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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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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
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Manuscripts

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7 2 **Study protocol of the BLANKET-trial: a cluster randomised**
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10 3 **controlled trial on the (cost-) effectiveness of a primary care**
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13 4 **intervention for fear of cancer recurrence in cancer survivors**
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18
19 6 **Yvonne L Luigjes-Huizer**

20
21 7 Scientific Research Department, Helen Dowling Instituut, Bilthoven, The Netherlands and
22
23 8 Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht,
24
25
26 9 Utrecht University, Utrecht, the Netherlands

27
28
29 10 y.l.huizer@umcutrecht.nl

30
31 11 **Marije L van der Lee**

32
33 12 Scientific Research Department, Helen Dowling Instituut, Bilthoven, The Netherlands

34
35
36 13 mvanderlee@hdi.nl

37
38 14 **Niek J de Wit**

39
40 15 Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht,
41
42
43 16 Utrecht University, Utrecht, the Netherlands

44
45
46 17 n.j.dewit@umcutrecht.nl

47
48 18 **Charles W Helsper**

49
50 19 Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht,

51
52
53 20 Utrecht University, Utrecht, the Netherlands

54
55
56 21 c.w.helsper-2@umcutrecht.nl

57
58 22 Corresponding author: Yvonne Luigjes yLuigjes@hdi.nl

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60 23 Word count: 3746 words

24 **Abstract**

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

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

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

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

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

48 **Strengths and limitations of this study**

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

- 1
2
3 50 • Quantitative and qualitative data are combined to provide comprehensive results.
4
5 51 • The intervention and trial were designed in close cooperation with patients and healthcare
6
7 52 workers.
8
9
10 53 • A cluster randomised design, randomising at practice level, was required, since practitioners who
11
12 54 have been trained on the intervention are unlikely to be able to provide usual care in the same
13
14 55 way as before training.
15
16 56 • Patients are actively invited to participate in the study, making them less representative of the
17
18 57 patients who currently seek care for FCR.
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23 59

60 **Introduction**

61 Advances in the medical field have caused the number of cancer survivors to rise steadily in the past
62 decades (1). With an increasing number of survivors, there is also an increasing need for survivorship
63 care (2). A systematic review showed that fatigue, depression and anxiety are commonly reported in
64 the ten years after primary cancer treatment (3). Fear of cancer recurrence (FCR) is a more prevalent
65 concern than any physical issue (2). In a study about unmet needs after breast cancer, FCR was the
66 most reported need in all age groups (38.2%), despite a relatively good prognosis (4).
67 FCR has been defined as “fear, worry, or concern relating to the possibility that cancer will come back
68 or progress” (5). A review by Simard (2013) found that an average of 73% of cancer survivors
69 experience FCR, 49% experience a moderate to high level of FCR and 7% experience a high level of
70 FCR (6). FCR is a multidimensional construct, as demonstrated by the subscales of the Fear of Cancer
71 Recurrence Inventory (FCRI): triggers, severity, psychological distress, coping strategies, functioning
72 impairments, insight and reassurance (7). In a 2-day colloquium with a group of experts and patient
73 advocates, five preliminary categories of potential characteristics of clinical FCR were identified using
74 the Delphi method. These are: preoccupation with cancer return or progression, unhelpful coping

1
2
3 75 strategies, impairments in daily functioning, great level of distress and limited ability to make plans
4
5 76 (5).

6
7 77 Many studies have explored factors that correlate with FCR development, with mixed results. The
8
9 78 evidence for correlations between FCR and age, gender and physical symptoms is strongest, whereby
10
11 79 younger patients, female patients and patients with more symptoms experience more FCR (6). In
12
13 80 contrast, social support, optimism, having detailed information and being conscientious correlate with
14
15 81 having less FCR (6,9,10). FCR can persist for many years after the end of cancer treatment (6,11). There
16
17 82 are also triggers that can temporarily increase FCR. These include: medical appointments, having
18
19 83 unexplainable symptoms, hearing about cancer in the media or hearing about the death of a fellow
20
21 84 patient (12).

22
23
24
25 85 The impact of FCR varies. Having some FCR can be protective, since it may lead to treatment
26
27 86 compliance and healthy lifestyle adaptations. However, severe FCR can significantly decrease quality
28
29 87 of life (13). Maladaptive coping styles include overuse of primary care for common acute symptoms,
30
31 88 but also avoidance of social and healthcare appointments. On average, healthcare uptake is increased
32
33 89 for people with high FCR (15). Cancer survivors with high consultation rates due to seeking reassurance
34
35 90 can inadvertently augment their fears and cause unnecessary healthcare costs (14). Yet, people who
36
37 91 respond to their fear by avoiding healthcare, risk delayed diagnosis of cancer recurrence.

38
39
40
41 92 A Danish study found that patients tended to discuss social or psychological aspects of cancer,
42
43 93 including fear of relapse, more with family and friends than with their GP, because they did not think
44
45 94 it was the GP's mandate to address the concerns (18). In a Dutch study, 75% of patients' physical
46
47 95 problems after having received a cancer diagnosis were discussed with GPs, compared to only one
48
49 96 third of emotional and social problems (17). When the need for psychosocial care is recognised, this
50
51 97 has a positive effect on quality of life, appreciation of care and communication with care providers
52
53 98 (19). Therefore, it seems of added value if GPs assess the presence of FCR when patients come in for
54
55 99 consultations, and refer to additional care when needed (20).

1
2
3 100 Treating FCR is different from treating other anxiety disorders, because most treatments for anxiety
4
5 101 are based on the presumption that patients incorrectly perceive something as a threat. Yet, in the case
6
7 102 of FCR, the fear is not irrational, since the threat is actual and significant (21). Currently, there are
8
9
10 103 different treatment options for FCR, which can be applied in a stepped care approach. The first level
11
12 104 involves psycho-education, normalisation and self-management. Next, cognitive behavioural therapy,
13
14 105 therapies focusing on acceptance (22) and pharmacological treatment (23) can be applied. In recent
15
16 106 years, several trials have shown the effectiveness of new FCR interventions (24,25), including
17
18 107 mindfulness programs (26–28), psychoeducation (29), cognitive behavioural therapy interventions
19
20 108 (30–32) and a gratitude intervention (33). Specialised psychological care for cancer is provided in
21
22
23 109 hospitals and institutes for psycho-oncology.

24
25 110 Unfortunately, travel distance, limited energy of ex-cancer patients and waiting lists for specialised
26
27 111 centres counteract accessibility (34). Also, most cancer survivors do not require intensive specialised
28
29 112 psychotherapy, but rather accessible psychological care. Online treatment may be a suitable
30
31 113 alternative. In addition to being easily accessible, it also allows patients to obtain care at moments
32
33 114 when they feel fit enough and for a duration that they can manage. However, a review on self-guided
34
35 115 online interventions specifically for cancer patients with psychological distress concludes that evidence
36
37 116 for the effectiveness of completely self-guided interventions is lacking, and that some level of therapist
38
39 117 involvement ('blended care') can help encourage engagement and promote adherence (36).

40
41 118 Concurrently, cancer care and survivorship care are increasingly being provided in primary care,
42
43 119 because of patient preference, increasing numbers of cancer patients and rising healthcare costs (1).
44
45 120 Primary care is comprehensive, longitudinal and integrated, provided by teams of different
46
47 121 professionals (1), increasingly including mental health professionals (37). Primary care providers know
48
49 122 their patients and their social and medical history and generally have a longstanding relation with the
50
51 123 patient (38,39). Patients view primary care staff as trusted professionals (40) and prefer coming to
52
53 124 primary care rather than specialised care for anxiety issues, because of both practical reasons and
54
55 125 stigma (41). General practitioners want to provide psychosocial support to cancer patients and feel
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1
2
3 126 they are well-positioned (42,43), but they face capacity challenges (44,45) and report a need for
4
5 127 training on cancer survivorship (46,47), in particular on treating psychological problems (44). Involving
6
7 128 and training auxiliary staff, such as primary care MHWs, in survivorship care, may help to overcome
8
9 129 both capacity challenges and the need for improved expertise in primary care (47).

12 130 **Aim**

13
14 131 The BLANKET study was designed to assess the effectiveness of a primary care delivered, blended care
15
16 132 intervention for fear of cancer recurrence, in reducing patients' severity of FCR, compared to usual
17
18 133 care. The target group for this intervention is patients with moderate FCR, who want FCR support.

19
20
21 134 We hypothesise that

- 22
23 135 1. the current FCR intervention will reduce FCR severity,
- 24
25 136 2. the current FCR intervention will reduce FCR related distress,
- 26
27 137 3. healthcare consumption of patients who have received the current FCR intervention will be
28
29 138 reduced.
- 30
31 139 4. the primary care FCR intervention will be considered desirable and of added value by patients
32
33 140 and practitioners.

34
35
36 141 The primary outcome is FCR severity. Secondary outcomes are FCR-related distress, FCR-related
37
38 142 healthcare use, FCR-related health costs, and satisfaction of patients and practitioners with support
39
40 143 provided by trained MHWs and GPs.

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42
43 144

44 45 145 **Methods**

46 47 146 **Study design**

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49
50 147 The BLANKET study is a two-armed cluster randomised clinical trial, in which the general practice is
51
52 148 the unit of randomisation.

53 54 149 **Study procedure**

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56
57 150 Participating practices will identify all of their patients who have successfully completed curative
58
59 151 cancer treatment between three months and ten years ago, and will send them an invitation letter
60

1
2
3 152 by mail. Patients are asked to participate if they desire support for FCR. After providing informed
4
5 153 consent, patients are asked to fill out an online baseline questionnaire. Patients also fill out
6
7 154 questionnaires after 3 months and after 12 months. At the end of the first questionnaire, they are
8
9
10 155 urged to make an appointment with their GP about support for FCR. During this consultation, the GPs
11
12 156 in the intervention group refer the patients to the MHW for the intervention, while GPs in the control
13
14 157 group provide usual care.

16 158 **Eligibility**

19 159 Clusters of collaborating GPs and MHWs in the Netherlands who are willing to receive training and to
20
21 160 implement it will be recruited. In the Dutch setting, almost all general practices employ mental health
22
23 161 workers (MHW, in Dutch: POH-GGZ), who support the general practitioner in providing care for
24
25 162 patients' psychological, psychosomatic and psychosocial issues (48).

27 163 Patients are eligible if they: (1) are registered at a general practice that is participating in the study,
28
29 164 (2) are 18 years or older, (3) have finished successful curative cancer treatment between 3 months
30
31 165 and 10 years ago, (4) desire support for FCR, and (5) have sufficient Dutch reading and writing skills
32
33 166 to receive the intervention and complete the questionnaires. If patients have a cancer recurrence
34
35 167 during the study, no more data will be collected.

38 168 **Recruitment**

41 169 The aim is to include 244 patients during 1,5 years. Patients are recruited using an invitation letter
42
43 170 sent by patients' own GPs. All of the patients of participating practices, who are 18 years or older and
44
45 171 have finished curative cancer treatment between 3 months and 10 years ago will receive the letter.
46
47 172 To spread the workload for the practitioners, invitation will be done in rounds, starting with patients
48
49 173 who most recently finished curative cancer treatment. In the invitation letter, patients who desire
50
51 174 support for FCR are asked to participate in the study. Patients who are willing to participate, provide
52
53 175 written informed consent to the researcher.

56 176 **Randomisation**

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1
2
3 177 Randomisation is done at practice level. GPs and MHWs will know in which group they have been
4
5 178 placed. Patients will not. Clusters are formed, in which all GPs and MHWs working in the same
6
7 179 building are grouped together, to decrease the risk of contamination. Minimisation is applied for size
8
9
10 180 of the practice and the socio-economic status (SES) of the neighbourhood they are located in, to
11
12 181 ensure balance between study arms (patients and professionals). For practice size, there are three
13
14 182 categories: small (1-3 GPs), middle-sized (4-6 GPs) or large (7 GPs or more). For SES, the list of
15
16 183 disadvantaged areas by postal code made by the Dutch government for general practices is used.
17
18 184 Practices will be assigned to the intervention or the control group, using the number generator at
19
20 185 Research Randomizer (randomizer.org). An external data manager will generate the numbers.
21
22
23 186 Practices are randomised in two blocks. The inclusion speed from the first block will help to confirm
24
25 187 how many more practices are needed for the second block.
26
27

28 188 **Intervention**

29
30 189 GPs and MHWs in the intervention group will provide an intervention specifically designed for FCR,
31
32 190 which focuses on normalisation, psychoeducation and self-management (49). This intervention was
33
34 191 developed at the Helen Dowling Institute based on cognitive behavioural therapy, clinical experience
35
36 192 and input from patients, and is currently being used by specialised psychologists for blended
37
38 193 treatment. The intervention is available online, and includes five contact moments with the MHW. GPs
39
40 194 and MHWs in the intervention group will receive training on the implementation of the intervention
41
42 195 at the beginning of the study. GPs and MHWs in the control group will provide usual care.
43
44

45 196 **Usual care**

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47
48 197 Patients in the control group receive usual care. In the literature, little is known about the usual care
49
50 198 that GPs provide for fear of cancer recurrence. Therefore, usual care will be mapped in this study, in
51
52 199 relation to the severity of FCR.
53

54 200 **Outcomes**

55
56
57 201 Participants will provide data using online self-report questionnaires hosted by ResearchOnline.com.
58
59 202 Participants will receive an invitational e-mail with a link to complete the questionnaires online.
60

1
2
3 203 These links will be sent at baseline (T0), after three months, once the intervention in the intervention
4
5 204 group is completed (T1), and one year after the baseline (T2). Participants who do not respond
6
7 205 receive reminders. If participants prefer to fill out the questionnaires on paper, this will be arranged.
8
9
10 206 If patients do not fill out the questionnaires, they are sent reminders.

11 207 **Primary outcome**

12
13
14 208 The primary outcome is the severity of fear of cancer recurrence after 3 months, comparing the FCR
15
16 209 intervention with usual care. To measure this, the severity scale (SF) of the Dutch version of the Fear
17
18 210 of Cancer Recurrence Inventory (FCRI-NL) will be used.

19 211 **Secondary outcomes**

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21
22
23 212 The secondary outcomes are the development from baseline to T1 to T2 of severity of fear of cancer
24
25 213 recurrence, FCR-related distress, FCR-related healthcare use and FCR-related health costs; and the
26
27 214 desirability and added value of the intervention.

28 215 **Covariates**

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32 216 If the intervention is found to be effective, relations between the outcomes and the following
33
34 217 variables will be explored, to identify groups of patients for whom the intervention might be more or
35
36 218 less effective.

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39 219 At the patient level: age, gender, level of education, coping style, severity of anxiety and depression,
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41 220 somatic complaints, severity of FCR at the start of the study, FCR related distress at the start of the
42
43 221 study, psychiatric history, previous health care use, additional care used by patients (e.g. alternative
44
45 222 care), time since the cancer diagnosis, time since the end of the curative cancer treatment, cancer
46
47 223 type.

