragmatic trial, we include all patients who want care for FCR at their GP practice.

We hypothesise that

1. the FCR intervention will reduce FCR severity,
2. the FCR intervention will reduce FCR related distress,
3. healthcare consumption of patients who have received the FCR intervention will be reduced,
4. the FCR intervention will be considered desirable and of added value by patients and practitioners.

The primary outcome is FCR severity. Secondary outcomes are FCR-related distress, FCR-related healthcare use, FCR-related health costs, and satisfaction of patients and practitioners with support provided by trained MHWs and GPs.

Methods

Study design

The BLANKET study is a two-armed cluster randomised clinical trial, in which the general practice is the unit of randomisation.

Study procedure

Participating practices will identify all of their patients who have successfully completed curative cancer treatment between three months and ten years ago, and will send them an invitation letter by mail. Patients are asked to participate if they desire support for FCR. After providing informed consent, patients are asked to fill out an online baseline questionnaire. Patients also fill out questionnaires 3 months and 12 months after baseline. At the end of the first questionnaire, they are urged to make an appointment with their GP about support for FCR. During this consultation, the GPs

in the intervention group refer the patients to the MHW for the intervention, while GPs in the control group provide usual care.

Eligibility

Clusters of collaborating GPs and MHWs in the Netherlands who are willing to receive training and to implement it will be recruited. In the Dutch setting, almost all general practices employ mental health workers (MHW, in Dutch: POH-GGZ) (48). Both a GP and an MHW need to agree to participate for the practice to be eligible to join the study.

Patients are eligible if they: (1) are registered at a general practice that is participating in the study, (2) are 18 years or older, (3) have finished successful curative cancer treatment between 3 months and 10 years ago, (4) desire support for FCR, and (5) have sufficient Dutch reading and writing skills to receive the intervention and complete the questionnaires. If patients have a cancer recurrence during the study, no more data will be collected. GPs select patients who can be invited for the study. GPs exclude vulnerable patients (e.g. severe psychiatric morbidity), who would be confused by the letter or unable to participate in the study.

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 nonetheless limited by FCR in daily life. We will train the MHW to refer patients who require specialized psychological care.

Recruitment

The aim is to include 244 patients during 1,5 years. Patients are recruited using an invitation letter sent by patients' own GPs. All of the patients of participating practices, who are 18 years or older and have finished curative cancer treatment between 3 months and 10 years ago will receive the letter. To spread the workload for the practitioners, invitation will be done in rounds, starting with patients who most recently finished cancer treatment.

Randomisation

Randomisation is done at practice level. GPs and MHWs will know in which group they have been placed. Patients will not. Clusters are formed, in which all GPs and MHWs working in the same building are grouped together, to decrease the risk of contamination. Minimisation is applied for size of the practice and the socio-economic status (SES) of the neighbourhood they are located in, to ensure balance between study arms (patients and professionals). For practice size, there are three categories: small (1-3 GPs), middle-sized (4-6 GPs) or large (7 GPs or more). For SES, the list of disadvantaged areas by postal code made by the Dutch government for general practices is used. Practices will be assigned to the intervention or the control group, using the number generator at Research Randomizer (randomizer.org). An external data manager will generate the numbers. Practices are randomised in two blocks. The inclusion rate from the first block will help to confirm how many more practices are needed for the second block.

Intervention

GPs and MHWs in the intervention group will provide an intervention specifically designed for FCR, with online modules, which focus on normalisation, psychoeducation and self-management (49). The modules were developed at the Helen Dowling Institute based on cognitive behavioural therapy, clinical experience and input from patients, and are currently being used by specialised psychologists for blended treatment. The intervention consists of two CBT modules, which include psycho-education on FCR, and five optional modules on rumination, avoidance, relaxing, reassuring and undertaking activities. The FCRI is used to determine which optional modules are most important for each patient. Patients can also choose additional modules.

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. 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. GPs and MHWs in the control group will provide usual care.

Usual care

Patients in the control group receive usual care. In the literature, little is known about the usual care that GPs provide for fear of cancer recurrence. Therefore, usual care will be mapped in this study, in relation to the severity of FCR.

