

ORIGINAL ARTICLE

The Trials within Cohorts design faced methodological advantages and disadvantages in the exercise oncology setting

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Abstract

Objectives: The Trials within Cohorts (TwICs) design is an alternative for pragmatic randomized controlled trials (RCTs) and might overcome disadvantages such as difficult recruitment, dropout after randomization to control, and contamination. We investigated the applicability of the TwICs design in an exercise oncology study regarding the recruitment process, representativeness of the study sample, contamination, participation, and dropout.

Methods: The Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation (UMBRELLA) Fit TwICs evaluates an exercise intervention in inactive breast cancer patients. Eligible patients participating in the prospective UMBRELLA were identified and randomized. Patients randomized to the intervention ($n = 130$) were offered the intervention, whereas controls ($n = 130$) were not informed.

Results: Fifty-two percent ($n = 68$) accepted the intervention. Because this rate was lower than expected, a larger sample size was required than initially estimated ($n = 166$). However, recruitment of 260 patients was still completed by one researcher within 30 months. Unselective eligibility screening and randomization before invitation improved representativeness. Disadvantage of the design might be inclusion of ineligible patients when cohort information is limited. Furthermore, the design faced higher noncompliance in the intervention group, but prevention of contamination.

Conclusion: The TwICs design improved logistics in recruitment and prevented contamination, but noncompliance due to refusal of the intervention was higher compared with conventional pragmatic exercise oncology RCTs, which may dilute the estimated intervention

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Ethics approval and consent to participate: This study was conducted according to the principles of the Declaration of Helsinki (Fortaleza, October 2013: <http://www.wma.net/en/30publications/10policies/b3/>) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The study has been approved by the Medical Ethics Committee of the University Medical Center Utrecht (15-166/D). Within the TwICs design, a stage-informed consent procedure is applied [10]. In the first stage, at cohort entry, patients are asked for consent to participate in the cohort study (collection of medical and patient-reported outcomes) and for consent to be randomized for future intervention studies within the cohort. Next, patients who are randomly selected for the intervention group in a randomized controlled trial within the cohort are asked for consent to participate in the intervention study.

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1. Introduction

The randomized controlled trial (RCT) is a powerful design for evaluating clinical interventions and is considered to generate a high level of evidence [1]. Randomly allocating participants to either the intervention or control group is expected to create prognostically comparable study groups, where the only difference between groups is the intervention. Hence, different sources of bias are minimized, especially when an RCT is double blinded (e.g., selection and information bias are possibly prevented) [1,2]. However, blinding is not possible in all fields of research. For example in exercise oncology RCTs, participants cannot be blinded for the intervention, which increases the risk of contamination between study groups, that is, controls also increase their physical activity level [3]. Another possible disadvantage of conventional RCTs in this field is difficult accrual and high dropout after randomization to control due to disappointment [4,5]. Also, participants in conventional RCTs are often a selected group of the population of interest because trial participation is (unconsciously) not offered to specific subgroups (although fitting the eligibility criteria). Patients who decline participation in an RCT tend to be different from those who agree [6,7]. This impairs representativeness of the study sample for the target population.

The Trials within Cohorts (TwiCs) design was proposed as an alternative to conventional pragmatic RCTs [8] and is also known as the cohort multiple RCT (cmRCT) design. With the TwiCs design, the intervention study is performed within an observational longitudinal cohort [8]. The Dutch “Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation” (UMBRELLA) was set up according to the TwiCs design [9]. The aim of UMBRELLA is to generate short- and long-term data on clinical and patient-reported outcomes undergoing radiotherapy and provide an infrastructure for multiple randomized evaluations of interventions. In UMBRELLA, a staged-informed consent model was implemented (Fig. 1) [10]. At cohort entry, consent is asked for participation in the cohort and, second, to be randomized into future intervention studies (stage 1). The second stage starts after randomization into an intervention study. Here, patients allocated to the intervention group are offered an intervention and asked to give informed consent to receive the intervention. The control group is not informed about being allocated to the control arm. Cohort-based regularly measured outcomes of the intervention group are compared with those that are measured in control group with the same frequency.