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49
50 224 At the practice level: general practice size and SES status of practice.

51
52 225 At the MHW level: number of years of work experience and educational background of the MHW.

53 226 **Data collection**

54
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56
57 227 The Dutch version of the fear of cancer recurrence inventory (FCRI-NL) will be used to measure FCR
58
59 228 severity, distress and coping. It contains 43 items, measuring seven subscales. The FCRI was
60

1
2
3 229 translated into Dutch and validated by van Helmond, van der Lee & de Vries (50). While for the FCRI,
4
5 230 it is recommended to use the total score of all subscales to obtain a score for FCR (7), this multi-
6
7 231 dimensional structure was not replicated in the validation of the FCRI-NL. Instead, the individual
8
9 232 subscales provide important information and are recommended to be used separately (50).
10
11
12 233 The 4DKL will be used to provide data on general distress, depression, anxiety and somatic
13
14 234 complaints. The 4DKL is a 50-item questionnaire that measures four dimensions: distress, depression,
15
16 235 anxiety and somatic complaints. The list is already used in some GP practices and is therefore
17
18 236 practically applicable.
19
20
21 237 Patients will also be surveyed about their educational level, current daily activity (e.g. work), reasons
22
23 238 for participating in the study, additional care used that is not in the EHR including alternative care,
24
25 239 and other factors that they think might have influenced their FCR.
26
27
28 240 In order to collect data on patients' cancer type, treatment and healthcare use, data will be obtained
29
30 241 from patients' electronic health records (EHR). Data will be collected on number of GP visits related
31
32 242 to cancer, FCR and neither, number of sessions with MHW and number of referrals for physical care
33
34 243 and for psychological care. At baseline, data on healthcare use per year since the end of curative
35
36 244 cancer treatment will also be obtained, to exploratively compare usual care in our control group with
37
38 245 usual care in the years prior to the study. FCR-related health costs will be calculated based on the
39
40 246 healthcare use.
41
42
43 247 The desirability and added value of the intervention will be evaluated using custom-made, non-
44
45 248 validated questionnaires and semi-structured interviews with a selection of patients and
46
47 249 practitioners at T1. The interviews will explore which aspects of the support are effective,
48
49 250 unnecessary, practical or pleasant and why. They will also explore whether the GP and MHW are
50
51 251 considered to be the right practitioners to provide this type of care and what changes with regard to
52
53 252 FCR are most desirable and sought after. Varied groups will be purposively sampled. For patients, in
54
55 253 terms of age, time since diagnosis, severity of FCR at T0, and severity of FCR at T1; for practitioners in
56
57 254 terms of professional background and years of work experience.
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1
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3 255 Additional information about data collection, data management, monitoring and dissemination of
4
5 256 results can be found in the study protocol.

7 257 **Sample size calculation**

9
10 258 When determining the required group size for finding a relevant difference between the groups, we
11
12 259 used a difference in means of 3 and a standard deviation of 7 on the FCRI severity scale. These
13
14 260 numbers were based on the FCRI-NL validation study by van Helmond et al. (2017) (50). Using an
15
16 261 alpha of 0.05 and beta of 0.8, we calculated a required sample size of 86 participants in both groups
17
18 262 for sufficient power. Because multiple patients are treated by the same MHW, there might be a
19
20 263 cluster effect. Based on an average of 15 inclusions per MHW and an intraclass correlation coefficient
21
22 264 (ICC) of 0.01, an inflation factor of 1.14 has been applied. This leads to a group size of 98 patients per
23
24 265 arm. Because the clusters (number of patients per MHW will probably not all have the same size, an
25
26 266 inflation factor of 10% is applied, leading to a group size of 108. We also assume a dropout of 12% of
27
28 267 patients. That is why we aim to include 122 patients in each group.

32 268 **Statistical analysis**

34 269 The primary outcome will be expressed as difference in the mean (with 95% CI and p-value) of the
35
36 270 severity scale of the FCRI-NL scale between intervention and control group at T1.

38 271 This will be analysed with a linear mixed model. A random intercept will be included to correct for
39
40 272 inclusion per MHW. We will include residual covariances in order to correct for repeated
41
42 273 measurement in each patient.

45 274 The analyses will be conducted in two steps. First, an analysis will be performed with time, treatment
46
47 275 and a time by treatment interaction. Second, a correction for baseline measurement of the outcome
48
49 276 will be added to the first model.

52 277 The validity of the models will be assessed with residual analyses (51).

54 278 A similar approach will be used to analyse secondary outcomes and covariates. Where applicable, a
55
56 279 generalised linear model will be used to analyse dichotomous and count outcomes (for binomial and
57
58 280 Poisson distributions respectively).

1
2
3 281 Healthcare utilisation is analysed using multilevel analyses. The number of visits to the GP between
4
5 282 T1 and T2 is compared between the intervention group and the control group. Shifts in type of visits
6
7 283 – physical vs. psychological – will also be explored. The healthcare uptake in the control group
8
9 284 between T1 and T2 will also be compared to the period before the baseline measurement to assess
10
11 285 whether healthcare uptake has changed since participating in the study.

12
13
14 286 The costs of healthcare are compared between the control group and the intervention group for the
15
16 287 period between T0-T1, T1-T2 and T0-T2. Healthcare costs are calculated based on healthcare
17
18 288 utilisation, according to the method of the *Guidelines for carrying out economic evaluations in health*
19
20 289 *care* (52).

21
22
23 290 For the outcomes for which the intervention is found to be effective, the effect of the covariates on
24
25 291 the outcomes will be explored.

26
27 292 First, intention to treat (ITT) analyses will be done. Then, per-protocol analyses will be carried out to
28
29 293 estimate the effectiveness of the intervention if executed per protocol. During the analyses, the
30
31 294 assessor will be blinded about the groups.

32
33 295 The validity of study results may be challenged by missing values, either at baseline or missing
34
35 296 outcomes at follow-up. Multiple imputation will be used to address missing values at baseline for
36
37 297 relevant variables. For missing outcomes, correction for relevant prognostic factors will be
38
39 298 considered to ensure the validity of the results (53).

40
41 299 Patient and practitioner satisfaction are measured qualitatively. Semi-structured interviews are held.
42
43 300 These are transcribed and then coded. Important themes will be identified, using the data as the
44
45 301 starting point.

302 **Patient and public involvement**

303
304 303 When developing the online intervention, patient provided input on the desired content and the
305
306 304 appearance of the online intervention, e.g. their preference for texts to be short. Once the
307
308 305 intervention was developed, patients used it and shared their experiences, and the intervention was
309
310 306 further adapted based on this, e.g. adding reminder e-mails.

1
2
3 307 When developing the study, patients provided input on the general idea. They also provided
4
5 308 feedback on the recruitment process and in particular on the invitation letter to patients. Based on
6
7 309 their input, the study and the letter were adapted.
8
9

10 310 Discussion

11 311 With an increased number of cancer survivors, there is an increased need for survivorship care.
12
13 312 Provision of psychological care for FCR in primary care may improve access and reduce the pressure
14
15 313 on specialised institutions. In the current study, the effectiveness of a primary care delivered FCR
16
17 314 intervention will be compared to usual care. An evaluation of healthcare consumption and costs is
18
19 315 included in the study to assess whether this can also decrease healthcare uptake and costs of
20
21 316 healthcare. To our knowledge, this is the first trial assessing the effectiveness of an FCR intervention
22
23 317 implemented in primary care. In addition, it is one of few implementation studies on FCR
24
25 318 interventions.
26
27
28

29 319 Heterogeneity of usual care

30 320 Furthermore, we have chosen to compare this intervention with usual care. Since no clear guidelines
31
32 321 are available for general practices for FCR, usual care may be quite diverse. Yet, since we want to
33
34 322 know whether this intervention is more effective than what is currently being offered, we chose to
35
36 323 compare with usual care, despite its heterogeneity, and to register usual care during the study.
37
38
39

40 324 Recruitment

41 325 Because prior research shows that patients often do not mention FCR to their GP, we chose to
42
43 326 actively invite patients who desire support for FCR to participate in the study. The disadvantage of
44
45 327 this choice is that we are activating our participants, making them less representative of the patients
46
47 328 who currently seek care for FCR. We made this choice, because we want to know whether this
48
49 329 intervention can help patients with FCR if they choose to seek care.
50
51
52

53 330 Usual care

54 331 We recognise that the usual care measured in this study might not fully reflect actual usual care,
55
56 332 since we have activated the patient population and made the general practices more aware of this
57
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1
2
3 333 issue. To assess the effect of this activation, we compare the healthcare use in the control group with
4
5 334 retrospective healthcare use.

6
7 335 Randomisation level

8
9
10 336 We chose to randomise practices and not patients to prevent contamination. Practitioners who have
11
12 337 been trained will have increased knowledge and awareness, and will no longer be able to provide
13
14 338 usual care the way they did before training. Also, patients at the same practice might discuss the
15
16 339 intervention they receive with one another and notice the differences. Patients are unaware of the
17
18 340 randomisation, to prevent patients in the control group from being disappointed and less motivated
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21 341 if they know that they are not receiving the intervention that is being studied.

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23 342 **Trial status**

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25 343 Invitation of primary care practices has started in October 2018. The first patient was included on
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27 344 April 15, 2019. Final results are expected in 2020.
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3 345 **Declarations**
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- 5 346 1. Ethics approval and consent to participate: The Medical Research Ethics Committee Utrecht
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7 347 (METC Utrecht) has reviewed the study in accordance with the Dutch Medical Research Involving
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9 348 Human Subjects Act (WMO) and other applicable Dutch and European regulations. Based on the
10
11 349 requirements of the WMO, the METC Utrecht has issued an approval of the above-mentioned
12
13 350 study. Any protocol amendments will be communicated to all relevant parties. Written consent is
14
15 351 obtained from study participants.
16
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18 352 2. Author contributions: All authors participated in the design of the study. YL wrote the draft
19
20 353 manuscript. ML, CH and NW improved the manuscript. All authors read and approved the final
21
22 354 manuscript.
23
24
25 355 3. Funding: This work was supported by the Dutch Cancer Society (KWF) grant number 10936. KWF
26
27 356 is not involved in study design, collection, management, analysis, and interpretation of data,
28
29 357 writing of the report, the decision to submit the report for publication, nor does it have authority
30
31 358 over the publications.
32
33
34 359 4. Competing interests: The authors declare that they have no competing interests.
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36 360 5. Sponsor: Helen Dowling Institute, Professor Bronkhorstlaan 20, 3723 MB Bilthoven
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39 361 6. Acknowledgements: Not applicable.
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362 **References**

- 363 1. Rubin G, Berendsen A, Crawford SM, Dommett R, Earle C, Emery J, et al. The expanding role of primary
364 care in cancer control. *Lancet Oncol.* 2015;16(12):1231–72.
- 365 2. Ness S, Kokal J, Fee-Schroeder K, Novotny P, Satele D, Barton D. Concerns Across the Survivorship
366 Trajectory: Results From a Survey of Cancer Survivors. *Oncol Nurs Forum.* 2013;40(1):35–42.
- 367 3. Harrington CB, Hansen JA, Moskowitz M, Todd BL, Feuerstein M. It's Not over When it's Over: Long-
368 Term Symptoms in Cancer Survivors—A Systematic Review. *Int J Psychiatry Med* [Internet].
369 2010;40(2):163–81. Available from: <http://journals.sagepub.com/doi/10.2190/PM.40.2.c>
- 370 4. Brennan ME, Butow P, Spillane AJ, Boyle F. Patient-reported quality of life, unmet needs and care
371 coordination outcomes: Moving toward targeted breast cancer survivorship care planning. *Asia Pac J*
372 *Clin Oncol.* 2016;12(2):e323–31.
- 373 5. Lebel S, Ozakinci G, Humphris G, Mutsaers B, Thewes B, Prins J, et al. From normal response to clinical
374 problem: definition and clinical features of fear of cancer recurrence. *Support Care Cancer* [Internet].
375 2016;24(8):3265–8. Available from: <http://dx.doi.org/10.1007/s00520-016-3272-5>
- 376 6. Simard S, Thewes B, Humphris G, Dixon M, Hayden C, Mireskandari S, et al. Fear of cancer recurrence in
377 adult cancer survivors: a systematic review of quantitative studies. *J Cancer Surviv.* 2013;7:300–22.
- 378 7. Simard S, Savard J. Fear of Cancer Recurrence Inventory: Development and initial validation of a
379 multidimensional measure of fear of cancer recurrence. *Support Care Cancer.* 2009;17(3):241–51.
- 380 8. Mutsaers B, Jones G, Rutkowski N, Tomei C, Séguin Leclair C, Petricone-Westwood D, et al. When fear
381 of cancer recurrence becomes a clinical issue: a qualitative analysis of features associated with clinical
382 fear of cancer recurrence. *Support Care Cancer* [Internet]. 2016;24(10):4207–18. Available from:
383 <http://dx.doi.org/10.1007/s00520-016-3248-5>
- 384 9. Hedman C, Strang P, Djärv T, Widberg I, Lundgren CI. Anxiety and Fear of Recurrence Despite a Good
385 Prognosis: An Interview Study with Differentiated Thyroid Cancer Patients. *Thyroid* [Internet].
386 2017;27(11):1417–23. Available from: <http://online.liebertpub.com/doi/10.1089/thy.2017.0346>
- 387 10. Liao KYH, Yeung NCY, Wong CCY, Warmoth K, Lu Q. Fear of cancer recurrence and physical well-being
388 among Chinese cancer survivors: the role of conscientiousness, positive reappraisal and hopelessness.
389 *Support Care Cancer.* 2017;25(4):1141–9.
- 390 11. Simard S, Savard J, Ivers H. Fear of cancer recurrence: Specific profiles and nature of intrusive thoughts.