Outcomes

Participants will provide data using online self-report questionnaires hosted by ResearchOnline.com. Participants will receive an invitational e-mail with a link to complete the questionnaires online. These links will be sent at baseline (T0), after three months, once the intervention in the intervention group is completed (T1), and one year after the baseline (T2). Participants who do not respond receive reminders. If participants prefer to fill out the questionnaires on paper, this will be arranged. If patients do not fill out the questionnaires, they are sent reminders.

Primary outcome

The primary outcome is the severity of fear of cancer recurrence after 3 months, comparing the FCR intervention with usual care. To measure this, the severity scale (SF) of the Dutch version of the Fear of Cancer Recurrence Inventory (FCRI-NL) will be used.

Secondary outcomes

The secondary outcomes are the development from baseline to T1 to T2 of severity of fear of cancer recurrence, FCR-related distress, FCR-related healthcare use and FCR-related health costs; and the desirability and added value of the intervention.

Covariates

If the intervention is found to be effective, relations between the outcomes and the following variables will be explored, to identify groups of patients for whom the intervention might be more or less effective.

At the patient level: age, gender, level of education, coping style, severity of anxiety and depression, somatic complaints, severity of FCR at the start of the study, FCR related distress at the start of the study, psychiatric history, previous health care use, additional care used by patients (e.g. alternative care), time since the cancer diagnosis, time since the end of the curative cancer treatment, cancer type.

At the practice level: general practice size and SES status of practice.

At the MHW level: number of years of work experience and educational background of the MHW.

Data collection

Patients will fill out the Dutch version of the fear of cancer recurrence inventory (FCRI-NL). It contains 43 items, measuring seven subscales. The severity, distress and coping subscales will be used to measure FCR severity, distress and coping. The FCRI was translated into Dutch and validated by van Helmondt, van der Lee & de Vries (50). While for the FCRI, it is recommended to use the total score of all subscales to obtain a score for FCR (7), this multi-dimensional structure was not replicated in the validation of the FCRI-NL. Instead, the individual subscales provide important information and are recommended to be used separately (50).

The 4DKL will be used to provide data on general distress, depression, anxiety and somatic complaints. The 4DKL is a 50-item questionnaire that measures four dimensions: distress, depression, anxiety and somatic complaints. The list is already used in some GP practices and is therefore practically applicable.

Patients will also be surveyed about their educational level, current daily activity (e.g. work), reasons for participating in the study, additional care used that is not in the electronic health records (EHR) including alternative care, and other factors that they think might have influenced their FCR.

In order to collect data on patients' cancer type, treatment and healthcare use, data will be obtained from patients' EHR. Data will be collected on number of GP visits related to cancer, FCR and neither, number of sessions with MHW and number of referrals for physical care and for psychological care. GP visits will only be considered FCR-related if FCR is specifically mentioned. Some patients may not

mention FCR but have increased healthcare uptake due to hyper-vigilance. If that is the case, we expect the number of cancer-related visits to decrease if FCR decreases. At baseline, data on healthcare use per year since the end of curative cancer treatment will also be obtained, to exploratively compare usual care in our control group with usual care in the years prior to the study. FCR-related health costs will be calculated based on the healthcare use.

The desirability and added value of the intervention will be evaluated using custom-made, non-validated questionnaires and semi-structured interviews with a selection of patients and practitioners at T1. The interviews will explore which aspects of the support are effective, unnecessary, practical or pleasant and why. They will also explore whether the GP and MHW are considered to be the right practitioners to provide this type of care and what changes with regard to FCR are most desirable and sought after. Varied groups will be purposively sampled. For patients, in terms of age, time since diagnosis, severity of FCR at T0, and severity of FCR at T1; for practitioners in terms of professional background and years of work experience.

Additional information about data collection, data management, monitoring and dissemination of results can be found in the trial master file.