A fundamental difference with the conventional RCT design, where either both groups are blinded or both are not, is that in a study using the TwiCs design control, patients are not informed about the existence of the intervention, whereas the intervention group is informed. This prevents contamination and reduces dropout of controls. At the same time, effect sizes are affected by the percentage of patients agreeing to undergo the intervention [11].

The UMBRELLA Fit study is the first trial using the TwiCs design in the field of exercise oncology [12]. In UMBRELLA Fit, inactive women with breast cancer who were randomized to the intervention group were offered a 12-week supervised exercise intervention. Patients randomized to the control group were not informed, and cohort measures will be used for effect evaluation.

Here, we compare methodological characteristics of UMBRELLA Fit to comparable conventional exercise oncology RCTs and studied whether the TwiCs design facilitates recruitment, improved representativeness of the study sample for the target population, and minimizes contamination and dropout in the control group. In addition, we will explore challenges that may arise when performing a study using the TwiCs design.

2. Methods

2.1. Recruitment and participants

Since September 2013, all patients with breast cancer referred to the Department of Radiation Oncology of the University Medical Center Utrecht are approached for UMBRELLA cohort participation [9]. At cohort entry, informed consent is asked for collection of medical information, providing patient-reported outcomes through questionnaires and for randomization into future intervention studies (Fig. 2). So far, almost 2,500 patients consented to cohort participation. Of the patients invited for the cohort between October 2013 and July 2016, 88% gave consent for participation, and 87% also gave consent for potential future randomization [13].

The UMBRELLA Fit study was conducted within UMBRELLA. Patients were eligible for UMBRELLA Fit when they provided consent for future randomization at previous cohort entry, aged between 18 and 75 years, 12–18 months postinclusion in UMBRELLA, and had a physically inactive lifestyle (i.e., <150 min/wk commuting activities, leisure time and sports activities, ≥ 4 metabolic equivalent [MET]) as measured by the regularly collected Short

What is new?**Key findings**

- Easier patient recruitment was facilitated by the cohort in this trial using the Trials within Cohorts (TwICs) design. However, cohort data were sometimes insufficient for appropriate eligibility screening.
- The staged-informed consent procedure better reflects clinical practice. This might result in a less selective study sample, improved representativeness of results, and no contamination.
- The acceptance rate of the intervention was lower than expected and, hence, noncompliance in the intervention group was higher compared to conventional randomized controlled trials (RCTs). Therefore, the sample size needed to be increased, and the recruitment period extended. Instrumental variable analyses could be applied to account for noncompliance, but this will not totally reflect the causal effect under full adherence.

What this adds to what was known?

- Difficult accrual and contamination, often observed in conventional RCT in exercise oncology, could be prevented with the TwICs design.

What is the implication and what should change now?

- For pragmatic trials, the TwICs design could be an alternative to overcome problems of conventional RCTs.
- Before applying the TwICs design, it is recommended to perform a pilot study to assess whether profound eligibility screening can be performed with the available routinely collected cohort data. A pilot study also provides feasibility insight, that is, information on the uptake of the intervention offer which is needed for the sample size calculation, and availability of eligible patients in the cohort.
- Update the sample size when the actual acceptance rate deviates from the expected acceptance rate.

expected acceptance rate of 70% in the intervention group, a clinically relevant 10-point difference in quality of life, a power of 80%, and an alpha of 0.05 [12]. After the recruitment of 152 patients, the actual acceptance rate was lower than expected (i.e., 55% instead of 70%) and the sample size was updated, as recommended by Candlish et al. [15], to 260 patients. Noticeably, this sample size modification was not based on interim analysis of the trial outcome. Patients randomized to the intervention group were offered a 12-week exercise program, for which second-stage consent was asked. The control group was not informed and continued to completed cohort measures and received usual care.