- 1
2
3 391 J Cancer Surviv. 2010;
4
5 392 12. Gil KM, Mishel MH, Belyea M, Germino B, Porter LS, Carlton LaNey I, et al. Triggers of Uncertainty
6
7 393 About Recurrence and Long-Term Treatment Side Effects in Older African American and Caucasian
8
9 394 Breast Cancer Survivors. *Oncol Nurs Forum*. 2004;31(3):633–9.
10
11 395 13. Simonelli LE, Siegel SD, Duffy NM. Fear of cancer recurrence: a theoretical review and its relevance for
12
13 396 clinical presentation and management. *Psychooncology*. 2017;26(10):1444–54.
14
15 397 14. Butow P, Sharpe L, Thewes B, Turner J, Gilchrist J, Beith J. Fear of Cancer Recurrence: A Practical Guide
16
17 398 for Clinicians. *Oncol J*. 2018;32(1):32–8.
18
19 399 15. Champagne A, Ivers H, Savard J. Utilization of Health Care Services in Cancer Patients with Elevated
20
21 400 Fear of Cancer Recurrence. *Psychooncology* [Internet]. 2018;(March):1–7. Available from:
22
23 401 <http://www.ncbi.nlm.nih.gov/pubmed/29719072><http://doi.wiley.com/10.1002/pon.4748>
24
25 402 16. Heins MJ, Korevaar JC, Rijken PM, Schellevis FG. For which health problems do cancer survivors visit
26
27 403 their General Practitioner? *Eur J Cancer* [Internet]. 2013;49(1):211–8. Available from:
28
29 404 <http://dx.doi.org/10.1016/j.ejca.2012.07.011>
30
31 405 17. NIVEL. Afstemming van zorg tussen huisarts en specialist bij kanker kan beter [Internet]. 2013 [cited
32
33 406 2018 May 22]. Available from: [https://www.nivel.nl/nl/nieuws/afstemming-van-zorg-tussen-huisarts-](https://www.nivel.nl/nl/nieuws/afstemming-van-zorg-tussen-huisarts-en-specialist-bij-kanker-kan-beter)
34
35 407 [en-specialist-bij-kanker-kan-beter](https://www.nivel.nl/nl/nieuws/afstemming-van-zorg-tussen-huisarts-en-specialist-bij-kanker-kan-beter)
36
37 408 18. Mikkelsen T, Sondergaard J, Sokolowski I, Jensen A, Olesen F. Cancer survivors' rehabilitation needs in a
38
39 409 primary health care context. *Fam Pract*. 2009;26(3):221–30.
40
41 410 19. NHG. NHG-standpunt Oncologische zorg in de huisartsenpraktijk. 2014.
42
43 411 20. Fann JR, Ell K, Sharpe M. Integrating psychosocial care into cancer services. *J Clin Oncol*.
44
45 412 2012;30(11):1178–86.
46
47 413 21. Curran L, Sharpe L, Butow P. Anxiety in the context of cancer: A systematic review and development of
48
49 414 an integrated model. *Clin Psychol Rev* [Internet]. 2017;56(June):40–54. Available from:
50
51 415 <http://dx.doi.org/10.1016/j.cpr.2017.06.003>
52
53 416 22. Volker C, van der Lee M, Pet A. Angst voor terugkeer van kanker. *GZ-Psychologie*. 2011;3:30–8.
54
55 417 23. Cupit-Link M, Syrjala KL, Hashmi SK. Damocles' syndrome revisited: Update on the fear of cancer
56
57 418 recurrence in the complex world of today's treatments and survivorship. *Hematol Oncol Stem Cell Ther*
58
59 419 [Internet]. 2018; Available from: <https://doi.org/10.1016/j.hemonc.2018.01.005>

- 1
2
3 420 24. Chen D, Sun W, Liu N, Wang J, Zhao J, Zhang Y, et al. Fear of cancer recurrence: A systematic review of
4
5 421 randomized, controlled trials. *Oncol Nurs Forum*. 2018;45(6):703–12.
6
7 422 25. Sharpe L, Thewes B, Butow P. Current directions in research and treatment of fear of cancer
8
9 423 recurrence. *Curr Opin Support Palliat Care*. 2017;11(3):191–6.
10
11 424 26. Crane-Okada R, Kiger H, Sugerman F, Uman GC, Shapiro SL, Wyman-McGinty W, et al. Mindful
12
13 425 movement program for older breast cancer survivors: A pilot study. *Cancer Nurs*. 2012;35(4):1–13.
14
15 426 27. Lengacher CA, Shelton MM, Reich RR, Barta MK, Johnson-Mallard V, Moscoso MS, et al. Mindfulness
16
17 427 based stress reduction (MBSR(BC)) in breast cancer: Evaluating fear of recurrence (FOR) as a mediator
18
19 428 of psychological and physical symptoms in a randomized control trial (RCT). *J Behav Med*.
20
21 429 2014;37(2):185–95.
22
23 430 28. Lengacher CA, Reich RR, Paterson CL, Ramesar S, Park JY, Alinat C, et al. Examination of broad symptom
24
25 431 improvement resulting from mindfulness-based stress reduction in breast cancer survivors: A
26
27 432 randomized controlled trial. *J Clin Oncol*. 2016;34(24):2827–34.
28
29 433 29. Dieng M, Butow PN, Costa DSJ, Morton RL, Menzies SW, Mireskandari S, et al. Psychoeducational
30
31 434 Intervention to Reduce Fear of Cancer Recurrence in People at High Risk of Developing Another Primary
32
33 435 Melanoma: Results of a Randomized Controlled Trial. *J Clin Oncol*. 2016;
34
35 436 30. Dodds SE, Pace TWW, Bell ML, Fiero M, Negi LT, Raison CL, et al. Feasibility of Cognitively-Based
36
37 437 Compassion Training (CBCT) for breast cancer survivors: a randomized, wait list controlled pilot study.
38
39 438 *Support Care Cancer*. 2015;23(12):3599–608.
40
41 439 31. Lichtenthal WG, Corner GW, Slivjak ET, Roberts KE, Li Y, Breitbart W, et al. A pilot randomized
42
43 440 controlled trial of cognitive bias modification to reduce fear of breast cancer recurrence. *Cancer*.
44
45 441 2017;123(8):1424–33.
46
47 442 32. Wal M, Thewes B, Gielissen M, Speckens A, Prins J, Van De Wal M, et al. Efficacy of blended cognitive
48
49 443 behavior therapy for high fear of recurrence in breast, prostate, and colorectal cancer survivors: The
50
51 444 SWORD study, a randomized controlled trial. *J Clin Oncol [Internet]*. 2017;35(19):2173–83. Available
52
53 445 from: [https://www.scopus.com/inward/record.uri?eid=2-s2.0-](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)
54
55 446 [85021649029&doi=10.1200%2FJCO.2016.70.5301&partnerID=40&md5=f159be668de252f5b14f60fe08](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)
56
57 447 [799680%0Ahttp://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/658/CN-](http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/658/CN-01395658/frame.html)
58
59 448 [01395658/frame.html](http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/658/CN-01395658/frame.html)
60

- 1
2
3 449 33. Otto AK, Szczesny EC, Soriano EC, Laurenceau J, Siegel SD. Supplemental Material for Effects of a
4
5 450 Randomized Gratitude Intervention on Death-Related Fear of Recurrence in Breast Cancer Survivors.
6
7 451 Heal Psychol [Internet]. 2016;35(12):1320–8. Available from:
8
9 452 http://supp.apa.org/psycarticles/supplemental/hea0000400/hea0000400_supp.html
10
11 453 34. Zernicke KA, Campbell TS, Specia M, McCabe-Ruff K, Flowers S, Carlson LE. A randomized wait-list
12
13 454 controlled trial of feasibility and efficacy of an online mindfulness-based cancer recovery program: The
14
15 455 eTherapy for cancer applying mindfulness trial. *Psychosom Med*. 2014;76(4):257–67.
16
17 456 35. Carlbring P, Andersson G, Cuijpers P, Riper H, Hedman-Lagerlöf E. Internet-based vs. face-to-face
18
19 457 cognitive behavior therapy for psychiatric and somatic disorders: an updated systematic review and
20
21 458 meta-analysis. *Cogn Behav Ther [Internet]*. 2018;47(1):1–18. Available from:
22
23 459 <http://doi.org/10.1080/16506073.2017.1401115>
24
25 460 36. Ugalde A, Haynes K, Boltong A, White V, Krishnasamy M, Schofield P, et al. Self-guided interventions for
26
27 461 managing psychological distress in people with cancer – A systematic review. *Patient Educ Couns*.
28
29 462 2017;100(5):846–57.
30
31 463 37. Elaine FH, Peter JB. On-site mental health workers delivering psychological therapy and psychosocial
32
33 464 interventions to patients in primary care: effects on the professional practice of primary care providers.
34
35 465 *Cochrane Database Syst Rev*. 2009;(1).
36
37 466 38. Del Giudice ME, Grunfeld E, Harvey BJ, Piliotis E, Verma S. Primary care physicians' views of routine
38
39 467 follow-up care of cancer survivors. *J Clin Oncol*. 2009;27(20):3338–45.
40
41 468 39. Johansen ML, Høltedahl KA, Rudebeck CE. How does the thought of cancer arise in a general practice
42
43 469 consultation? Interviews with GPs. *Scand J Prim Health Care*. 2012;30(3):135–40.
44
45 470 40. Mitchell AJ, Vahabzadeh A, Magruder K. Screening for distress and depression in cancer settings: 10
46
47 471 lessons from 40 years of primary-care research. *Psychooncology*. 2011;20(6):572–84.
48
49 472 41. Curran GM, Sullivan G, Mendel P, Craske MG, Sherbourne CD, Stein MB, et al. Implementation of the
50
51 473 CALM intervention for anxiety disorders: A qualitative study. *Implement Sci*. 2012;7(1):1–11.
52
53 474 42. Lawrence RA, McLoone JK, Wakefield CE, Cohn RJ. Primary Care Physicians' Perspectives of Their Role in
54
55 475 Cancer Care: A Systematic Review. *J Gen Intern Med [Internet]*. 2016;31(10):1222–36. Available from:
56
57 476 <http://dx.doi.org/10.1007/s11606-016-3746-7>
58
59 477 43. Berrett-Abebe J, Cadet T, Vitello J, Maramaldi P. Developing content for an interprofessional training on

- 1
2
3 478 fear of cancer recurrence (FCR): Key informant interviews of healthcare professionals, researchers and
4
5 479 cancer survivors. *J Psychosoc Oncol* [Internet]. 2018;0(0):1–15. Available from:
6
7 480 <https://doi.org/10.1080/07347332.2018.1443987>
8
9 481 44. Berrett-Abebe J, Cadet T, Nekhlyudov L, Vitello J, Maramaldi P. Impact of an Interprofessional Primary
10
11 482 Care Training on Fear of Cancer Recurrence on Clinicians' Knowledge, Self-Efficacy, Anticipated Practice
12
13 483 Behaviors, and Attitudes Toward Survivorship Care. *J Cancer Educ*. 2018;1–7.
14
15 484 45. Fidjeland HL, Brekke M, Vistad I. Scandinavian Journal of Primary Health Care General practitioners'
16
17 485 attitudes toward follow-up after cancer treatment: A cross-sectional questionnaire study. *Scand J Prim*
18
19 486 *Health Care* [Internet]. 2015;334(4):223–32. Available from:
20
21 487 <http://www.tandfonline.com/action/journalInformation?journalCode=ipri20%0Ahttp://dx.doi.org/10.3>
22
23 488 [109/02813432.2015.1118836](http://dx.doi.org/10.3109/02813432.2015.1118836)
24
25 489 46. Nekhlyudov L, O'malley DM, Hudson S V. Integrating primary care providers in the care of cancer
26
27 490 survivors: gaps in evidence and future opportunities. *Lancet Oncol* [Internet]. 2017;18(1):e30–8.
28
29 491 Available from: [http://dx.doi.org/10.1016/S1470-2045\(16\)30570-8](http://dx.doi.org/10.1016/S1470-2045(16)30570-8)
30
31 492 47. Adam R, Watson E. The role of primary care in supporting patients living with and beyond cancer.
32
33 493 2018;261–7. Available from: www.supportiveandpalliativecare.com
34
35 494 48. Landelijke vereniging POH-GGZ. Functie-en competentieprofiel POH-GGZ. 2014;17.
36
37 495 49. Helmond SJ Van, Lee ML Van Der, Vries J De. Study protocol of the CAREST-trial : a randomised
38
39 496 controlled trial on the (cost -) effectiveness of a CBT-based online self- help training for fear of cancer
40
41 497 recurrence in women with curatively treated breast cancer. *BMC Cancer* [Internet]. 2016;1–11.
42
43 498 Available from: <http://dx.doi.org/10.1186/s12885-016-2562-0>
44
45 499 50. van Helmond SJ, van der Lee ML, de Vries J. Translation and validation of the Dutch version of the Fear
46
47 500 of Cancer Recurrence Inventory (FCRI-NL). *J Psychosom Res* [Internet]. 2017;102(August):21–8.
48
49 501 Available from: <http://dx.doi.org/10.1016/j.jpsychores.2017.09.001>
50
51 502 51. Fitzmaurice GM, Laird NM, Ware JH. *Applied Longitudinal Analysis*. 2nd ed. Hoboken: John Wiley &
52
53 503 sons; 2004.
54
55 504 52. Assessment MT. Verdiepingsmodule Kostenevaluatie. Available from:
56
57 505 <https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren->
58
59 506 [van-economische-evaluaties-in-de-gezondheidszorg](https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg)

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41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

507 53. Groenwold RHH, Moons KGM, Vandenbroucke JP. Randomized trials with missing outcome data: How
508 to analyze and what to report. Cmaj. 2014;186(15):1153–7.
509

For peer review only



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

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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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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

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17
18 6 **Yvonne L Luigjes-Huizer**

19
20
21 7 Scientific Research Department, Helen Dowling Instituut, Bilthoven, The Netherlands and
22
23 8 Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht,
24
25 9 Utrecht University, Utrecht, the Netherlands

26
27
28 10 y.l.huizer@umcutrecht.nl

29
30 11 **Marije L van der Lee**

31
32
33 12 Scientific Research Department, Helen Dowling Instituut, Bilthoven, The Netherlands
34
35 13 mvanderlee@hdi.nl

36
37 14 **Niek J de Wit**

38
39
40 15 Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht,
41
42 16 Utrecht University, Utrecht, the Netherlands
43
44 17 n.j.dewit@umcutrecht.nl

45
46 18 **Charles W Helsper**

47
48
49 19 Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht,
50
51 20 Utrecht University, Utrecht, the Netherlands
52
53 21 c.w.helsper-2@umcutrecht.nl