Sample size calculation

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 (50). Using an alpha of 0.05 and beta of 0.8, we calculated a required sample size of 86 participants in both groups for sufficient power. Because multiple patients are treated by the same MHW, there might be a cluster effect. Based on an average of 15 inclusions per MHW and an intraclass correlation coefficient (ICC) of 0.01, an inflation factor of 1.14 has been applied. This leads to a group size of 98 patients per arm. Because the clusters (number of patients per MHW) will probably not all have the

same size, an inflation factor of 10% is applied, leading to a group size of 108. We also assume a dropout of 12% of patients. That is why we aim to include 122 patients in each group.

Statistical analysis

The primary outcome will be expressed as difference in the mean (with 95% CI and p-value) of the severity scale of the FCRI-NL scale between intervention and control group at T1.

This will be analysed with a linear mixed model. A random intercept will be included to correct for inclusion per MHW. We will include residual covariances in order to correct for repeated measurement in each patient.

The analyses will be conducted in two steps. First, an analysis will be performed with time, treatment and a time by treatment interaction. Second, a correction for baseline measurement of the outcome will be added to the first model.

The validity of the models will be assessed with residual analyses (51).

A similar approach will be used to analyse secondary outcomes and covariates. Where applicable, a generalised linear model will be used to analyse dichotomous and count outcomes (for binomial and Poisson distributions respectively).

Healthcare utilisation is analysed using multilevel analyses. The number of visits to the GP between T1 and T2 is compared between the intervention group and the control group. Shifts in type of visits – physical vs. psychological – will also be explored. The healthcare uptake in the control group between T1 and T2 will also be compared to the period before the baseline measurement to assess whether healthcare uptake has changed since participating in the study.

The costs of healthcare are compared between the control group and the intervention group for the period between T0-T1, T1-T2 and T0-T2, whereby T0-T2 is most important since it combines the costs of the intervention and the potential change in costs in the 9 months after the intervention.

Healthcare costs are calculated based on healthcare utilisation, according to the method of the *Guidelines for carrying out economic evaluations in health care* (52).

For the outcomes for which the intervention is found to be effective, the effect of the covariates on the outcomes will be explored.

First, intention to treat (ITT) analyses will be done. Then, per-protocol analyses will be carried out to estimate the effectiveness of the intervention if executed per protocol. During the analyses, the assessor will be blinded about the groups.

The validity of study results may be challenged by missing values, either at baseline or missing outcomes at follow-up. Multiple imputation will be used to address missing values at baseline for relevant variables. For missing outcomes, correction for relevant prognostic factors will be considered to ensure the validity of the results (53).

The desirability and feasibility of the intervention according to patients and practitioners will be measured qualitatively. Semi-structured interviews will be held. These will be transcribed, and then coded by two independent researchers. Differences in coding will be discussed until consensus is reached. Important themes will be identified, using the data as the starting point.

Patient and public involvement

When developing the intervention, patients provided input on desired content and appearance, e.g. preference for short texts. Once implemented, the intervention was further adapted based on patient feedback.

When developing the study, patients provided input on the general idea. They also provided feedback on the recruitment process and in particular on the invitation letter to patients. Based on their input, the study and the letter were adapted.

Discussion

With an increased number of cancer survivors, there is an increased need for survivorship care. Providing survivorship care in primary care may improve access and reduce the pressure on specialised institutions. In this study, the effectiveness of a primary care FCR intervention will be compared to usual care. An evaluation of healthcare consumption and costs will assess whether this can also decrease healthcare uptake and costs. To our knowledge, this is the first trial assessing the

effectiveness of a primary care FCR intervention. In addition, it is one of few pragmatic trials on FCR interventions.

Heterogeneity of usual care

To assess whether this intervention is more effective than what is currently being offered, we chose to compare with usual care. No clear guidelines are available for GPs for FCR, so usual care may be quite diverse. Therefore, we will register usual care during the study.

Recruitment

Because prior research shows that patients often do not mention FCR to their GP, we chose to actively invite patients to participate in the study. The disadvantage of this choice is that we are activating our participants, making them less representative of the patients who currently seek care for FCR. However, we want to know whether this intervention can help patients with FCR, if they choose to seek care.