The 12-week exercise program consisted of two 1-hour fitness sessions per week, supervised by a physiotherapist. Each session comprised a combination of moderate-to-vigorous aerobic and strength training [12]. The program was tailored to the patient's physical fitness level. In addition, patients were stimulated to be physically active for at least 30 min/day, according to the guidelines for patients with cancer [16]. An activity tracker was provided to support an active lifestyle.

2.2. Conventional pragmatic exercise oncology RCTs

To compare UMBRELLA Fit with conventional exercise oncology RCTs, PubMed was searched to identify systematic reviews up to May 2018, using the following MeSH terms: “Breast Neoplasms,” “Exercise,” “Quality of Life,” in combination with “Review” or “Meta-Analysis.” Eight systematic reviews published between 2011 and 2018 were screened for RCTs [17–24]. RCTs were eligible when the effect of a supervised exercise intervention on quality of life in inactive and/or sedentary breast cancer survivors after primary treatment was evaluated [18,19]. Studies investigating yoga and pilot studies were excluded. Finally, five RCTs were included (Supplementary Table 1) [25–29]. To assess the methodological quality of these RCTs, the Cochrane risk of bias tool was used [30]. All RCTs were classified as having a low risk of bias (Supplementary Table 2) [25–29].

In two of these RCTs, patients were 1–2 years post-treatment (except for adjuvant hormonal treatment) [25,27], and in three RCTs, patients were 3–6 years post-diagnosis [26,28,29]. The RCTs compared a supervised exercise intervention with usual care [26,28], wait-list control [27], or a placebo program, for example, light-intensity body conditioning/stretching [25,29]. Intervention duration varied from 8 to 12 weeks [25,28] to 12 months [29]. In some RCTs, home-based training was added to the intervention [26,28,29].

We compared characteristics of the recruitment process, representativeness of the study sample, contamination, participation, and dropout of UMBRELLA Fit with these five RCTs. Representativeness is defined as the representation of the study sample for the target population according

Questionnaire to ASsess Health-enhancing physical activity questionnaire [14]. Patients with self-reported contraindications (e.g., neurologic problems, arrhythmias, and walking problems) to exercise were excluded.

Recruitment started in October 2015 and was completed in March 2018. Before the start of the study, a required sample size of 166 patients was estimated based on an

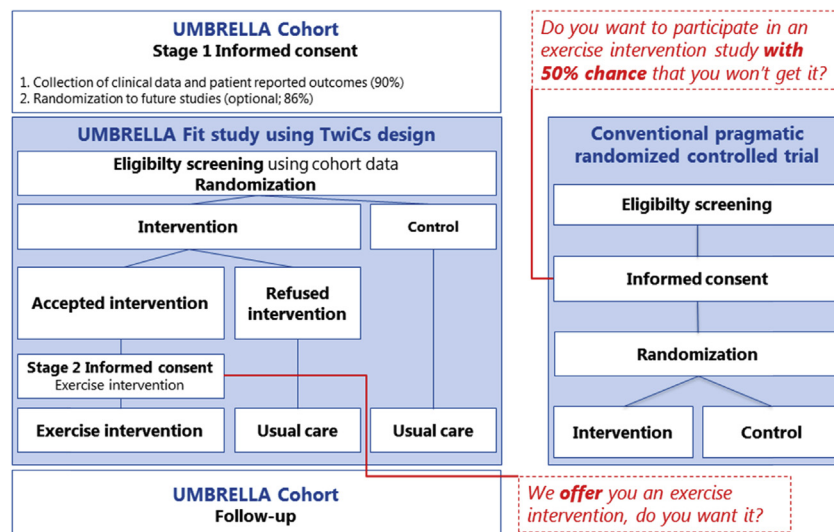


Fig. 1. The flow diagram of the UMBRELLA Fit study using the Trials within Cohorts (TwiCs) design (left side) vs. a conventional pragmatic randomized controlled trial design (right side). UMBRELLA, Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation.

to the study-specific inclusion and exclusion criteria. No general definition of contamination in physical exercise trials is available. Therefore, we used the definition of Waters et al. [31], as was earlier used in a systematic review on contamination in exercise oncology [3]. Contamination was defined as an increase of 60 minutes of moderate-to-vigorous physical activity (≥ 4 MET) per week in the control group or a 10% increase in the proportion of patients in the control group meeting the study exercise prescription. In addition, contamination was also scored to be present if reported by the authors.