54
55 22 Corresponding author: Yvonne Luigjes yluigjes@hdi.nl

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24 **Abstract**

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

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

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

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

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

49 **Strengths and limitations of this study**

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

59

60

61 **Introduction**

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

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

1
2
3 76 cancer return or progression, unhelpful coping strategies, impairments in daily functioning, great
4
5 77 level of distress and limited ability to make plans (5).
6
7 78 Many studies have explored factors that correlate with FCR development, with mixed results. The
8
9 79 evidence for correlations between FCR and age, gender and physical symptoms is strongest, whereby
10
11 80 younger patients, female patients and patients with more symptoms experience more FCR (6). In
12
13 81 contrast, social support, optimism, having detailed information and being conscientious correlate with
14
15 82 having less FCR (6,9,10). Notably, associations between FCR and psychological factors (e.g.
16
17 83 metacognitions) are generally stronger than associations between FCR and demographic factors (11).
18
19 84 FCR can persist for many years after the end of cancer treatment (6,12). There are also triggers that
20
21 85 can temporarily increase FCR. These include: medical appointments, having unexplainable symptoms,
22
23 86 hearing about cancer in the media or hearing about the death of a fellow patient (13).
24
25 87 The impact of FCR varies. Having some FCR can be protective, since it may lead to treatment
26
27 88 compliance and healthy lifestyle adaptations. However, severe FCR can significantly decrease quality
28
29 89 of life (14). Maladaptive coping styles include overuse of primary care for common acute symptoms,
30
31 90 but also avoidance of social and healthcare appointments. On average, healthcare uptake is increased
32
33 91 for people with high FCR (15). Cancer survivors with high consultation rates due to seeking reassurance
34
35 92 can inadvertently augment their fears and cause unnecessary healthcare costs (16). Yet, people who
36
37 93 respond to their fear by avoiding healthcare, risk delayed diagnosis of cancer recurrence.
38
39 94 A Danish study found that patients tended to discuss social or psychological aspects of cancer,
40
41 95 including fear of relapse, more with family and friends than with their GP, because they did not think
42
43 96 it was the GP's mandate to address the concerns (17). In a Dutch study, 75% of patients' physical
44
45 97 problems after having received a cancer diagnosis were discussed with GPs, compared to only one
46
47 98 third of emotional and social problems (18). When the need for psychosocial care is recognised, this
48
49 99 has a positive effect on quality of life, appreciation of care and communication with care providers
50
51 100 (19). Therefore, it seems of added value if GPs assess the presence of FCR when patients come in for
52
53 101 consultations, and refer to additional care when needed (20).
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3 102 Treating FCR is different from treating other anxiety disorders, because most treatments for anxiety
4
5 103 are based on the presumption that patients incorrectly perceive something as a threat. Yet, in the case
6
7 104 of FCR, the fear is not irrational, since the threat is actual and significant (21). Currently, there are
8
9
10 105 different treatment options for FCR, which can be applied in a stepped care approach. The first level
11
12 106 involves psycho-education, normalisation and self-management. Next, cognitive behavioural therapy,
13
14 107 therapies focusing on acceptance (22) and pharmacological treatment (23) can be applied. In recent
15
16 108 years, several trials have shown the effectiveness of new FCR interventions (24,25), including
17
18 109 mindfulness programs (26–28), psychoeducation (29), cognitive behavioural therapy interventions
19
20 110 (30–32), an intervention based on metacognitive therapy (33) and a gratitude intervention (34). The
21
22
23 111 SWORD study found that blended treatment using an online FCR program with five face-to-face and
24
25 112 three online sessions with a specialized psychologist reduced FCR significantly more than usual care
26
27 113 (32). Specialised psychological care for cancer is typically provided in hospitals and institutes for
28
29 114 psycho-oncology.

30
31
32 115 Unfortunately, travel distance, limited energy of ex-cancer patients and waiting lists for specialised
33
34 116 centres counteract accessibility (35). Also, most cancer survivors do not require intensive specialised
35
36 117 psychotherapy, but rather accessible psychological care. Online treatment may be a suitable
37
38 118 alternative. In addition to being easily accessible, it also allows patients to obtain care at moments
39
40 119 when they feel fit enough and for a duration that they can manage. However, a review on the
41
42 120 effectiveness of self-guided interventions among cancer patients with psychological distress concludes
43
44 121 that evidence for the effectiveness of completely self-guided interventions is lacking, and that some
45
46 122 level of therapist involvement ('blended care') can help encourage engagement and promote
47
48 123 adherence (36).

49
50
51
52 124 Concurrently, cancer care and survivorship care are increasingly being provided in primary care,
53
54 125 because of patient preference, increasing numbers of cancer patients and rising healthcare costs (1).
55
56 126 Primary care is comprehensive, longitudinal and integrated, provided by teams of different
57
58 127 professionals (1), increasingly including mental health professionals (37). Primary care providers know
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3 128 their patients and their social and medical history and generally have a longstanding relation with the
4
5 129 patient (38,39). Patients view primary care staff as trusted professionals (40) and prefer coming to
6
7 130 primary care rather than specialised care for anxiety issues, because of both practical reasons and
8
9 131 stigma (41). General practitioners want to provide psychosocial support to cancer patients and feel
10
11 132 they are well-positioned (42,43), but they face capacity challenges (44,45) and report a need for
12
13 133 training on cancer survivorship (46,47), in particular on treating psychological problems (44). Involving
14
15 134 and training auxiliary staff, such as primary care MHWs, in survivorship care, may help to overcome
16
17 135 both capacity challenges and the need for improved expertise in primary care (47).
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20

21 136 **Aim**

22
23 137 The BLANKET study was designed to assess the effectiveness of a primary care delivered, blended care
24
25 138 intervention for fear of cancer recurrence, in reducing patients' severity of FCR, compared to usual
26
27 139 care. We aim to include patients with moderate FCR, who want FCR support.
28
29

30 140 We hypothesise that

- 31
32 141 1. the FCR intervention will reduce FCR severity,
- 33
34 142 2. the FCR intervention will reduce FCR related distress,
- 35
36 143 3. healthcare consumption of patients who have received the FCR intervention will be reduced.
- 37
38 144 4. the FCR intervention will be considered desirable and of added value by patients and
39
40 145 practitioners.
- 41
42

43 146 The primary outcome is FCR severity. Secondary outcomes are FCR-related distress, FCR-related
44
45 147 healthcare use, FCR-related health costs, and satisfaction of patients and practitioners with support
46
47 148 provided by trained MHWs and GPs.
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50 149

51 52 150 **Methods**

53 54 151 **Study design**

55 152 The BLANKET study is a two-armed cluster randomised clinical trial, in which the general practice is
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57 153 the unit of randomisation.
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154 **Study procedure**

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

163 **Eligibility**

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

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

176 **Recruitment**

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

1
2
3 180 To spread the workload for the practitioners, invitation will be done in rounds, starting with patients
4
5 181 who most recently finished curative cancer treatment. In the invitation letter, patients who desire
6
7 182 support for FCR are asked to participate in the study. Patients who are willing to participate, provide
8
9 183 written informed consent to the researcher.

12 184 **Randomisation**

14 185 Randomisation is done at practice level. GPs and MHWs will know in which group they have been
15
16 186 placed. Patients will not. Clusters are formed, in which all GPs and MHWs working in the same
17
18 187 building are grouped together, to decrease the risk of contamination. Minimisation is applied for size
19
20 188 of the practice and the socio-economic status (SES) of the neighbourhood they are located in, to
21
22 189 ensure balance between study arms (patients and professionals). For practice size, there are three
23
24 190 categories: small (1-3 GPs), middle-sized (4-6 GPs) or large (7 GPs or more). For SES, the list of
25
26 191 disadvantaged areas by postal code made by the Dutch government for general practices is used.
27
28 192 Practices will be assigned to the intervention or the control group, using the number generator at
29
30 193 Research Randomizer (randomizer.org). An external data manager will generate the numbers.
31
32 194 Practices are randomised in two blocks. The inclusion rate from the first block will help to confirm
33
34 195 how many more practices are needed for the second block.

39 196 **Intervention**

41 197 GPs and MHWs in the intervention group will provide an intervention specifically designed for FCR,
42
43 198 with online modules, which focus on normalisation, psychoeducation and self-management (49). The
44
45 199 modules were developed at the Helen Dowling Institute based on cognitive behavioural therapy,
46
47 200 clinical experience and input from patients, and are currently being used by specialised psychologists
48
49 201 for blended treatment. The intervention consists of two CBT modules, which include psycho-education
50
51 202 on FCR, and five optional modules on rumination, avoidance, relaxing, reassuring and undertaking
52
53 203 activities. Optional modules can be used depending on the specific needs of the patients. The GP's role
54
55 204 is to assess the need for care during an intake. The MHW's role is to assign and discuss the modules
56
57 205 with the patients during five contact moments. GPs and MHWs in the intervention group will receive
58
59
60

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

208 **Usual care**

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

212 **Outcomes**

213 Participants will provide data using online self-report questionnaires hosted by ResearchOnline.com.

214 Participants will receive an invitational e-mail with a link to complete the questionnaires online.

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

218 If patients do not fill out the questionnaires, they are sent reminders.

219 **Primary outcome**

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

223 **Secondary outcomes**

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

227 **Covariates**

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

1
2
3 231 At the patient level: age, gender, level of education, coping style, severity of anxiety and depression,
4
5 232 somatic complaints, severity of FCR at the start of the study, FCR related distress at the start of the
6
7 233 study, psychiatric history, previous health care use, additional care used by patients (e.g. alternative
8
9 234 care), time since the cancer diagnosis, time since the end of the curative cancer treatment, cancer
10
11 235 type.

12
13
14 236 At the practice level: general practice size and SES status of practice.

15
16 237 At the MHW level: number of years of work experience and educational background of the MHW.

17 238 **Data collection**

18
19 239 Patients will fill out the Dutch version of the fear of cancer recurrence inventory (FCRI-NL). It contains
20
21 240 43 items, measuring seven subscales. The severity, distress and coping subscales will be used to
22
23 241 measure FCR severity, distress and coping. The FCRI was translated into Dutch and validated by van
24
25 242 Helmond, van der Lee & de Vries (50). While for the FCRI, it is recommended to use the total score
26
27 243 of all subscales to obtain a score for FCR (7), this multi-dimensional structure was not replicated in
28
29 244 the validation of the FCRI-NL. Instead, the individual subscales provide important information and are
30
31 245 recommended to be used separately (50).

32
33 246 The 4DKL will be used to provide data on general distress, depression, anxiety and somatic
34
35 247 complaints. The 4DKL is a 50-item questionnaire that measures four dimensions: distress, depression,
36
37 248 anxiety and somatic complaints. The list is already used in some GP practices and is therefore
38
39 249 practically applicable.

40
41 250 Patients will also be surveyed about their educational level, current daily activity (e.g. work), reasons
42
43 251 for participating in the study, additional care used that is not in the electronic health records (EHR)
44
45 252 including alternative care, and other factors that they think might have influenced their FCR.

46
47 253 In order to collect data on patients' cancer type, treatment and healthcare use, data will be obtained
48
49 254 from patients' EHR. Data will be collected on number of GP visits related to cancer, FCR and neither,
50
51 255 number of sessions with MHW and number of referrals for physical care and for psychological care.
52
53 256 GP visits will only be considered FCR-related if FCR is specifically mentioned. Some patients may not
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3 257 mention FCR but have increased healthcare uptake due to hyper-vigilance. If that is the case, we
4
5 258 expect the number of cancer-related visits to decrease if FCR decreases. At baseline, data on
6
7 259 healthcare use per year since the end of curative cancer treatment will also be obtained, to
8
9 260 exploratively compare usual care in our control group with usual care in the years prior to the study.
10
11 261 FCR-related health costs will be calculated based on the healthcare use.
12
13
14 262 The desirability and added value of the intervention will be evaluated using custom-made, non-
15
16 263 validated questionnaires and semi-structured interviews with a selection of patients and
17
18 264 practitioners at T1. The interviews will explore which aspects of the support are effective,
19
20 265 unnecessary, practical or pleasant and why. They will also explore whether the GP and MHW are
21
22 266 considered to be the right practitioners to provide this type of care and what changes with regard to
23
24 267 FCR are most desirable and sought after. Varied groups will be purposively sampled. For patients, in
25
26 268 terms of age, time since diagnosis, severity of FCR at T0, and severity of FCR at T1; for practitioners in
27
28 269 terms of professional background and years of work experience.
29
30 270 Additional information about data collection, data management, monitoring and dissemination of
31
32 271 results can be found in the trial master file.
33
34
35

36 272 **Sample size calculation**

37
38
39 273 When determining the required group size for finding a relevant difference between the groups, we
40
41 274 used a difference in means of 3 and a standard deviation of 7 on the FCRI severity scale. The
42
43 275 difference in means was based on expert opinion. The standard deviation was based on the FCRI-NL
44
45 276 validation study by van Helmond et al. (2017), which found an SD of 7 on the severity scale (50).
46
47
48 277 Using an alpha of 0.05 and beta of 0.8, we calculated a required sample size of 86 participants in both
49
50 278 groups for sufficient power. Because multiple patients are treated by the same MHW, there might be
51
52 279 a cluster effect. Based on an average of 15 inclusions per MHW and an intraclass correlation
53
54 280 coefficient (ICC) of 0.01, an inflation factor of 1.14 has been applied. This leads to a group size of 98
55
56 281 patients per arm. Because the clusters (number of patients per MHW) will probably not all have the
57
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282 same size, an inflation factor of 10% is applied, leading to a group size of 108. We also assume a
283 dropout of 12% of patients. That is why we aim to include 122 patients in each group.

284 **Statistical analysis**

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

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

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

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

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

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

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

305 Healthcare costs are calculated based on healthcare utilisation, according to the method of the

306 *Guidelines for carrying out economic evaluations in health care* (52).

1
2
3 307 For the outcomes for which the intervention is found to be effective, the effect of the covariates on
4
5 308 the outcomes will be explored.

6
7 309 First, intention to treat (ITT) analyses will be done. Then, per-protocol analyses will be carried out to
8
9 310 estimate the effectiveness of the intervention if executed per protocol. During the analyses, the
10
11 311 assessor will be blinded about the groups.

12
13
14 312 The validity of study results may be challenged by missing values, either at baseline or missing
15
16 313 outcomes at follow-up. Multiple imputation will be used to address missing values at baseline for
17
18 314 relevant variables. For missing outcomes, correction for relevant prognostic factors will be
19
20 315 considered to ensure the validity of the results (53).

21
22
23 316 The desirability and feasibility of the intervention according to patients and practitioners will be
24
25 317 measured qualitatively. Semi-structured interviews will be held. These will be transcribed, and then
26
27 318 coded by two independent researchers. Differences in coding will be discussed until consensus is
28
29 319 reached. Important themes will be identified, using the data as the starting point.

30 31 32 320 **Patient and public involvement**

33
34 321 When developing the online intervention, patients provided input on the desired content and the
35
36 322 appearance of the online intervention, e.g. their preference for texts to be short. Once the
37
38 323 intervention was developed, patients used it and shared their experiences, and the intervention was
39
40 324 further adapted based on this, e.g. adding reminder e-mails.

41
42
43 325 When developing the study, patients provided input on the general idea. They also provided
44
45 326 feedback on the recruitment process and in particular on the invitation letter to patients. Based on
46
47 327 their input, the study and the letter were adapted.