Usual care

We recognise that the usual care measured in this study might not fully reflect actual usual care, since we have activated the patient population and made the general practices more aware of this issue. To assess the effect of this activation, we compare the healthcare use in the control group with retrospective healthcare use. Also, practices who agree to participate in the study might have increased interest and expertise in FCR. To assess this, we ask them about any education on FCR or related topics they have received.

Randomisation level

We chose to randomise practices and not patients to prevent contamination. Practitioners who have been trained will have increased knowledge and awareness, and will no longer provide usual care the way they did before training. Also, patients at the same practice might discuss the intervention they receive and notice the differences. Patients are unaware of the randomisation, to prevent patients in the control group from being disappointed and less motivated.

Trial status

Invitation of primary care practices has started in October 2018. The first patient was included on April 15, 2019. Final results are expected in 2020.

Declarations

1. Ethics approval and consent to participate: The Medical Research Ethics Committee Utrecht (METC Utrecht) has reviewed the study in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO) and other applicable Dutch and European regulations. Based on the requirements of the WMO, the METC Utrecht has issued an approval of the above-mentioned study. Any protocol amendments will be communicated to all relevant parties. Written consent is obtained from study participants.
2. Author contributions: All authors participated in the design of the study. YL wrote the draft manuscript. ML, CH and NW improved the manuscript. All authors read and approved the final manuscript.
3. Funding: This work was supported by the Dutch Cancer Society (KWF) grant number 10936. KWF is not involved in study design, collection, management, analysis, and interpretation of data, writing of the report, the decision to submit the report for publication, nor does it have authority over the publications.
4. Competing interests: The authors declare that they have no competing interests.
5. Sponsor: Helen Dowling Institute, Professor Bronkhorstlaan 20, 3723 MB Bilthoven
6. Acknowledgements: Not applicable.

References

1. Rubin G, Berendsen A, Crawford SM, Dommett R, Earle C, Emery J, et al. The expanding role of primary care in cancer control. Lancet Oncol. 2015;16(12):1231–72.
2. Ness S, Kokal J, Fee-Schroeder K, Novotny P, Satele D, Barton D. Concerns Across the Survivorship Trajectory: Results From a Survey of Cancer Survivors. Oncol Nurs Forum. 2013;40(1):35–42.
3. Harrington CB, Hansen JA, Moskowitz M, Todd BL, Feuerstein M. It's Not over When it's Over: Long-Term Symptoms in Cancer Survivors—A Systematic Review. Int J Psychiatry Med [Internet]. 2010;40(2):163–81. Available from: http://journals.sagepub.com/doi/10.2190/PM.40.2.c
4. Brennan ME, Butow P, Spillane AJ, Boyle F. Patient-reported quality of life, unmet needs and care coordination outcomes: Moving toward targeted breast cancer survivorship care planning. Asia Pac J Clin Oncol. 2016;12(2):e323–31.
5. Lebel S, Ozakinci G, Humphris G, Mutsaers B, Thewes B, Prins J, et al. From normal response to clinical problem: definition and clinical features of fear of cancer recurrence. Support Care Cancer [Internet]. 2016;24(8):3265–8. Available from: http://dx.doi.org/10.1007/s00520-016-3272-5
6. Simard S, Thewes B, Humphris G, Dixon M, Hayden C, Mireskandari S, et al. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. J Cancer Surviv. 2013;7:300–22.
7. Simard S, Savard J. Fear of Cancer Recurrence Inventory: Development and initial validation of a multidimensional measure of fear of cancer recurrence. Support Care Cancer. 2009;17(3):241–51.
8. Simard S, Savard J. Screening and comorbidity of clinical levels of fear of cancer recurrence. J Cancer Surviv. 2015;9(3):481–91.
9. Hedman C, Strang P, Djärv T, Widberg I, Lundgren CI. Anxiety and Fear of Recurrence Despite a Good Prognosis: An Interview Study with Differentiated Thyroid Cancer Patients. Thyroid [Internet]. 2017;27(11):1417–23. Available from: http://online.liebertpub.com/doi/10.1089/thy.2017.0346
10. Liao KYH, Yeung NCY, Wong CCY, Warmoth K, Lu Q. Fear of cancer recurrence and physical well-being among Chinese cancer survivors: the role of conscientiousness, positive reappraisal and hopelessness. Support Care Cancer. 2017;25(4):1141–9.
11. Smith A Ben, Sharpe L, Thewes B, Turner J, Gilchrist J, Fardell JE, et al. 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. 2018;4207–16.