3. Results

3.1. Recruitment

For UMBRELLA Fit, the initial sample size was 166. This sample was among others based on an expected

acceptance rate of 70% [12]. It took 18 months to identify and randomize these 166 patients. As recommended by Candlish et al. [15], we updated the sample size after the recruitment of 152 patients because the actual acceptance rate (55%) of the intervention deviated from the expected rate (70%). Twelve additional months were needed to reach the updated sample size ($n = 260$). In the sample of conventional exercise oncology RCTs, the sample size ranged from 75 to 222 patients (Table 1). In UMBRELLA Fit, eligible patients were identified from the UMBRELLA cohort, based on information from the routine cohort measurements, and randomized to either the intervention or control group. In the conventional RCTs, multiple recruitment strategies were used to reach the required sample size, including screening of potential eligible patients from cancer registries or medical records followed by an invitation letter from the treating physician [25,26,29], community

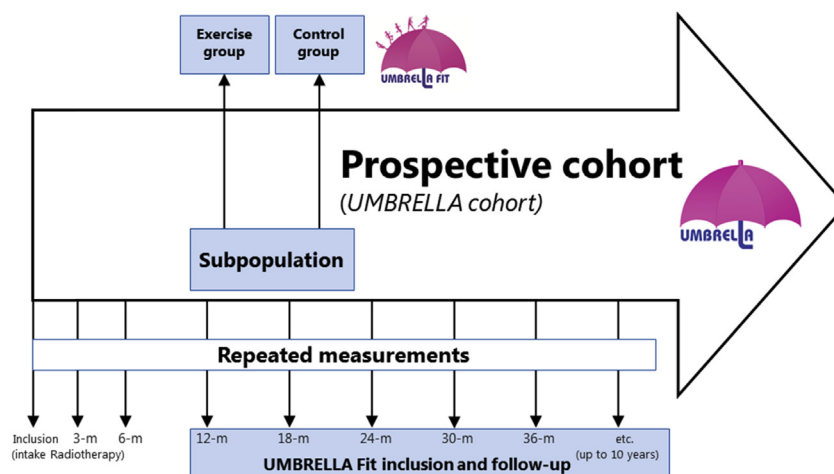


Fig. 2. The UMBRELLA Fit study using the Trials within Cohorts (TwiCs) design (adapted from Relton et al.). UMBRELLA, Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation.

Table 1. Participant flow in UMBRELLA Fit and conventional exercise oncology RCT

Study	Recruitment strategy	Number of patients screened	Number of patients randomized (% of patients screened)	Recruitment duration in months	Mean number of patients randomized per month
UMBRELLA Fit					
Gal et al. (2017)	Eligible patients identified from a cohort and randomized, and the intervention group was invited by a researcher	260	260 (100)	30	8.7
Conventional RCTs					
Daley et al. (2007)	Response to invitation letters of patients (identified from hospital records) and community strategies in cancer support groups and breast cancer nurses	572	108 (19)	30	3.6
Irwin et al. (2009)	Patients identified from a tumor registry received a recruitment packet or self-referral through media	788	75 (10)	22	3.4
Ohira et al. (2006)	Response to flyers sent to support groups/centers, cancer clinics, and physicians	350	86 (25)	9	9.6
Rogers et al. (2015)	Response to advertisement or referral by an oncologist, 453 within the target population	453	222 (49)	31	7.2
Winters-Stone et al. (2012)	Recruitment through a cancer registry, community events, study advertisements and information sessions, or clinician referral	359	106 (30)	14	7.6

Abbreviations: RCT, randomized controlled trials; UMBRELLA, Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation.

advertisements (e.g., advertisements, cancer support groups, and (social) media [25–29]), and referral by the treating physician [28]. The final number of patients randomized was only a fraction of the invited or screened patients, ranging from 9.5% to 36.4%. The number of patients recruited per month varied from 3 to 10. In contrast, in UMBRELLA Fit, it took 30 months to recruit 260 patients, that is, an average recruitment of nine patients per month and recruitment could be done by one researcher.