48 49 50 328 **Discussion**

51
52 329 With an increased number of cancer survivors, there is an increased need for survivorship care.
53
54 330 Provision of psychological care for FCR in primary care may improve access and reduce the pressure
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56 331 on specialised institutions. In the current study, the effectiveness of a primary care delivered FCR
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58 332 intervention will be compared to usual care. An evaluation of healthcare consumption and costs is
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3 333 included in the study to assess whether this can also decrease healthcare uptake and costs of
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5 334 healthcare. To our knowledge, this is the first trial assessing the effectiveness of an FCR intervention
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7 335 implemented in primary care. In addition, it is one of few pragmatic trials on FCR interventions.
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10 336 Heterogeneity of usual care

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12 337 Furthermore, we have chosen to compare this intervention with usual care. Since no clear guidelines
13
14 338 are available for general practices for FCR, usual care may be quite diverse. Yet, since we want to
15
16 339 know whether this intervention is more effective than what is currently being offered, we chose to
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18 340 compare with usual care, despite its heterogeneity, and to register usual care during the study.
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20 21 341 Recruitment

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23 342 Because prior research shows that patients often do not mention FCR to their GP, we chose to
24
25 343 actively invite patients who desire support for FCR to participate in the study. The disadvantage of
26
27 344 this choice is that we are activating our participants, making them less representative of the patients
28
29 345 who currently seek care for FCR. We made this choice, because we want to know whether this
30
31 346 intervention can help patients with FCR if they choose to seek care.
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34 347 Usual care

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36 348 We recognise that the usual care measured in this study might not fully reflect actual usual care,
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38 349 since we have activated the patient population and made the general practices more aware of this
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40 350 issue. To assess the effect of this activation, we compare the healthcare use in the control group with
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42 351 retrospective healthcare use. In addition, practices who agree to participate in the study might have
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44 352 increased interest and expertise in providing care for FCR. To assess this, we ask them about any
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46 353 education on FCR or related topics they have received.
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50 354 Randomisation level

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52 355 We chose to randomise practices and not patients to prevent contamination. Practitioners who have
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54 356 been trained will have increased knowledge and awareness, and will no longer be able to provide
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56 357 usual care the way they did before training. Also, patients at the same practice might discuss the
57
58 358 intervention they receive with one another and notice the differences. Patients are unaware of the
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3 359 randomisation, to prevent patients in the control group from being disappointed and less motivated
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5 360 if they know that they are not receiving the intervention that is being studied.
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7 361 **Trial status**

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9 362 Invitation of primary care practices has started in October 2018. The first patient was included on
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12 363 April 15, 2019. Final results are expected in 2020.
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For peer review only

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3 364 **Declarations**
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- 5 365 1. Ethics approval and consent to participate: The Medical Research Ethics Committee Utrecht
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7 366 (METC Utrecht) has reviewed the study in accordance with the Dutch Medical Research Involving
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9 367 Human Subjects Act (WMO) and other applicable Dutch and European regulations. Based on the
10
11 368 requirements of the WMO, the METC Utrecht has issued an approval of the above-mentioned
12
13 369 study. Any protocol amendments will be communicated to all relevant parties. Written consent is
14
15 370 obtained from study participants.
16
17 371 2. Author contributions: All authors participated in the design of the study. YL wrote the draft
18
19 372 manuscript. ML, CH and NW improved the manuscript. All authors read and approved the final
20
21 373 manuscript.
22
23 374 3. Funding: This work was supported by the Dutch Cancer Society (KWF) grant number 10936. KWF
24
25 375 is not involved in study design, collection, management, analysis, and interpretation of data,
26
27 376 writing of the report, the decision to submit the report for publication, nor does it have authority
28
29 377 over the publications.
30
31 378 4. Competing interests: The authors declare that they have no competing interests.
32
33 379 5. Sponsor: Helen Dowling Institute, Professor Bronkhorstlaan 20, 3723 MB Bilthoven
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35 380 6. Acknowledgements: Not applicable.
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381 **References**

- 382 1. Rubin G, Berendsen A, Crawford SM, Dommett R, Earle C, Emery J, et al. The expanding role of primary
383 care in cancer control. *Lancet Oncol.* 2015;16(12):1231–72.
- 384 2. Ness S, Kokal J, Fee-Schroeder K, Novotny P, Satele D, Barton D. Concerns Across the Survivorship
385 Trajectory: Results From a Survey of Cancer Survivors. *Oncol Nurs Forum.* 2013;40(1):35–42.
- 386 3. Harrington CB, Hansen JA, Moskowitz M, Todd BL, Feuerstein M. It's Not over When it's Over: Long-
387 Term Symptoms in Cancer Survivors—A Systematic Review. *Int J Psychiatry Med [Internet].*
388 2010;40(2):163–81. Available from: <http://journals.sagepub.com/doi/10.2190/PM.40.2.c>
- 389 4. Brennan ME, Butow P, Spillane AJ, Boyle F. Patient-reported quality of life, unmet needs and care
390 coordination outcomes: Moving toward targeted breast cancer survivorship care planning. *Asia Pac J*
391 *Clin Oncol.* 2016;12(2):e323–31.
- 392 5. Lebel S, Ozakinci G, Humphris G, Mutsaers B, Thewes B, Prins J, et al. From normal response to clinical
393 problem: definition and clinical features of fear of cancer recurrence. *Support Care Cancer [Internet].*
394 2016;24(8):3265–8. Available from: <http://dx.doi.org/10.1007/s00520-016-3272-5>
- 395 6. Simard S, Thewes B, Humphris G, Dixon M, Hayden C, Mireskandari S, et al. Fear of cancer recurrence in
396 adult cancer survivors: a systematic review of quantitative studies. *J Cancer Surviv.* 2013;7:300–22.
- 397 7. Simard S, Savard J. Fear of Cancer Recurrence Inventory: Development and initial validation of a
398 multidimensional measure of fear of cancer recurrence. *Support Care Cancer.* 2009;17(3):241–51.
- 399 8. Simard S, Savard J. Screening and comorbidity of clinical levels of fear of cancer recurrence. *J Cancer*
400 *Surviv.* 2015;9(3):481–91.
- 401 9. Hedman C, Strang P, Djärv T, Widberg I, Lundgren CI. Anxiety and Fear of Recurrence Despite a Good
402 Prognosis: An Interview Study with Differentiated Thyroid Cancer Patients. *Thyroid [Internet].*
403 2017;27(11):1417–23. Available from: <http://online.liebertpub.com/doi/10.1089/thy.2017.0346>
- 404 10. Liao KYH, Yeung NCY, Wong CCY, Warmoth K, Lu Q. Fear of cancer recurrence and physical well-being
405 among Chinese cancer survivors: the role of conscientiousness, positive reappraisal and hopelessness.
406 *Support Care Cancer.* 2017;25(4):1141–9.
- 407 11. Smith A Ben, Sharpe L, Thewes B, Turner J, Gilchrist J, Fardell JE, et al. Medical , demographic and
408 psychological correlates of fear of cancer recurrence (FCR) morbidity in breast , colorectal and
409 melanoma cancer survivors with probable clinically significant FCR seeking psychological treatment

- 1
2
3 410 through the ConquerFear study. 2018;4207–16.
4
5 411 12. Simard S, Savard J, Ivers H. Fear of cancer recurrence: Specific profiles and nature of intrusive thoughts.
6
7 412 J Cancer Surviv. 2010;
8
9 413 13. Gil KM, Mishel MH, Belyea M, Germino B, Porter LS, Carlton LaNey I, et al. Triggers of Uncertainty
10
11 414 About Recurrence and Long-Term Treatment Side Effects in Older African American and Caucasian
12
13 415 Breast Cancer Survivors. *Oncol Nurs Forum*. 2004;31(3):633–9.
14
15 416 14. Simonelli LE, Siegel SD, Duffy NM. Fear of cancer recurrence: a theoretical review and its relevance for
16
17 417 clinical presentation and management. *Psychooncology*. 2017;26(10):1444–54.
18
19 418 15. Champagne A, Ivers H, Savard J. Utilization of Health Care Services in Cancer Patients with Elevated
20
21 419 Fear of Cancer Recurrence. *Psychooncology* [Internet]. 2018;(March):1–7. Available from:
22
23 420 <http://www.ncbi.nlm.nih.gov/pubmed/29719072> <http://doi.wiley.com/10.1002/pon.4748>
24
25 421 16. Butow P, Sharpe L, Thewes B, Turner J, Gilchrist J, Beith J. Fear of Cancer Recurrence: A Practical Guide
26
27 422 for Clinicians. *Oncol J*. 2018;32(1):32–8.
28
29 423 17. Mikkelsen T, Sondergaard J, Sokolowski I, Jensen A, Olesen F. Cancer survivors' rehabilitation needs in a
30
31 424 primary health care context. *Fam Pract*. 2009;26(3):221–30.
32
33 425 18. NIVEL. Afstemming van zorg tussen huisarts en specialist bij kanker kan beter [Internet]. 2013 [cited
34
35 426 2018 May 22]. Available from: [https://www.nivel.nl/nl/nieuws/afstemming-van-zorg-tussen-huisarts-](https://www.nivel.nl/nl/nieuws/afstemming-van-zorg-tussen-huisarts-en-specialist-bij-kanker-kan-beter)
36
37 427 [en-specialist-bij-kanker-kan-beter](https://www.nivel.nl/nl/nieuws/afstemming-van-zorg-tussen-huisarts-en-specialist-bij-kanker-kan-beter)
38
39 428 19. NHG. NHG-standpunt Oncologische zorg in de huisartsenpraktijk. 2014.
40
41 429 20. Fann JR, Eli K, Sharpe M. Integrating psychosocial care into cancer services. *J Clin Oncol*.
42
43 430 2012;30(11):1178–86.
44
45 431 21. Curran L, Sharpe L, Butow P. Anxiety in the context of cancer: A systematic review and development of
46
47 432 an integrated model. *Clin Psychol Rev* [Internet]. 2017;56(June):40–54. Available from:
48
49 433 <http://dx.doi.org/10.1016/j.cpr.2017.06.003>
50
51 434 22. Volker C, van der Lee M, Pet A. Angst voor terugkeer van kanker. *GZ-Psychologie*. 2011;3:30–8.
52
53 435 23. Cupit-Link M, Syrjala KL, Hashmi SK. Damocles' syndrome revisited: Update on the fear of cancer
54
55 436 recurrence in the complex world of today's treatments and survivorship. *Hematol Oncol Stem Cell Ther*
56
57 437 [Internet]. 2018; Available from: <https://doi.org/10.1016/j.hemonc.2018.01.005>
58
59 438 24. Chen D, Sun W, Liu N, Wang J, Zhao J, Zhang Y, et al. Fear of cancer recurrence: A systematic review of

- 1
2
3 439 randomized, controlled trials. *Oncol Nurs Forum*. 2018;45(6):703–12.
4
5 440 25. Sharpe L, Thewes B, Butow P. Current directions in research and treatment of fear of cancer
6
7 441 recurrence. *Curr Opin Support Palliat Care*. 2017;11(3):191–6.
8
9 442 26. Crane-Okada R, Kiger H, Sugerman F, Uman GC, Shapiro SL, Wyman-McGinty W, et al. Mindful
10
11 443 movement program for older breast cancer survivors: A pilot study. *Cancer Nurs*. 2012;35(4):1–13.
12
13 444 27. Lengacher CA, Shelton MM, Reich RR, Barta MK, Johnson-Mallard V, Moscoso MS, et al. Mindfulness
14
15 445 based stress reduction (MBSR(BC)) in breast cancer: Evaluating fear of recurrence (FOR) as a mediator
16
17 446 of psychological and physical symptoms in a randomized control trial (RCT). *J Behav Med*.
18
19 447 2014;37(2):185–95.
20
21 448 28. Lengacher CA, Reich RR, Paterson CL, Ramesar S, Park JY, Alinat C, et al. Examination of broad symptom
22
23 449 improvement resulting from mindfulness-based stress reduction in breast cancer survivors: A
24
25 450 randomized controlled trial. *J Clin Oncol*. 2016;34(24):2827–34.
26
27 451 29. Dieng M, Butow PN, Costa DSJ, Morton RL, Menzies SW, Mireskandari S, et al. Psychoeducational
28
29 452 Intervention to Reduce Fear of Cancer Recurrence in People at High Risk of Developing Another Primary
30
31 453 Melanoma: Results of a Randomized Controlled Trial. *J Clin Oncol*. 2016;
32
33 454 30. Dodds SE, Pace TWW, Bell ML, Fiero M, Negi LT, Raison CL, et al. Feasibility of Cognitively-Based
34
35 455 Compassion Training (CBCT) for breast cancer survivors: a randomized, wait list controlled pilot study.
36
37 456 *Support Care Cancer*. 2015;23(12):3599–608.
38
39 457 31. Lichtenthal WG, Corner GW, Slivjak ET, Roberts KE, Li Y, Breitbart W, et al. A pilot randomized
40
41 458 controlled trial of cognitive bias modification to reduce fear of breast cancer recurrence. *Cancer*.
42
43 459 2017;123(8):1424–33.
44
45 460 32. van de Wal M, Thewes B, Gielissen M, Speckens A, Prins J. Efficacy of blended cognitive behavior
46
47 461 therapy for high fear of recurrence in breast, prostate, and colorectal cancer survivors: The SWORD
48
49 462 study, a randomized controlled trial. *J Clin Oncol* [Internet]. 2017;35(19):2173–83. Available from:
50
51 463 [https://www.scopus.com/inward/record.uri?eid=2-s2.0-](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)
52
53 464 [85021649029&doi=10.1200%2FJCO.2016.70.5301&partnerID=40&md5=f159be668de252f5b14f60fe08](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)
54
55 465 [799680%0Ahttp://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/658/CN-](http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/658/CN-01395658/frame.html)
56
57 466 [01395658/frame.html](http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/658/CN-01395658/frame.html)
58
59 467 33. Butow P, Turner J, Gilchrist J, Sharpe L, Smith A Ben, Fardell JE, et al. Randomized trial of ConquerFear:

- 1
2
3 468 A novel, theoretically based psychosocial intervention for fear of cancer recurrence. *J Clin Oncol*.
4
5 469 2017;35(36):4066–77.
6
7 470 34. Otto AK, Szczesny EC, Soriano EC, Laurenceau J, Siegel SD. Supplemental Material for Effects of a
8
9 471 Randomized Gratitude Intervention on Death-Related Fear of Recurrence in Breast Cancer Survivors.
10
11 472 *Heal Psychol* [Internet]. 2016;35(12):1320–8. Available from:
12
13 473 http://supp.apa.org/psycarticles/supplemental/hea0000400/hea0000400_supp.html
14
15 474 35. Zernicke KA, Campbell TS, Specia M, McCabe-Ruff K, Flowers S, Carlson LE. A randomized wait-list
16
17 475 controlled trial of feasibility and efficacy of an online mindfulness-based cancer recovery program: The
18
19 476 eTherapy for cancer applying mindfulness trial. *Psychosom Med*. 2014;76(4):257–67.
20
21 477 36. Ugalde A, Haynes K, Boltong A, White V, Krishnasamy M, Schofield P, et al. Self-guided interventions for
22
23 478 managing psychological distress in people with cancer – A systematic review. *Patient Educ Couns*.
24
25 479 2017;100(5):846–57.
26
27 480 37. Elaine FH, Peter JB. On-site mental health workers delivering psychological therapy and psychosocial
28
29 481 interventions to patients in primary care: effects on the professional practice of primary care providers.
30
31 482 *Cochrane Database Syst Rev*. 2009;(1).
32
33 483 38. Del Giudice ME, Grunfeld E, Harvey BJ, Piliotis E, Verma S. Primary care physicians' views of routine
34
35 484 follow-up care of cancer survivors. *J Clin Oncol*. 2009;27(20):3338–45.
36
37 485 39. Johansen ML, Høltedahl KA, Rudebeck CE. How does the thought of cancer arise in a general practice
38
39 486 consultation? Interviews with GPs. *Scand J Prim Health Care*. 2012;30(3):135–40.
40
41 487 40. Mitchell AJ, Vahabzadeh A, Magruder K. Screening for distress and depression in cancer settings: 10
42
43 488 lessons from 40 years of primary-care research. *Psychooncology*. 2011;20(6):572–84.
44
45 489 41. Curran GM, Sullivan G, Mendel P, Craske MG, Sherbourne CD, Stein MB, et al. Implementation of the
46
47 490 CALM intervention for anxiety disorders: A qualitative study. *Implement Sci*. 2012;7(1):1–11.
48
49 491 42. Lawrence RA, McLoone JK, Wakefield CE, Cohn RJ. Primary Care Physicians' Perspectives of Their Role in
50
51 492 Cancer Care: A Systematic Review. *J Gen Intern Med* [Internet]. 2016;31(10):1222–36. Available from:
52
53 493 <http://dx.doi.org/10.1007/s11606-016-3746-7>
54
55 494 43. Berrett-Abebe J, Cadet T, Vitello J, Maramaldi P. Developing content for an interprofessional training on
56
57 495 fear of cancer recurrence (FCR): Key informant interviews of healthcare professionals, researchers and
58
59 496 cancer survivors. *J Psychosoc Oncol* [Internet]. 2018;0(0):1–15. Available from:

- 1
2
3 497 <https://doi.org/10.1080/07347332.2018.1443987>
4
5 498 44. Berrett-Abebe J, Cadet T, Nekhlyudov L, Vitello J, Maramaldi P. Impact of an Interprofessional Primary
6
7 499 Care Training on Fear of Cancer Recurrence on Clinicians' Knowledge, Self-Efficacy, Anticipated Practice
8
9 500 Behaviors, and Attitudes Toward Survivorship Care. *J Cancer Educ.* 2018;1–7.
10
11 501 45. Fidjeland HL, Brekke M, Vistad I. Scandinavian Journal of Primary Health Care General practitioners'
12
13 502 attitudes toward follow-up after cancer treatment: A cross-sectional questionnaire study. *Scand J Prim*
14
15 503 *Health Care [Internet].* 2015;334(4):223–32. Available from:
16
17 504 <http://www.tandfonline.com/action/journalInformation?journalCode=ipri20%0Ahttp://dx.doi.org/10.3>
18
19 505 [109/02813432.2015.1118836](http://dx.doi.org/10.3109/02813432.2015.1118836)
20
21 506 46. Nekhlyudov L, O'malley DM, Hudson S V. Integrating primary care providers in the care of cancer
22
23 507 survivors: gaps in evidence and future opportunities. *Lancet Oncol [Internet].* 2017;18(1):e30–8.
24
25 508 Available from: [http://dx.doi.org/10.1016/S1470-2045\(16\)30570-8](http://dx.doi.org/10.1016/S1470-2045(16)30570-8)
26
27 509 47. Adam R, Watson E. The role of primary care in supporting patients living with and beyond cancer.
28
29 510 2018;261–7. Available from: www.supportiveandpalliativecare.com
30
31 511 48. Landelijke vereniging POH-GGZ. Functie-en competentieprofiel POH-GGZ. 2014;17.
32
33 512 49. Helmond SJ Van, Lee ML Van Der, Vries J De. Study protocol of the CAREST-trial : a randomised
34
35 513 controlled trial on the (cost-) effectiveness of a CBT-based online self- help training for fear of cancer
36
37 514 recurrence in women with curatively treated breast cancer. *BMC Cancer [Internet].* 2016;1–11.
38
39 515 Available from: <http://dx.doi.org/10.1186/s12885-016-2562-0>
40
41 516 50. van Helmond SJ, van der Lee ML, de Vries J. Translation and validation of the Dutch version of the Fear
42
43 517 of Cancer Recurrence Inventory (FCRI-NL). *J Psychosom Res [Internet].* 2017;102(August):21–8.
44
45 518 Available from: <http://dx.doi.org/10.1016/j.jpsychores.2017.09.001>
46
47 519 51. Fitzmaurice GM, Laird NM, Ware JH. *Applied Longitudinal Analysis.* 2nd ed. Hoboken: John Wiley &
48
49 520 sons; 2004.
50
51 521 52. Assessment MT. Verdiepingsmodule Kostenevaluatie. Available from:
52
53 522 <https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren->
54
55 523 [van-economische-evaluaties-in-de-gezondheidszorg](https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg)
56
57 524 53. Groenwold RHH, Moons KGM, Vandenbroucke JP. Randomized trials with missing outcome data: How
58
59 525 to analyze and what to report. *Cmaj.* 2014;186(15):1153–7.

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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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" 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

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6 2 **Study protocol of the BLANKET-trial: a cluster randomised**
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10 3 **controlled trial on the (cost-) effectiveness of a primary care**
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13 4 **intervention for fear of cancer recurrence in cancer survivors**
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17
18 6 **Yvonne L Luigjes-Huizer**

19
20
21 7 Scientific Research Department, Helen Dowling Instituut, Bilthoven, The Netherlands and
22
23 8 Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht,
24
25 9 Utrecht University, Utrecht, the Netherlands

26
27
28 10 y.l.huizer@umcutrecht.nl

29
30 11 **Marije L van der Lee**

31
32
33 12 Scientific Research Department, Helen Dowling Instituut, Bilthoven, The Netherlands
34
35 13 mvanderlee@hdi.nl

36
37 14 **Niek J de Wit**

38
39
40 15 Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht,
41
42 16 Utrecht University, Utrecht, the Netherlands
43
44 17 n.j.dewit@umcutrecht.nl

45
46 18 **Charles W Helsper**

47
48
49 19 Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht,
50
51 20 Utrecht University, Utrecht, the Netherlands
52
53 21 c.w.helsper-2@umcutrecht.nl

54
55 22 Corresponding author: Yvonne Luigjes yluigjes@hdi.nl

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24 **Abstract**

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

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

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

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

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

48 **Strengths and limitations of this study**

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

- 1
2
3 50 • Quantitative and qualitative data are combined to provide comprehensive results.
4
5 51 • The intervention and trial were designed in close cooperation with patients and healthcare
6
7 52 workers.
8
9
10 53 • A cluster randomised design, randomising at practice level, was required, since practitioners who
11
12 54 have been trained on the intervention are unlikely to be able to provide usual care in the same
13
14 55 way as before training.
15
16 56 • Patients are actively invited to participate in the study, making them less representative of the
17
18 57 patients who currently seek care for FCR.
19
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21 58
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23 59

60 **Introduction**

61 Advances in the medical field have caused the number of cancer survivors to rise steadily in the past
62 decades (1). With an increasing number of survivors, there is also an increasing need for survivorship
63 care (2). A systematic review showed that fatigue, depression and anxiety are commonly reported in
64 the ten years after primary cancer treatment (3). Fear of cancer recurrence (FCR) is a more prevalent
65 concern than any physical issue (2). In a study about unmet needs after breast cancer, FCR was the
66 most reported need in all age groups (38.2%), despite a relatively good prognosis (4).
67 FCR has been defined as “fear, worry, or concern relating to the possibility that cancer will come back
68 or progress” (5). A review by Simard (2013) found that an average of 73% of cancer survivors
69 experience FCR, 49% experience a moderate to high level of FCR and 7% experience a high level of FCR
70 (6). FCR is a multidimensional construct, as demonstrated by the subscales of the Fear of Cancer
71 Recurrence Inventory (FCRI): triggers, severity, psychological distress, coping strategies, functioning
72 impairments, insight and reassurance (7). FCR exists on a scale from normal to clinical (8). In a 2-day
73 colloquium with a group of experts and patient advocates, five preliminary categories of potential
74 characteristics of clinical FCR were identified using the Delphi method. These are: preoccupation with

1
2
3 75 cancer return or progression, unhelpful coping strategies, impairments in daily functioning, great level
4
5 76 of distress and limited ability to make plans (5).
6
7 77 Many studies have explored factors that correlate with FCR development, with mixed results. The
8
9 78 evidence for correlations between FCR and age, gender and physical symptoms is strongest, whereby
10
11 79 younger patients, female patients and patients with more symptoms experience more FCR (6). In
12
13 80 contrast, social support, optimism, having detailed information and being conscientious correlate with
14
15 81 having less FCR (6,9,10). Notably, associations between FCR and psychological factors (e.g.
16
17 82 metacognitions) are generally stronger than associations between FCR and demographic factors (11).
18
19 83 FCR can persist for many years after the end of cancer treatment (6,12). There are also triggers that
20
21 84 can temporarily increase FCR, including: medical appointments, having unexplainable symptoms and
22
23 85 hearing about cancer in the media (13).
24
25 86 The impact of FCR varies. Having some FCR can be protective, if it leads to treatment compliance and
26
27 87 healthy lifestyle adaptations. However, severe FCR can significantly decrease quality of life (14).
28
29 88 Maladaptive coping styles include overuse of primary care for common acute symptoms, which can
30
31 89 inadvertently augment fears and cause unnecessary healthcare costs (15), but also avoidance of social
32
33 90 and healthcare appointments, risking delayed diagnosis of cancer recurrence. On average, healthcare
34
35 91 uptake is increased for people with high FCR (16).
36
37 92 A Danish study found that patients discussed social or psychological aspects of cancer, including FCR,
38
39 93 more with family and friends than with their GP, because they thought it was not the GP's mandate to
40
41 94 address these concerns (17). In a Dutch study, 75% of patients' physical problems after having received
42
43 95 a cancer diagnosis were discussed with GPs, compared to only one third of emotional and social
44
45 96 problems (18). When the need for psychosocial care is recognised, this positively affects quality of life,
46
47 97 appreciation of care, and communication with care providers (19). Therefore, it seems of added value
48
49 98 if GPs assess the presence of FCR and refer to additional care when needed (20).
50
51 99 Treating FCR is different from treating other anxiety disorders, because FCR is not irrational, since the
52
53 100 threat is actual and significant (21). Currently, there are different treatment options for FCR, which can
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1
2
3 101 be applied in a stepped care approach. The first level involves psycho-education, normalisation and
4
5 102 self-management. Next, cognitive behavioural therapy (CBT), therapies focusing on acceptance (22)
6
7 103 and pharmacological treatment (23) can be applied. In recent years, several trials have shown the
8
9 104 effectiveness of new FCR interventions (24,25), including mindfulness programs (26–28),
10
11 105 psychoeducation (29), cognitive behavioural therapy interventions (30–32), an intervention based on
12
13 106 metacognitive therapy (33) and a gratitude intervention (34). The SWORD study found that blended
14
15 107 treatment with a specialized psychologist and an online FCR program reduced FCR significantly more
16
17 108 than usual care (32).
18
19 109 Specialised psychological care for cancer is typically provided in hospitals and specialized institutes.
20
21 110 Unfortunately, travel distance, limited energy of ex-cancer patients and waiting lists counteract
22
23 111 accessibility (35). Also, most cancer survivors do not require intensive specialised psychotherapy, but
24
25 112 rather accessible psychological care. Online treatment is easily accessible, and allows patients to obtain
26
27 113 care when they feel fit enough and for a manageable duration. However, evidence for the effectiveness
28
29 114 of completely self-guided interventions among cancer patients with psychological distress is lacking.
30
31 115 Some level of therapist involvement can help encourage engagement and promote adherence (36).
32
33 116 Concurrently, cancer care and survivorship care are increasingly being provided in primary care,
34
35 117 because of patient preference, increasing numbers of cancer patients and rising healthcare costs (1).
36
37 118 Primary care is comprehensive, longitudinal and integrated, provided by teams of different
38
39 119 professionals (1), increasingly including mental health professionals (37). Primary care providers
40
41 120 generally have a longstanding relation with the patient (38,39). Patients view primary care staff as
42
43 121 trusted professionals (40) and prefer coming to primary care for anxiety issues, because of practical
44
45 122 reasons and stigma (41). General practitioners want to provide psychosocial support to cancer patients
46
47 123 and feel they are well-positioned (42,43), but they face capacity challenges (44,45) and report a need
48
49 124 for training on cancer survivorship (46,47), in particular on treating psychological problems (44).
50
51 125 Involving and training auxiliary staff, such as primary care MHWs, in survivorship care, may help to
52
53 126 overcome both capacity challenges and the need for improved expertise in primary care (47).
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1
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3 127 **Aim**
4

5 128 The BLANKET study was designed to assess the effectiveness of a primary care delivered, blended care
6
7 129 intervention for FCR, in reducing patients' severity of FCR, compared to usual care. Since this is a
8
9 130 pragmatic trial, we include all patients who want care for FCR at their GP practice.
10

11 131 We hypothesise that

- 12
13
14 132 1. the FCR intervention will reduce FCR severity,
15
16 133 2. the FCR intervention will reduce FCR related distress,
17
18 134 3. healthcare consumption of patients who have received the FCR intervention will be reduced,
19
20 135 4. the FCR intervention will be considered desirable and of added value by patients and
21
22 136 practitioners.
23
24

25 137 The primary outcome is FCR severity. Secondary outcomes are FCR-related distress, FCR-related
26
27 138 healthcare use, FCR-related health costs, and satisfaction of patients and practitioners with support
28
29 139 provided by trained MHWs and GPs.
30
31

32 140

33
34 141 **Methods**

35
36 142 **Study design**

37
38 143 The BLANKET study is a two-armed cluster randomised clinical trial, in which the general practice is
39
40 144 the unit of randomisation.
41

42
43 145 **Study procedure**

44
45 146 Participating practices will identify all of their patients who have successfully completed curative
46
47 147 cancer treatment between three months and ten years ago, and will send them an invitation letter
48
49 148 by mail. Patients are asked to participate if they desire support for FCR. After providing informed
50
51 149 consent, patients are asked to fill out an online baseline questionnaire. Patients also fill out
52
53 150 questionnaires 3 months and 12 months after baseline. At the end of the first questionnaire, they are
54
55 151 urged to make an appointment with their GP about support for FCR. During this consultation, the GPs
56
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1
2
3 152 in the intervention group refer the patients to the MHW for the intervention, while GPs in the control
4
5 153 group provide usual care.