12. Simard S, Savard J, Ivers H. Fear of cancer recurrence: Specific profiles and nature of intrusive thoughts. J Cancer Surviv. 2010;

13. 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):633–9.

14. Simonelli LE, Siegel SD, Duffy NM. Fear of cancer recurrence: a theoretical review and its relevance for clinical presentation and management. Psychooncology. 2017;26(10):1444–54.

15. Butow P, Sharpe L, Thewes B, Turner J, Gilchrist J, Beith J. Fear of Cancer Recurrence: A Practical Guide for Clinicians. Oncol J. 2018;32(1):32–8.

16. Champagne A, Ivers H, Savard J. Utilization of Health Care Services in Cancer Patients with Elevated Fear of Cancer Recurrence. Psychooncology [Internet]. 2018;(March):1–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29719072%0Ahttp://doi.wiley.com/10.1002/pon.4748

17. Mikkelsen T, Sondergaard J, Sokolowski I, Jensen A, Olesen F. Cancer survivors' rehabilitation needs in a primary health care context. Fam Pract. 2009;26(3):221–30.

18. NIVEL. Afstemming van zorg tussen huisarts en specialist bij kanker kan beter [Internet]. 2013 [cited 2018 May 22]. Available from: https://www.nivel.nl/nl/nieuws/afstemming-van-zorg-tussen-huisarts-en-specialist-bij-kanker-kan-beter

19. NHG. NHG-standpunt Oncologische zorg in de huisartsenpraktijk. 2014.

20. Fann JR, Ell K, Sharpe M. Integrating psychosocial care into cancer services. J Clin Oncol. 2012;30(11):1178–86.

21. Curran L, Sharpe L, Butow P. Anxiety in the context of cancer: A systematic review and development of an integrated model. Clin Psychol Rev [Internet]. 2017;56(June):40–54. Available from: http://dx.doi.org/10.1016/j.cpr.2017.06.003

22. Volker C, van der Lee M, Pet A. Angst voor terugkeer van kanker. GZ-Psychologie. 2011;3:30–8.

23. Cupit-Link M, Syrjala KL, Hashmi SK. Damocles' syndrome revisited: Update on the fear of cancer recurrence in the complex world of today's treatments and survivorship. Hematol Oncol Stem Cell Ther [Internet]. 2018; Available from: https://doi.org/10.1016/j.hemonc.2018.01.005

24. Chen D, Sun W, Liu N, Wang J, Zhao J, Zhang Y, et al. Fear of cancer recurrence: A systematic review of

randomized, controlled trials. Oncol Nurs Forum. 2018;45(6):703–12.

25. Sharpe L, Thewes B, Butow P. Current directions in research and treatment of fear of cancer recurrence. Curr Opin Support Palliat Care. 2017;11(3):191–6.

26. Crane-Okada R, Kiger H, Sugerman F, Uman GC, Shapiro SL, Wyman-McGinty W, et al. Mindful movement program for older breast cancer survivors: A pilot study. Cancer Nurs. 2012;35(4):1–13.

27. Lengacher CA, Shelton MM, Reich RR, Barta MK, Johnson-Mallard V, Moscoso MS, et al. Mindfulness based stress reduction (MBSR(BC)) in breast cancer: Evaluating fear of recurrence (FOR) as a mediator of psychological and physical symptoms in a randomized control trial (RCT). J Behav Med. 2014;37(2):185–95.

28. Lengacher CA, Reich RR, Paterson CL, Ramesar S, Park JY, Alinat C, et al. Examination of broad symptom improvement resulting from mindfulness-based stress reduction in breast cancer survivors: A randomized controlled trial. J Clin Oncol. 2016;34(24):2827–34.

29. 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;

30. Dodds SE, Pace TWW, Bell ML, Fiero M, Negi LT, Raison CL, et al. Feasibility of Cognitively-Based Compassion Training (CBCT) for breast cancer survivors: a randomized, wait list controlled pilot study. Support Care Cancer. 2015;23(12):3599–608.