The information available from the routine cohort measurements appeared sometimes insufficient to exclude an ineligible patient. Nineteen patients refused the intervention because of limitations in physical functioning or diseases hampering participation in the exercise program. Conditions were, for example, another cancer diagnosis, heart disease, and one woman had six broken ribs and a broken collarbone from a car accident (Table 2).

3.2. Contamination

Mean change in physical activity level in the control group was 17 min/wk (95% confidence interval [CI] = −17, 52; Table 3). Physical activity increased in the intervention group with 72 min/wk (95% CI = 33–111).

One of the five conventional RCTs reported contamination [25]. In the RCT of Daley et al. [25], 64% of the

exercise placebo group (body conditioning/stretching program) and 9% of the usual care group became active during the intervention period (i.e., at least three activities per week). Two RCTs reported an increase in physical activity in the control group, but not sufficient to characterize it as contamination [26,28]. Two RCTs did not report postintervention physical activity data or mentioned contamination [27,29].

3.3. Participation and loss to follow-up

In UMBRELLA Fit, 48% ($n = 62/130$) refused the exercise intervention (Fig. 3). Of the patients refusing the exercise intervention, 31% ($n = 19/62$) refused because it was physically (e.g., heart failure and fibromyalgia) or mentally too demanding, and 36% ($n = 22/62$) refused because of lack of time. In addition, 24% ($n = 15/62$) refused the exercise intervention because they considered their lifestyle as already active.

Fifty-two percent of the patients ($n = 68/130$) accepted the exercise intervention. Of the patients who accepted the exercise intervention, 81% reported limitations in physical functioning, physical complaints, or diseases at the time the intervention was offered. Joint pain and arthritis were most often reported (60%; Table 2), followed by musculoskeletal problems (34%; e.g., a ruptured tendon in the shoulder and neuropathy in the feet). Of the 68 patients who started with

Table 2. Limitations in physical functioning, physical complaints or diseases of patients participating in the UMBRELLA Fit study

Limitations, <i>n</i> (%)	Accepted intervention, ^a <i>N</i> = 68	Refused intervention, ^b <i>N</i> = 62
Joint pain, arthritis, joint wear	41 (60)	
Musculoskeletal problems	23 (34)	10 (53)
Hypertension	13 (19)	
Heart failure/cardiac insufficiency (e.g., palpitations, mitral valve, hypertrophic cardiomyopathy)	12 (18)	2 (11)
Edema, pain in treated area	6 (9)	
Fibromyalgia	5 (7)	
Lung diseases (e.g., tension pneumothorax, asthma)	12 (18)	1 (5)
Diabetes mellitus	5 (7)	
COPD	2 (3)	
Mental problems, for example, anxiety, depression	2 (3)	
Other cancer diagnosis		2 (11)
Other comorbidities	19 (28)	4 (21)
No comorbidities	13 (19)	

