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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

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ABSTRACT

Introduction Many successfully treated patients with cancer 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 (GPs) and mental health workers (MHWs) 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 socioeconomic status and randomised. 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 will fill out questionnaires at baseline, after 3 months and after 12 months. Data on healthcare use will be collected from their electronic health records. Qualitative interviews are held at T1 with patients and practitioners in the intervention group.

Ethics and dissemination The Medical Research Ethics Committee (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. Results will be dispersed through peer-reviewed publications and scientific presentations.

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

Strengths and limitations of this study

- A robust, pragmatic trial design reflecting daily care will be implemented in general practices.
- 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 10 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 *et al*. 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 (eg, 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 with 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 psychoeducation, 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 programmes,[26–28] psychoeducation,[29] CBT interventions,[30–32] an intervention based on metacognitive therapy[33] and a gratitude intervention.[34] The Survivors Worries of Recurrent Disease (SWORD) study found that blended treatment with a specialised psychologist and an online FCR programme reduced FCR significantly more than usual care.[32]

Specialised psychological care for cancer is typically provided in hospitals and specialised institutes. Unfortunately, travel distance, limited energy of patients who had cancer 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 of the effectiveness of completely self-guided interventions among patients with cancer 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 patients with cancer 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 long-standing 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 (GPs) want to provide psychosocial support to patients with cancer 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 mental health workers (MHWs), in survivorship care may help to overcome both capacity challenges and the need for improved expertise in primary care.[47]

Aim

The BLANKET (blended care for fear of cancer recurrence, Dutch acronym) study was designed to assess the effectiveness of a primary care delivered, blended care intervention for FCR, in reducing patients' severity of FCR, compared with 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 3 months and 10 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 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 undergo training and to implement it will be recruited. In the Dutch setting, almost all general practices employ MHWs (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 to 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 (eg, 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 specialised 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 socioeconomic 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 (one to three GPs), middle-sized (four to six GPs) or large (seven 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 that focus on normalisation, psychoeducation and self-management.[49] The modules were developed at the Helen Dowling Institute based on CBT, 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 psychoeducation 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 undergo a 1-hour online training. MHWs in the intervention group will undergo 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, normalise fears, apply CBT and discuss what was gained from the modules. Any related questions and issues that come 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 FCR. 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 email with a link to complete the questionnaires online. These links will be sent at baseline (T0), after 3 months, once the intervention in the intervention group is completed (T1) and 1 year after the baseline (T2). Participants who do not respond will 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 will be sent reminders.

Primary outcome

The primary outcome is the severity of FCR 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 the severity of FCR, 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.

Covariates at the patient level include 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 healthcare use, additional care used by patients (eg, alternative care), time since the cancer diagnosis, time since the end of the curative cancer treatment and cancer type.

Covariates at the practice level include the general practice size and the SES status of the practice.

Covariates at the MHW level include the number of years of work experience and the educational background of the MHW.

Data collection

Patients will fill out the 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 *et al*.[50] While for the FCRI it is recommended to use the total score of all subscales to obtain a score for FCR,[7] this multidimensional 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 Four-Dimensional Symptom Questionnaire (4DSQ) will be used to provide data on general distress, depression, anxiety and somatic complaints. The 4DSQ is a Dutch 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 (eg, work), reasons for participating in the study, additional care used that is not in the electronic health records (EHRs), 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 the number of GP visits related to cancer, FCR and neither, the number of sessions with the MHW, and the 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 hypervigilance. 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 semistructured 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; and 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 an SD of 7 on the FCRI-SF. The

difference in means was based on expert opinion. The SD was based on the FCRI-NL validation study by van Helmondt *et al*,[50] which found an SD of 7 on the SF.[50] Using an alpha of 0.05 and a 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 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 SF of the FCRI-NL scale between the intervention and control groups 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 use 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 versus psychological—will also be explored. The healthcare uptake in the control group between T1 and T2 will also be compared with 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 and T1, T1 and T2, and T0 and T2, whereby the period between T0 and 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 use, according to the method of the *Guidelines for Carrying Out Economic Evaluations in Healthcare*.[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 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 the 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. Semistructured 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 the desired content and appearance, for example, 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 with 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 choose 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 choose 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 choose 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 started in October 2018. The first patient was included on 15 April 2019. Final results are expected in 2020.

Contributors All authors participated in the design of the study. YLL wrote the draft of the manuscript. MLvdL, CWH and NJdW improved the manuscript. All authors read and approved the final manuscript.

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