31. Lichtenthal WG, Corner GW, Slivjak ET, Roberts KE, Li Y, Breitbart W, et al. A pilot randomized controlled trial of cognitive bias modification to reduce fear of breast cancer recurrence. Cancer. 2017;123(8):1424–33.

32. van de Wal M, Thewes B, Gielissen M, Speckens A, Prins J. Efficacy of blended cognitive behavior therapy for high fear of recurrence in breast, prostate, and colorectal cancer survivors: The SWORD study, a randomized controlled trial. J Clin Oncol [Internet]. 2017;35(19):2173–83. Available from: https://www.scopus.com/inward/record.uri?eid=2-s2.0-85021649029&doi=10.1200%2FJCO.2016.70.5301&partnerID=40&md5=f159be668de252f5b14f60fe08799680%0Ahttp://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/658/CN-01395658/frame.html

33. Butow P, Turner J, Gilchrist J, Sharpe L, Smith A Ben, Fardell JE, et al. Randomized trial of ConquerFear:

A novel, theoretically based psychosocial intervention for fear of cancer recurrence. J Clin Oncol. 2017;35(36):4066–77.

34. Otto AK, Szczesny EC, Soriano EC, Laurenceau J, Siegel SD. Supplemental Material for Effects of a Randomized Gratitude Intervention on Death-Related Fear of Recurrence in Breast Cancer Survivors. Heal Psychol [Internet]. 2016;35(12):1320–8. Available from: http://supp.apa.org/psycarticles/supplemental/hea0000400/hea0000400_supp.html

35. Zernicke KA, Campbell TS, Speca M, Mccabe-Ruff K, Flowers S, Carlson LE. A randomized wait-list controlled trial of feasibility and efficacy of an online mindfulness-based cancer recovery program: The eTherapy for cancer applying mindfulness trial. Psychosom Med. 2014;76(4):257–67.

36. Ugalde A, Haynes K, Boltong A, White V, Krishnasamy M, Schofield P, et al. Self-guided interventions for managing psychological distress in people with cancer – A systematic review. Patient Educ Couns. 2017;100(5):846–57.

37. Elaine FH, Peter JB. On-site mental health workers delivering psychological therapy and psychosocial interventions to patients in primary care: effects on the professional practice of primary care providers. Cochrane Database Syst Rev. 2009;(1).

38. Del Giudice ME, Grunfeld E, Harvey BJ, Piliotis E, Verma S. Primary care physicians' views of routine follow-up care of cancer survivors. J Clin Oncol. 2009;27(20):3338–45.

39. Johansen ML, Holtedahl KA, Rudebeck CE. How does the thought of cancer arise in a general practice consultation? Interviews with GPs. Scand J Prim Health Care. 2012;30(3):135–40.

40. Mitchell AJ, Vahabzadeh A, Magruder K. Screening for distress and depression in cancer settings: 10 lessons from 40 years of primary-care research. Psychooncology. 2011;20(6):572–84.

41. Curran GM, Sullivan G, Mendel P, Craske MG, Sherbourne CD, Stein MB, et al. Implementation of the CALM intervention for anxiety disorders: A qualitative study. Implement Sci. 2012;7(1):1–11.

42. Lawrence RA, McLoone JK, Wakefield CE, Cohn RJ. Primary Care Physicians' Perspectives of Their Role in Cancer Care: A Systematic Review. J Gen Intern Med [Internet]. 2016;31(10):1222–36. Available from: http://dx.doi.org/10.1007/s11606-016-3746-7

43. Berrett-Abebe J, Cadet T, Vitello J, Maramaldi P. Developing content for an interprofessional training on fear of cancer recurrence (FCR): Key informant interviews of healthcare professionals, researchers and cancer survivors. J Psychosoc Oncol [Internet]. 2018;0(0):1–15. Available from:

https://doi.org/10.1080/07347332.2018.1443987

44. Berrett-Abebe J, Cadet T, Nekhlyudov L, Vitello J, Maramaldi P. Impact of an Interprofessional Primary Care Training on Fear of Cancer Recurrence on Clinicians' Knowledge, Self-Efficacy, Anticipated Practice Behaviors, and Attitudes Toward Survivorship Care. J Cancer Educ. 2018;1–7.