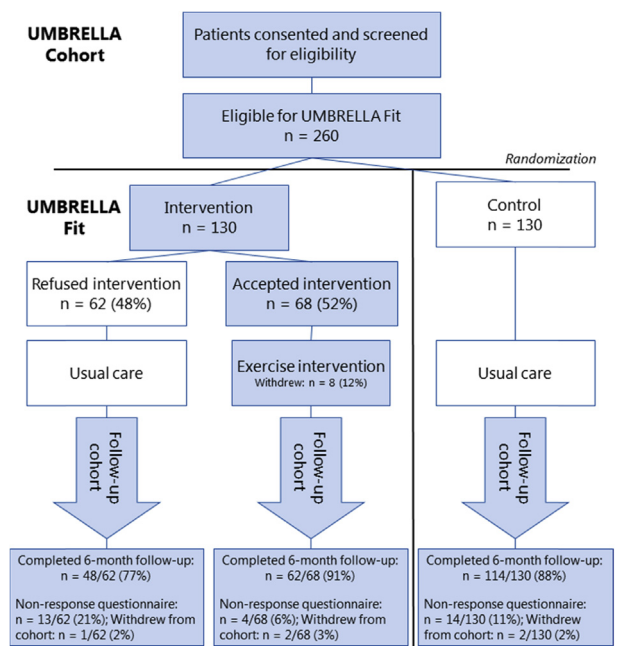
Abbreviations: COPD, chronic obstructive pulmonary disease; UMBRELLA, Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation.

^a Limitations that were present before the start of the intervention in patients who accepted the intervention. Patients could report multiple limitations.

^b Limitations considered as a reason to refuse the intervention. Patients could report multiple limitations.

the exercise program, 12% (*n* = 8/68) withdrew after a while because of medical conditions (*n* = 4), because of time constraints (*n* = 1), not liking exercising (*n* = 1), and other reasons (*n* = 2).

The next routine cohort measurement after inclusion to UMBRELLA Fit will be used to estimate intervention effectiveness. Therefore, loss to follow-up could result from cohort withdrawal or nonresponse to the follow-up questionnaire. In the control group, 12% (*n* = 16/130) did not

**Fig. 3.** Flow chart of the UMBRELLA Fit study. UMBRELLA, Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation.

complete the next cohort measurement, that is, 14 patients did not return the questionnaire, and two patients withdrew from the cohort. In the conventional RCTs, dropout in the control group ranged from 2% to 43% (Supplementary Table 1).

In the UMBRELLA Fit intervention group, 15% (*n* = 20/130) did not complete the next cohort measurement. This was 9% (*n* = 6/68, four nonresponses, two withdrawals) of the patients who accepted the intervention, and 23% (*n* = 14/62, 13 nonresponses and one withdrawal) of the patients who refused the intervention. The dropout rate in the intervention arm of conventional RCTs was below 10%, with the exception of the RCT of Winters-Stone et al. [29], where the dropout rate was 31%. The latter investigated a 12-month intervention, whereas duration in the other conventional RCTs was <6 months.

Table 3. Physical activity level at baseline and change between baseline and 6-month follow-up in UMBRELLA Fit

Measure	Control group, <i>N</i> = 130		Intervention group, <i>N</i> = 130	
	<i>n</i>	Median (IQR)	<i>n</i>	Median (IQR)
Physical activity level ^a at baseline in minutes per week	130	60 (0, 180)	128	60 (0, 120)
	<i>n</i>	mean (95% CI)	<i>n</i>	mean (95% CI)
Change between baseline and follow-up ^b in minutes per week	113	17 (−17, 52)	104	72 (33, 111)

Abbreviations: CI, confidence interval; IQR, interquartile range; UMBRELLA, Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation.

^a Including moderate-to-vigorous commuting activity, leisure time and sports activities, ≥4 metabolic equivalent.

^b Data on change in physical activity level were only available from patients who already completed the 6-mo follow-up questionnaire.

4. Discussion

This article describes the first experiences with a trial using the TwiCs design in the field of exercise oncology research. We experienced advantages and disadvantages compared with conventional RCTs. As a consequence of the design, refusal of the intervention and, hence, noncompliance was higher compared with conventional RCTs. Although a larger sample size compared with conventional RCTs was needed due to noncompliance, the cohort facilitated easier recruitment. The recruitment of 260 patients could be completed by one researcher in a reasonable time frame of 30 months. Unselective eligibility screening and the timing of randomization (i.e., before invitation) improved representativeness of the study sample. On the other hand, ineligible patients (for the specific study) might be included as a result of limited information provided by routine cohort measurement for eligibility screening. By design, contamination in the control group was prevented and thereby dilution of the intervention effect. Otherwise, noncompliance in the intervention group might dilute the effect, but this might better reflect clinical practice.