7 154 **Eligibility**

9
10 155 Clusters of collaborating GPs and MHWs in the Netherlands who are willing to receive training and to
11
12 156 implement it will be recruited. In the Dutch setting, almost all general practices employ mental health
13
14 157 workers (MHW, in Dutch: POH-GGZ) (48). Both a GP and an MHW need to agree to participate for the
15
16 158 practice to be eligible to join the study.

18
19 159 Patients are eligible if they: (1) are registered at a general practice that is participating in the study, (2)
20
21 160 are 18 years or older, (3) have finished successful curative cancer treatment between 3 months and 10
22
23 161 years ago, (4) desire support for FCR, and (5) have sufficient Dutch reading and writing skills to receive
24
25 162 the intervention and complete the questionnaires. If patients have a cancer recurrence during the
26
27 163 study, no more data will be collected. GPs select patients who can be invited for the study. GPs exclude
28
29 164 vulnerable patients (e.g. severe psychiatric morbidity), who would be confused by the letter or unable
30
31 165 to participate in the study.

33
34 166 Since this is a pragmatic real world trial, we include all patients who want care for FCR at their GP
35
36 167 practice. We chose not to screen for level of FCR as an inclusion criterion, because this would not
37
38 168 reflect daily practice. This intervention could also be relevant for patients with non-clinical levels of
39
40 169 FCR who are nonetheless limited by FCR in daily life. We will train the MHW to refer patients who
41
42 170 require specialized psychological care.

45 171 **Recruitment**

47
48 172 The aim is to include 244 patients during 1,5 years. Patients are recruited using an invitation letter
49
50 173 sent by patients' own GPs. All of the patients of participating practices, who are 18 years or older and
51
52 174 have finished curative cancer treatment between 3 months and 10 years ago will receive the letter.
53
54 175 To spread the workload for the practitioners, invitation will be done in rounds, starting with patients
55
56 176 who most recently finished cancer treatment.

59 177 **Randomisation**

1
2
3 178 Randomisation is done at practice level. GPs and MHWs will know in which group they have been
4
5 179 placed. Patients will not. Clusters are formed, in which all GPs and MHWs working in the same
6
7 180 building are grouped together, to decrease the risk of contamination. Minimisation is applied for size
8
9
10 181 of the practice and the socio-economic status (SES) of the neighbourhood they are located in, to
11
12 182 ensure balance between study arms (patients and professionals). For practice size, there are three
13
14 183 categories: small (1-3 GPs), middle-sized (4-6 GPs) or large (7 GPs or more). For SES, the list of
15
16 184 disadvantaged areas by postal code made by the Dutch government for general practices is used.
17
18
19 185 Practices will be assigned to the intervention or the control group, using the number generator at
20
21 186 Research Randomizer (randomizer.org). An external data manager will generate the numbers.
22
23 187 Practices are randomised in two blocks. The inclusion rate from the first block will help to confirm
24
25 188 how many more practices are needed for the second block.

189 **Intervention**

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

198 GPs in the intervention group will receive a 1-hour online training. MHWs in the intervention group
199 will receive two 2-hour training sessions by an experienced clinical psychologist, including role plays
200 with an actor playing a patient. The trainings will be about FCR and how to provide the intervention.
201 In between sessions the MHWs will practice using the online modules, both as a patient and as a
202 practitioner. In providing the intervention, the GP's role is to assess the need for care during an intake
203 and to refer to the MHW. The MHW's role is to assign and discuss the modules with the patients during

1
2
3 204 five contact moments. MHWs will openly listen to the patients' experiences, normalize fears, apply
4
5 205 CBT and discuss what was gained from the modules. Any related questions and issues that came up
6
7 206 will also be discussed. GPs and MHWs in the control group will provide usual care.
8
9

10 207 **Usual care**

11
12 208 Patients in the control group receive usual care. In the literature, little is known about the usual care
13
14 209 that GPs provide for fear of cancer recurrence. Therefore, usual care will be mapped in this study, in
15
16 210 relation to the severity of FCR.
17

18 211 **Outcomes**

19
20 212 Participants will provide data using online self-report questionnaires hosted by ResearchOnline.com.
21
22

23 213 Participants will receive an invitational e-mail with a link to complete the questionnaires online.
24

25 214 These links will be sent at baseline (T0), after three months, once the intervention in the intervention
26
27 215 group is completed (T1), and one year after the baseline (T2). Participants who do not respond
28
29 216 receive reminders. If participants prefer to fill out the questionnaires on paper, this will be arranged.
30
31

32 217 If patients do not fill out the questionnaires, they are sent reminders.
33

34 218 **Primary outcome**

35
36 219 The primary outcome is the severity of fear of cancer recurrence after 3 months, comparing the FCR
37
38 220 intervention with usual care. To measure this, the severity scale (SF) of the Dutch version of the Fear
39
40 221 of Cancer Recurrence Inventory (FCRI-NL) will be used.
41
42

43 222 **Secondary outcomes**

44
45 223 The secondary outcomes are the development from baseline to T1 to T2 of severity of fear of cancer
46
47 224 recurrence, FCR-related distress, FCR-related healthcare use and FCR-related health costs; and the
48
49 225 desirability and added value of the intervention.
50
51

52 226 **Covariates**

53
54 227 If the intervention is found to be effective, relations between the outcomes and the following
55
56 228 variables will be explored, to identify groups of patients for whom the intervention might be more or
57
58 229 less effective.
59
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3 230 At the patient level: age, gender, level of education, coping style, severity of anxiety and depression,
4
5 231 somatic complaints, severity of FCR at the start of the study, FCR related distress at the start of the
6
7 232 study, psychiatric history, previous health care use, additional care used by patients (e.g. alternative
8
9 233 care), time since the cancer diagnosis, time since the end of the curative cancer treatment, cancer
10
11 234 type.

12
13
14 235 At the practice level: general practice size and SES status of practice.

15
16 236 At the MHW level: number of years of work experience and educational background of the MHW.

17 237 **Data collection**

18
19 238 Patients will fill out the Dutch version of the fear of cancer recurrence inventory (FCRI-NL). It contains
20
21 239 43 items, measuring seven subscales. The severity, distress and coping subscales will be used to
22
23 240 measure FCR severity, distress and coping. The FCRI was translated into Dutch and validated by van
24
25 241 Helmond, van der Lee & de Vries (50). While for the FCRI, it is recommended to use the total score
26
27 242 of all subscales to obtain a score for FCR (7), this multi-dimensional structure was not replicated in
28
29 243 the validation of the FCRI-NL. Instead, the individual subscales provide important information and are
30
31 244 recommended to be used separately (50).

32
33 245 The 4DKL will be used to provide data on general distress, depression, anxiety and somatic
34
35 246 complaints. The 4DKL is a 50-item questionnaire that measures four dimensions: distress, depression,
36
37 247 anxiety and somatic complaints. The list is already used in some GP practices and is therefore
38
39 248 practically applicable.

40
41 249 Patients will also be surveyed about their educational level, current daily activity (e.g. work), reasons
42
43 250 for participating in the study, additional care used that is not in the electronic health records (EHR)
44
45 251 including alternative care, and other factors that they think might have influenced their FCR.

46
47 252 In order to collect data on patients' cancer type, treatment and healthcare use, data will be obtained
48
49 253 from patients' EHR. Data will be collected on number of GP visits related to cancer, FCR and neither,
50
51 254 number of sessions with MHW and number of referrals for physical care and for psychological care.
52
53 255 GP visits will only be considered FCR-related if FCR is specifically mentioned. Some patients may not
54
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2
3 256 mention FCR but have increased healthcare uptake due to hyper-vigilance. If that is the case, we
4
5 257 expect the number of cancer-related visits to decrease if FCR decreases. At baseline, data on
6
7 258 healthcare use per year since the end of curative cancer treatment will also be obtained, to
8
9
10 259 exploratively compare usual care in our control group with usual care in the years prior to the study.
11
12 260 FCR-related health costs will be calculated based on the healthcare use.
13
14 261 The desirability and added value of the intervention will be evaluated using custom-made, non-
15
16 262 validated questionnaires and semi-structured interviews with a selection of patients and
17
18 263 practitioners at T1. The interviews will explore which aspects of the support are effective,
19
20 264 unnecessary, practical or pleasant and why. They will also explore whether the GP and MHW are
21
22 265 considered to be the right practitioners to provide this type of care and what changes with regard to
23
24 266 FCR are most desirable and sought after. Varied groups will be purposively sampled. For patients, in
25
26 267 terms of age, time since diagnosis, severity of FCR at T0, and severity of FCR at T1; for practitioners in
27
28 268 terms of professional background and years of work experience.
29
30
31 269 Additional information about data collection, data management, monitoring and dissemination of
32
33 270 results can be found in the trial master file.
34
35

36 271 **Sample size calculation**

37
38
39 272 When determining the required group size for finding a relevant difference between the groups, we
40
41 273 used a difference in means of 3 and a standard deviation of 7 on the FCRI severity scale. The
42
43 274 difference in means was based on expert opinion. The standard deviation was based on the FCRI-NL
44
45 275 validation study by van Helmond et al. (2017), which found an SD of 7 on the severity scale (50).
46
47
48 276 Using an alpha of 0.05 and beta of 0.8, we calculated a required sample size of 86 participants in both
49
50 277 groups for sufficient power. Because multiple patients are treated by the same MHW, there might be
51
52 278 a cluster effect. Based on an average of 15 inclusions per MHW and an intraclass correlation
53
54 279 coefficient (ICC) of 0.01, an inflation factor of 1.14 has been applied. This leads to a group size of 98
55
56 280 patients per arm. Because the clusters (number of patients per MHW) will probably not all have the
57
58
59
60

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

283 **Statistical analysis**

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

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

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

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

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

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

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

304 Healthcare costs are calculated based on healthcare utilisation, according to the method of the

305 *Guidelines for carrying out economic evaluations in health care* (52).

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3 306 For the outcomes for which the intervention is found to be effective, the effect of the covariates on
4
5 307 the outcomes will be explored.

6
7 308 First, intention to treat (ITT) analyses will be done. Then, per-protocol analyses will be carried out to
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9 309 estimate the effectiveness of the intervention if executed per protocol. During the analyses, the
10
11 310 assessor will be blinded about the groups.

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14 311 The validity of study results may be challenged by missing values, either at baseline or missing
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16 312 outcomes at follow-up. Multiple imputation will be used to address missing values at baseline for
17
18 313 relevant variables. For missing outcomes, correction for relevant prognostic factors will be
19
20 314 considered to ensure the validity of the results (53).

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23 315 The desirability and feasibility of the intervention according to patients and practitioners will be
24
25 316 measured qualitatively. Semi-structured interviews will be held. These will be transcribed, and then
26
27 317 coded by two independent researchers. Differences in coding will be discussed until consensus is
28
29 318 reached. Important themes will be identified, using the data as the starting point.

30 31 32 319 **Patient and public involvement**

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34 320 When developing the intervention, patients provided input on desired content and appearance, e.g.
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36 321 preference for short texts. Once implemented, the intervention was further adapted based on
37
38 322 patient feedback.

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41 323 When developing the study, patients provided input on the general idea. They also provided
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43 324 feedback on the recruitment process and in particular on the invitation letter to patients. Based on
44
45 325 their input, the study and the letter were adapted.

46 47 326 **Discussion**

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50 327 With an increased number of cancer survivors, there is an increased need for survivorship care.
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52 328 Providing survivorship care in primary care may improve access and reduce the pressure on
53
54 329 specialised institutions. In this study, the effectiveness of a primary care FCR intervention will be
55
56 330 compared to usual care. An evaluation of healthcare consumption and costs will assess whether this
57
58 331 can also decrease healthcare uptake and costs. To our knowledge, this is the first trial assessing the
59
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332 effectiveness of a primary care FCR intervention. In addition, it is one of few pragmatic trials on FCR
333 interventions.

334 Heterogeneity of usual care

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

338 Recruitment

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

344 Usual care

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

351 Randomisation level

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

357 **Trial status**

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

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3 360 **Declarations**
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- 5 361 1. Ethics approval and consent to participate: The Medical Research Ethics Committee Utrecht
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7 362 (METC Utrecht) has reviewed the study in accordance with the Dutch Medical Research Involving
8
9 363 Human Subjects Act (WMO) and other applicable Dutch and European regulations. Based on the
10
11 364 requirements of the WMO, the METC Utrecht has issued an approval of the above-mentioned
12
13 365 study. Any protocol amendments will be communicated to all relevant parties. Written consent is
14
15 366 obtained from study participants.
16
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18 367 2. Author contributions: All authors participated in the design of the study. YL wrote the draft
19
20 368 manuscript. ML, CH and NW improved the manuscript. All authors read and approved the final
21
22 369 manuscript.
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25 370 3. Funding: This work was supported by the Dutch Cancer Society (KWF) grant number 10936. KWF
26
27 371 is not involved in study design, collection, management, analysis, and interpretation of data,
28
29 372 writing of the report, the decision to submit the report for publication, nor does it have authority
30
31 373 over the publications.
32
33
34 374 4. Competing interests: The authors declare that they have no competing interests.
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37 375 5. Sponsor: Helen Dowling Institute, Professor Bronkhorstlaan 20, 3723 MB Bilthoven
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40 376 6. Acknowledgements: Not applicable.
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377 **References**

- 378 1. Rubin G, Berendsen A, Crawford SM, Dommett R, Earle C, Emery J, et al. The expanding role of primary
379 care in cancer control. *Lancet Oncol.* 2015;16(12):1231–72.
- 380 2. Ness S, Kokal J, Fee-Schroeder K, Novotny P, Satele D, Barton D. Concerns Across the Survivorship
381 Trajectory: Results From a Survey of Cancer Survivors. *Oncol Nurs Forum.* 2013;40(1):35–42.
- 382 3. Harrington CB, Hansen JA, Moskowitz M, Todd BL, Feuerstein M. It's Not over When it's Over: Long-
383 Term Symptoms in Cancer Survivors—A Systematic Review. *Int J Psychiatry Med [Internet].*
384 2010;40(2):163–81. Available from: <http://journals.sagepub.com/doi/10.2190/PM.40.2.c>
- 385 4. Brennan ME, Butow P, Spillane AJ, Boyle F. Patient-reported quality of life, unmet needs and care
386 coordination outcomes: Moving toward targeted breast cancer survivorship care planning. *Asia Pac J*
387 *Clin Oncol.* 2016;12(2):e323–31.
- 388 5. Lebel S, Ozakinci G, Humphris G, Mutsaers B, Thewes B, Prins J, et al. From normal response to clinical
389 problem: definition and clinical features of fear of cancer recurrence. *Support Care Cancer [Internet].*
390 2016;24(8):3265–8. Available from: <http://dx.doi.org/10.1007/s00520-016-3272-5>
- 391 6. Simard S, Thewes B, Humphris G, Dixon M, Hayden C, Mireskandari S, et al. Fear of cancer recurrence in
392 adult cancer survivors: a systematic review of quantitative studies. *J Cancer Surviv.* 2013;7:300–22.
- 393 7. Simard S, Savard J. Fear of Cancer Recurrence Inventory: Development and initial validation of a
394 multidimensional measure of fear of cancer recurrence. *Support Care Cancer.* 2009;17(3):241–51.
- 395 8. Simard S, Savard J. Screening and comorbidity of clinical levels of fear of cancer recurrence. *J Cancer*
396 *Surviv.* 2015;9(3):481–91.
- 397 9. Hedman C, Strang P, Djärv T, Widberg I, Lundgren CI. Anxiety and Fear of Recurrence Despite a Good
398 Prognosis: An Interview Study with Differentiated Thyroid Cancer Patients. *Thyroid [Internet].*
399 2017;27(11):1417–23. Available from: <http://online.liebertpub.com/doi/10.1089/thy.2017.0346>
- 400 10. Liao KYH, Yeung NCY, Wong CCY, Warmoth K, Lu Q. Fear of cancer recurrence and physical well-being
401 among Chinese cancer survivors: the role of conscientiousness, positive reappraisal and hopelessness.
402 *Support Care Cancer.* 2017;25(4):1141–9.
- 403 11. Smith A Ben, Sharpe L, Thewes B, Turner J, Gilchrist J, Fardell JE, et al. Medical , demographic and
404 psychological correlates of fear of cancer recurrence (FCR) morbidity in breast , colorectal and
405 melanoma cancer survivors with probable clinically significant FCR seeking psychological treatment