45. Fidjeland HL, Brekke M, Vistad I. Scandinavian Journal of Primary Health Care General practitioners' attitudes toward follow-up after cancer treatment: A cross-sectional questionnaire study. Scand J Prim Health Care [Internet]. 2015;334(4):223–32. Available from: http://www.tandfonline.com/action/journalInformation?journalCode=ipri20%0Ahttp://dx.doi.org/10.3109/02813432.2015.1118836

46. Nekhlyudov L, O'malley DM, Hudson S V. Integrating primary care providers in the care of cancer survivors: gaps in evidence and future opportunities. Lancet Oncol [Internet]. 2017;18(1):e30–8. Available from: http://dx.doi.org/10.1016/S1470-2045(16)30570-8

47. Adam R, Watson E. The role of primary care in supporting patients living with and beyond cancer. 2018;261–7. Available from: www.supportiveandpalliativecare.com

48. Landelijke verening POH-GGZ. Functie-en competentieprofiel POH-GGZ. 2014;17.

49. Helmondt SJ Van, Lee ML Van Der, Vries J De. Study protocol of the CAREST-trial : a randomised controlled trial on the (cost-) effectiveness of a CBT-based online self- help training for fear of cancer recurrence in women with curatively treated breast cancer. BMC Cancer [Internet]. 2016;1–11. Available from: http://dx.doi.org/10.1186/s12885-016-2562-0

50. van Helmondt SJ, van der Lee ML, de Vries J. Translation and validation of the Dutch version of the Fear of Cancer Recurrence Inventory (FCRI-NL). J Psychosom Res [Internet]. 2017;102(August):21–8. Available from: http://dx.doi.org/10.1016/j.jpsychores.2017.09.001

51. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. 2nd ed. Hoboken: John Wiley & sons; 2004.

52. Assessment MT. Verdiepingsmodule Kostenevaluatie. Available from: https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg

53. Groenwold RHH, Moons KGM, Vandenbroucke JP. Randomized trials with missing outcome data: How to analyze and what to report. Cmaj. 2014;186(15):1153–7.

522

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed in protocol
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page, line 2-4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract, line 45

	2b	All items from the World Health Organization Trial Registration Data Set	Title page, line 2-4, 22 Abstract, line 32, 45, Introduction, line 130-143 Methods, line 158-167, 168-175, 176-187, 188-199, 207-214 Trial status, 342-344 Declarations, line 355
Protocol version	3	Date and version identifier	Footer
Funding	4	Sources and types of financial, material, and other support	Declarations, 355-358
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page, line 6-21
	5b	Name and contact information for the trial sponsor	Declarations, 360
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Declarations, 355-358

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Methods, 255-256
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Introduction, 100-117, 130-143
	6b	Explanation for choice of comparators	Methods, 196-199 Discussion, 330-334
Objectives	7	Specific objectives or hypotheses	Introduction, 130-143
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Methods, 147-148
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Methods, 159-160
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Methods, 158-167

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Methods, 188-195
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	n.a.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Methods, 193-195
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n.a.
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Methods, 207-256
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Methods, 149-157
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Methods, 257-267
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Methods, 169-171
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Methods, 176-187
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Methods, 176-187
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Methods, 177-178, 185
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Methods, 177-178, 255-256, 331-333
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n.a.
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Methods, 226-256
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Methods, 166-167, 206, 255-256

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Methods, 255-256
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Methods, 268-301
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Methods, 268-301
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Methods, 292-293, 296-297
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Methods, 255-256
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n.a.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Methods, 255-256
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Methods, 255-256
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Declarations 345-351

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Declarations, 350
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Methods, 174-175
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Methods, 255-256
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Declarations, 359
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Methods, 255-256
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Methods, 256-256
	31b	Authorship eligibility guidelines and any intended use of professional writers	Declarations, 352-354
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable

Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See attachment
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n.a.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.