4.1. Recruitment

During the recruitment phase, the actual acceptance rate turned out to be lower than expected, and we had to increase our sample size and extend our recruitment period [11,32]. Fortunately, UMBRELLA Fit was performed within a dynamic cohort with continuous recruitment of eligible patients. For trials performed in fixed cohorts, updating the sample size could be problematic, resulting in underpowered trials [11]. Because of intervention refusal, the final sample size of our TwiCs study was larger compared with the sample sizes of the conventional RCTs. However, it took us less effort to reach the required sample size because we recruited from a large observational cohort, and recruitment could be done by a single researcher. Establishing and maintaining a cohort is expensive and labor-intensive in itself, but when established, the cohort provides an infrastructure for multiple RCTs, and efficiency is increased [8]. Also, physicians do not have to inform patients about (trial) interventions patients might not receive; only patients randomized to the intervention group (here the exercise intervention) were informed. This is in contrast to conventional RCTs that often experience recruitment as a time-consuming and especially labor-intensive process, usually requiring multiple recruitment strategies and/or failure to reach the required sample size. Because recruitment in UMBRELLA Fit was more efficient, a high number of patients were recruited per month, and this was performed by one researcher. Efficiency may outweigh the larger sample size, resulting in a reasonable duration of the (extended) recruitment period compared with conventional RCTs.

4.2. Representativeness

Eligibility screening is usually based on information from medical records, physician's judgment, and/or screening by the study team. Medical staff may (unconsciously) deem patients with physical complaints or fatigue as ineligible or unsuitable for trial participation, although the patient meets the eligibility criteria [33]. Many conventional RCTs excluded patients with comorbid conditions to minimize selective dropout or adjustments to the exercise program. As a result, older, more fatigued, or patients with more (severe) comorbidities are less frequently enrolled, and study samples are less representative for the general breast cancer population [33,34]. In contrast, eligibility in UMBRELLA Fit was based on information from routine cohort measurements and, therefore, unaffected by selection of treating physician or the study team. The level of comorbid conditions in UMBRELLA Fit illustrates that the study sample was more representative for the general inactive breast cancer population (who was treated with radiotherapy); 81% of the patients who accepted the intervention reported limitations in physical functioning, physical complaints or comorbid diseases. As a consequence, we had to make adaptations to the exercise program for patients when necessary. This was acceptable because UMBRELLA Fit is a pragmatic trial, and individual adaptations dependent on patient's condition will be done in practice as well. On the other hand, the information available from the routine cohort measurements appeared sometimes insufficient, resulting in patients who were randomized but appeared to not fitting all eligibility criteria. For example, current contraindicated limitations in physical functioning or diseases were not routinely documented in hospital-based medical records or reported by patients in the questionnaires, for example, heart failure or second cancer diagnosis. Presumably, however, ineligible patients were included in both study arms.

In conventional RCTs, after eligibility screening, the number of randomized patients is only a (selective) fraction of the patients invited, which has implications for representativeness of study results, that is, patients who participate often have higher education or a better lifestyle [35]. In UMBRELLA Fit, consent from patients in the intervention group was asked after randomization and refusers remained part of the intervention group, inducing a more representative study sample. In general, representativeness of the study sample when using the TwiCs design is dependent on the representativeness of the cohort participants for the target population. In the UMBRELLA cohort, participation was relatively high (88% consented for participation, and 87% consented for potential future randomization [13]), and we assume that it is a representative cohort of breast cancer patients (undergoing radiotherapy). We could not compare our study sample to the patients included in the conventional RCTs because eligibility criteria (e.g., age, postmenopausal status, nonsmoking) and intervention

characteristics (e.g., duration, level of supervision, intensity of physical exercise) differed between studies.