- 1
2
3 406 through the ConquerFear study. 2018;4207–16.
4
5 407 12. Simard S, Savard J, Ivers H. Fear of cancer recurrence: Specific profiles and nature of intrusive thoughts.
6
7 408 J Cancer Surviv. 2010;
8
9 409 13. Gil KM, Mishel MH, Belyea M, Germino B, Porter LS, Carlton LaNey I, et al. Triggers of Uncertainty
10
11 410 About Recurrence and Long-Term Treatment Side Effects in Older African American and Caucasian
12
13 411 Breast Cancer Survivors. *Oncol Nurs Forum*. 2004;31(3):633–9.
14
15 412 14. Simonelli LE, Siegel SD, Duffy NM. Fear of cancer recurrence: a theoretical review and its relevance for
16
17 413 clinical presentation and management. *Psychooncology*. 2017;26(10):1444–54.
18
19 414 15. Butow P, Sharpe L, Thewes B, Turner J, Gilchrist J, Beith J. Fear of Cancer Recurrence: A Practical Guide
20
21 415 for Clinicians. *Oncol J*. 2018;32(1):32–8.
22
23 416 16. Champagne A, Ivers H, Savard J. Utilization of Health Care Services in Cancer Patients with Elevated
24
25 417 Fear of Cancer Recurrence. *Psychooncology* [Internet]. 2018;(March):1–7. Available from:
26
27 418 <http://www.ncbi.nlm.nih.gov/pubmed/29719072><http://doi.wiley.com/10.1002/pon.4748>
28
29 419 17. Mikkelsen T, Sondergaard J, Sokolowski I, Jensen A, Olesen F. Cancer survivors' rehabilitation needs in a
30
31 420 primary health care context. *Fam Pract*. 2009;26(3):221–30.
32
33 421 18. NIVEL. Afstemming van zorg tussen huisarts en specialist bij kanker kan beter [Internet]. 2013 [cited
34
35 422 2018 May 22]. Available from: <https://www.nivel.nl/nl/nieuws/afstemming-van-zorg-tussen-huisarts->
36
37 423 [en-specialist-bij-kanker-kan-beter](https://www.nivel.nl/nl/nieuws/afstemming-van-zorg-tussen-huisarts-)
38
39 424 19. NHG. NHG-standpunt Oncologische zorg in de huisartsenpraktijk. 2014.
40
41 425 20. Fann JR, Eli K, Sharpe M. Integrating psychosocial care into cancer services. *J Clin Oncol*.
42
43 426 2012;30(11):1178–86.
44
45 427 21. Curran L, Sharpe L, Butow P. Anxiety in the context of cancer: A systematic review and development of
46
47 428 an integrated model. *Clin Psychol Rev* [Internet]. 2017;56(June):40–54. Available from:
48
49 429 <http://dx.doi.org/10.1016/j.cpr.2017.06.003>
50
51 430 22. Volker C, van der Lee M, Pet A. Angst voor terugkeer van kanker. *GZ-Psychologie*. 2011;3:30–8.
52
53 431 23. Cupit-Link M, Syrjala KL, Hashmi SK. Damocles' syndrome revisited: Update on the fear of cancer
54
55 432 recurrence in the complex world of today's treatments and survivorship. *Hematol Oncol Stem Cell Ther*
56
57 433 [Internet]. 2018; Available from: <https://doi.org/10.1016/j.hemonc.2018.01.005>
58
59 434 24. Chen D, Sun W, Liu N, Wang J, Zhao J, Zhang Y, et al. Fear of cancer recurrence: A systematic review of

- 1
2
3 435 randomized, controlled trials. *Oncol Nurs Forum*. 2018;45(6):703–12.
4
5 436 25. Sharpe L, Thewes B, Butow P. Current directions in research and treatment of fear of cancer
6
7 437 recurrence. *Curr Opin Support Palliat Care*. 2017;11(3):191–6.
8
9 438 26. Crane-Okada R, Kiger H, Sugerman F, Uman GC, Shapiro SL, Wyman-McGinty W, et al. Mindful
10
11 439 movement program for older breast cancer survivors: A pilot study. *Cancer Nurs*. 2012;35(4):1–13.
12
13 440 27. Lengacher CA, Shelton MM, Reich RR, Barta MK, Johnson-Mallard V, Moscoso MS, et al. Mindfulness
14
15 441 based stress reduction (MBSR(BC)) in breast cancer: Evaluating fear of recurrence (FOR) as a mediator
16
17 442 of psychological and physical symptoms in a randomized control trial (RCT). *J Behav Med*.
18
19 443 2014;37(2):185–95.
20
21 444 28. Lengacher CA, Reich RR, Paterson CL, Ramesar S, Park JY, Alinat C, et al. Examination of broad symptom
22
23 445 improvement resulting from mindfulness-based stress reduction in breast cancer survivors: A
24
25 446 randomized controlled trial. *J Clin Oncol*. 2016;34(24):2827–34.
26
27 447 29. Dieng M, Butow PN, Costa DSJ, Morton RL, Menzies SW, Mireskandari S, et al. Psychoeducational
28
29 448 Intervention to Reduce Fear of Cancer Recurrence in People at High Risk of Developing Another Primary
30
31 449 Melanoma: Results of a Randomized Controlled Trial. *J Clin Oncol*. 2016;
32
33 450 30. Dodds SE, Pace TWW, Bell ML, Fiero M, Negi LT, Raison CL, et al. Feasibility of Cognitively-Based
34
35 451 Compassion Training (CBCT) for breast cancer survivors: a randomized, wait list controlled pilot study.
36
37 452 *Support Care Cancer*. 2015;23(12):3599–608.
38
39 453 31. Lichtenthal WG, Corner GW, Slivjak ET, Roberts KE, Li Y, Breitbart W, et al. A pilot randomized
40
41 454 controlled trial of cognitive bias modification to reduce fear of breast cancer recurrence. *Cancer*.
42
43 455 2017;123(8):1424–33.
44
45 456 32. van de Wal M, Thewes B, Gielissen M, Speckens A, Prins J. Efficacy of blended cognitive behavior
46
47 457 therapy for high fear of recurrence in breast, prostate, and colorectal cancer survivors: The SWORD
48
49 458 study, a randomized controlled trial. *J Clin Oncol* [Internet]. 2017;35(19):2173–83. Available from:
50
51 459 [https://www.scopus.com/inward/record.uri?eid=2-s2.0-](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)
52
53 460 [85021649029&doi=10.1200%2FJCO.2016.70.5301&partnerID=40&md5=f159be668de252f5b14f60fe08](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)
54
55 461 [799680%0Ahttp://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/658/CN-](http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/658/CN-01395658/frame.html)
56
57 462 [01395658/frame.html](http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/658/CN-01395658/frame.html)
58
59 463 33. Butow P, Turner J, Gilchrist J, Sharpe L, Smith A Ben, Fardell JE, et al. Randomized trial of ConquerFear:

- 1
2
3 464 A novel, theoretically based psychosocial intervention for fear of cancer recurrence. *J Clin Oncol*.
4
5 465 2017;35(36):4066–77.
6
7 466 34. Otto AK, Szczesny EC, Soriano EC, Laurenceau J, Siegel SD. Supplemental Material for Effects of a
8
9 467 Randomized Gratitude Intervention on Death-Related Fear of Recurrence in Breast Cancer Survivors.
10
11 468 *Heal Psychol* [Internet]. 2016;35(12):1320–8. Available from:
12
13 469 http://supp.apa.org/psycarticles/supplemental/hea0000400/hea0000400_supp.html
14
15 470 35. Zernicke KA, Campbell TS, Specia M, McCabe-Ruff K, Flowers S, Carlson LE. A randomized wait-list
16
17 471 controlled trial of feasibility and efficacy of an online mindfulness-based cancer recovery program: The
18
19 472 eTherapy for cancer applying mindfulness trial. *Psychosom Med*. 2014;76(4):257–67.
20
21 473 36. Ugalde A, Haynes K, Boltong A, White V, Krishnasamy M, Schofield P, et al. Self-guided interventions for
22
23 474 managing psychological distress in people with cancer – A systematic review. *Patient Educ Couns*.
24
25 475 2017;100(5):846–57.
26
27 476 37. Elaine FH, Peter JB. On-site mental health workers delivering psychological therapy and psychosocial
28
29 477 interventions to patients in primary care: effects on the professional practice of primary care providers.
30
31 478 *Cochrane Database Syst Rev*. 2009;(1).
32
33 479 38. Del Giudice ME, Grunfeld E, Harvey BJ, Piliotis E, Verma S. Primary care physicians' views of routine
34
35 480 follow-up care of cancer survivors. *J Clin Oncol*. 2009;27(20):3338–45.
36
37 481 39. Johansen ML, Høltedahl KA, Rudebeck CE. How does the thought of cancer arise in a general practice
38
39 482 consultation? Interviews with GPs. *Scand J Prim Health Care*. 2012;30(3):135–40.
40
41 483 40. Mitchell AJ, Vahabzadeh A, Magruder K. Screening for distress and depression in cancer settings: 10
42
43 484 lessons from 40 years of primary-care research. *Psychooncology*. 2011;20(6):572–84.
44
45 485 41. Curran GM, Sullivan G, Mendel P, Craske MG, Sherbourne CD, Stein MB, et al. Implementation of the
46
47 486 CALM intervention for anxiety disorders: A qualitative study. *Implement Sci*. 2012;7(1):1–11.
48
49 487 42. Lawrence RA, McLoone JK, Wakefield CE, Cohn RJ. Primary Care Physicians' Perspectives of Their Role in
50
51 488 Cancer Care: A Systematic Review. *J Gen Intern Med* [Internet]. 2016;31(10):1222–36. Available from:
52
53 489 <http://dx.doi.org/10.1007/s11606-016-3746-7>
54
55 490 43. Berrett-Abebe J, Cadet T, Vitello J, Maramaldi P. Developing content for an interprofessional training on
56
57 491 fear of cancer recurrence (FCR): Key informant interviews of healthcare professionals, researchers and
58
59 492 cancer survivors. *J Psychosoc Oncol* [Internet]. 2018;0(0):1–15. Available from:

- 1
2
3 493 <https://doi.org/10.1080/07347332.2018.1443987>
4
5 494 44. Berrett-Abebe J, Cadet T, Nekhlyudov L, Vitello J, Maramaldi P. Impact of an Interprofessional Primary
6
7 495 Care Training on Fear of Cancer Recurrence on Clinicians' Knowledge, Self-Efficacy, Anticipated Practice
8
9 496 Behaviors, and Attitudes Toward Survivorship Care. *J Cancer Educ.* 2018;1–7.
10
11 497 45. Fidjeland HL, Brekke M, Vistad I. Scandinavian Journal of Primary Health Care General practitioners'
12
13 498 attitudes toward follow-up after cancer treatment: A cross-sectional questionnaire study. *Scand J Prim*
14
15 499 *Health Care [Internet].* 2015;334(4):223–32. Available from:
16
17 500 <http://www.tandfonline.com/action/journalInformation?journalCode=ipri20%0Ahttp://dx.doi.org/10.3>
18
19 501 [109/02813432.2015.1118836](http://dx.doi.org/10.3109/02813432.2015.1118836)
20
21 502 46. Nekhlyudov L, O'malley DM, Hudson S V. Integrating primary care providers in the care of cancer
22
23 503 survivors: gaps in evidence and future opportunities. *Lancet Oncol [Internet].* 2017;18(1):e30–8.
24
25 504 Available from: [http://dx.doi.org/10.1016/S1470-2045\(16\)30570-8](http://dx.doi.org/10.1016/S1470-2045(16)30570-8)
26
27 505 47. Adam R, Watson E. The role of primary care in supporting patients living with and beyond cancer.
28
29 506 2018;261–7. Available from: www.supportiveandpalliativecare.com
30
31 507 48. Landelijke vereniging POH-GGZ. Functie-en competentieprofiel POH-GGZ. 2014;17.
32
33 508 49. Helmond SJ Van, Lee ML Van Der, Vries J De. Study protocol of the CAREST-trial : a randomised
34
35 509 controlled trial on the (cost-) effectiveness of a CBT-based online self- help training for fear of cancer
36
37 510 recurrence in women with curatively treated breast cancer. *BMC Cancer [Internet].* 2016;1–11.
38
39 511 Available from: <http://dx.doi.org/10.1186/s12885-016-2562-0>
40
41 512 50. van Helmond SJ, van der Lee ML, de Vries J. Translation and validation of the Dutch version of the Fear
42
43 513 of Cancer Recurrence Inventory (FCRI-NL). *J Psychosom Res [Internet].* 2017;102(August):21–8.
44
45 514 Available from: <http://dx.doi.org/10.1016/j.jpsychores.2017.09.001>
46
47 515 51. Fitzmaurice GM, Laird NM, Ware JH. *Applied Longitudinal Analysis.* 2nd ed. Hoboken: John Wiley &
48
49 516 sons; 2004.
50
51 517 52. Assessment MT. Verdiepingsmodule Kostenevaluatie. Available from:
52
53 518 <https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren->
54
55 519 [van-economische-evaluaties-in-de-gezondheidszorg](https://www.zorginstituutnederland.nl/publicaties/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg)
56
57 520 53. Groenwold RHH, Moons KGM, Vandenbroucke JP. Randomized trials with missing outcome data: How
58
59 521 to analyze and what to report. *Cmaj.* 2014;186(15):1153–7.

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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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.