In future trials using the TwiCs design, we recommend performing a pilot study first, especially in fixed cohorts, to get more insight into the acceptance rate of the intervention and recruitment timelines. This was also recommended by Reeves et al. [11] who performed a trial within a fixed cohort, which makes pilot testing even more important. When noncompliance is higher than expected, resulting in a larger sample size, the trial might not be feasible in the cohort when the fixed cohort contains not enough eligible participants. Compared with conventional RCTs, a pilot of a trial using the TwiCs design can be done more easily because the participants can be recruited from the cohort, and the trial infrastructure is already available within the cohort. In addition, we recommend optimizing eligibility screening by carefully checking before the start of the study whether all relevant information is available in the cohort or how this information can be obtained. Linking with data from general practice might be an option to assess real-time medical conditions.

4.3. Contamination

In UMBRELLA Fit, the control group was not informed about their role as control, and hence, contamination of controls was prevented. Any change in physical activity in the control group reflects the natural course. Also, the small increase in physical activity in our control group did not meet the definition of contamination [31]. In control groups of conventional RCTs, increase of physical activity levels is rather common [3,25,26,28] and might be due to study participation (i.e., contamination), natural course, or a combination of both. In a review of exercise oncology RCTs in mixed cancer types, contamination was reported in 78% of the exercise trials where control patients were asked to maintain their usual level of physical activity, and no intervention was offered after the study period [3]. Contamination may have resulted in underestimation of the real effect of exercise interventions. With the TwiCs design, we can exclude contamination and its consequences on the intervention effect.

4.4. Participation and loss to follow-up

In TwiCs, by design, refusers of the intervention are part of the intervention group. Consequently, noncompliance in the intervention group is higher in a trial using the TwiCs design. An intention-to-treat (ITT) analysis provides an estimation of the effect of offering the intervention to patients. However, when noncompliance increases, the intervention effect may be increasingly diluted when applying the ITT analysis [36]. Instrumental variable analyses could be applied to account for noncompliance and may provide a better estimate of the intervention effect than the ITT

analyses [36,37]. However, this will not totally reflect the causal effect under full adherence [38].

In UMBRELLA Fit, control patients could not withdraw trial participation because they were not informed about their role as control. Only loss to follow-up due to cohort withdrawal and nonresponse to cohort questionnaires may occur. This was 12% in the control group, which was not lower but comparable with the conventional exercise oncology RCTs [25–28]. In the same way, loss to follow-up was 15% in the intervention group and was slightly higher compared with the conventional RCTs. Loss to follow-up was highest among those who refused the intervention. This differential loss to follow-up may bias the results and will be an increasing problem when the length of follow-up increases [9].

5. Conclusion

The UMBRELLA Fit study is the first trial using the TwiCs design in the field of exercise oncology. Based on our experiences, the design holds the promise to overcome shortcomings of conventional pragmatic RCTs, in particular, in terms of easier recruitment, prevention of contamination, and higher representativeness of the study sample. At the same time, we faced challenges regarding limited information provided by the routinely measured data from the cohort, which may decrease the representativeness of the study sample, high noncompliance in the intervention group requiring a larger sample size, and higher loss to follow-up than expected. Further research will show the implications of (selective) refusal of the intervention and loss to follow-up on effect estimation. Future trials, taking our recommendations into account, will provide further insights in what settings, populations, and treatments the TwiCs design is most applicable.

CRediT authorship contribution statement

Roxanne Gal: Methodology, Writing - original draft, Writing - review & editing. **Evelyn M. Monninkhof:** Methodology, Supervision, Writing - review & editing. **Carla H. van Gils:** Methodology, Writing - review & editing. **Rolf H.H. Groenwold:** Methodology, Writing - review & editing. **Desirée H.J.G. van den Bongard:** Methodology, Writing - review & editing. **Petra H.M. Peeters:** Methodology, Writing - review & editing. **Helena M. Verkooyen:** Methodology, Writing - review & editing. **Anne M. May:** Funding acquisition, Methodology, Supervision, Writing - review & editing.

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Supplementary data

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