The trials within cohorts design facilitated efficient patient enrollment and generalizability in oncology setting

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Abstract

Objectives: The trials within cohorts (TwiCs) design aims to improve recruitment efficiency. We conducted the first TwiCs in radiation oncology and described efficiency of the design and generalizability of the results.

Study Design and Setting: In two radiotherapy centers, patients with rectal cancer were asked to participate in a prospective cohort study and to provide broad consent for randomization and patient-reported outcomes (PROs). Consenting patients who met the trial criteria were randomized directly after cohort enrollment. The intervention arm was offered a radiotherapy boost. We evaluated acceptance rate, its impact on sample size, and compared clinical characteristics between trial participants and patients of the Dutch national cancer registry.

Results: 128 of the 200 eligible patients (64%) were randomized. Sixty-two patients did not consent (in time) to cohort participation, to broad randomization, or to PROs. Of the 64 patients in the intervention arm, 52 (81%) accepted the intervention. During the trial, the acceptance rate dropped temporarily, after which sample size was adapted. Trial patients were comparable in age, comorbidity, and disease stage to the national rectal cancer population.

Conclusions: The TwiCs design is feasible, allows enrollment of a high proportion of randomizable patients, with positive impact on trial efficiency and generalizability of results in a clinical oncology setting. © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Keywords: Study design; Clinical trial; Trials within cohorts; Patient recruitment; RCT

1. Introduction

In conventional randomized controlled trials (RCTs), patient recruitment is challenging and poses a burden on physicians and researchers [1]. This prolongs trial duration, increases costs, and delays availability of beneficial treatments for patients [2,3]. Important reasons for patients not to participate in RCTs include preference for one of the treatment arms, difficulties understanding the concept of an RCT and dislike (or anxiety) of the concept of randomization [4]. The trials within cohorts (TwiCs) design, also known as the cohort multiple RCT design, aims to improve recruitment efficiency of participants in pragmatic trials [5]. In contrast to conventional RCTs, informed consent for the experimental interventions in TwiCs is obtained after randomization and only from those who are randomized to the intervention arm [6],

The key element of the TwiCs design is a large prospective cohort of individuals with a condition of interest in which longitudinal outcome measurements are collected [5]. In

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What is new?

Key findings
- The trials within cohorts (TwiCs) design resulted in efficient patient recruitment and improved generalizability and allowed easy sample size adaptation in a radiation oncology trial for patients with locally advanced rectal cancer.

What this adds to what was known?
- Prior TwiCs studies used batch randomization in longitudinal large cohorts. Our study is the first example of TwiCs in which patients were randomized directly after cohort enrollment, showing that this approach is feasible and efficient.

What is the implication and what should change now?
- The TwiCs design may be considered more often for pragmatic trials in a clinical oncology setting as it may improve generalizability of the trial results and shorten trial duration.

some TwiCs settings, participants provide broad consent for future randomization at time of cohort enrollment [6]. By giving broad consent for future randomization, participants agree to be randomized to experimental interventions when eligible, which they can accept or refuse. If accepted, additional informed consent is signed. Participants who refuse the intervention undergo standard treatment (treatment as usual) and remain in the intervention group for intention to treat analysis. Participants randomized to the control group will not be informed about the experimental intervention or the trial, and their clinical data are used comparatively. TwiCs has the potential to improve recruitment efficiency and to avoid disappointment bias, contamination, and cross-over of control group participants [7].

Timing of randomization of eligible cohort participants in TwiCs varies according to the intervention under study, as does the approach of randomization of patients from the cohort. Some TwiCs have used an approach in which all eligible cohort participants were randomized at one moment in time (Fig. 1A) [8,9]. Here, a random sample is offered the intervention and all other cohort participants are assigned to the control group. This 'single-batch sampling approach' is feasible in closed or recruiting cohorts [10,11]. A second method described in literature is the 'multiple-batch sampling approach', where a subgroup of eligible cohort participants is randomized at one moment in time (Fig. 1B) [12]. In this approach, the cohort (closed or recruiting) continues to include eligible individuals who are not allocated to either the treatment or control arm after the first round of randomization. Multiple rounds of randomization are applied to achieve the final sample size. The biggest advantage of these two approaches is the highly time efficient patient recruitment.
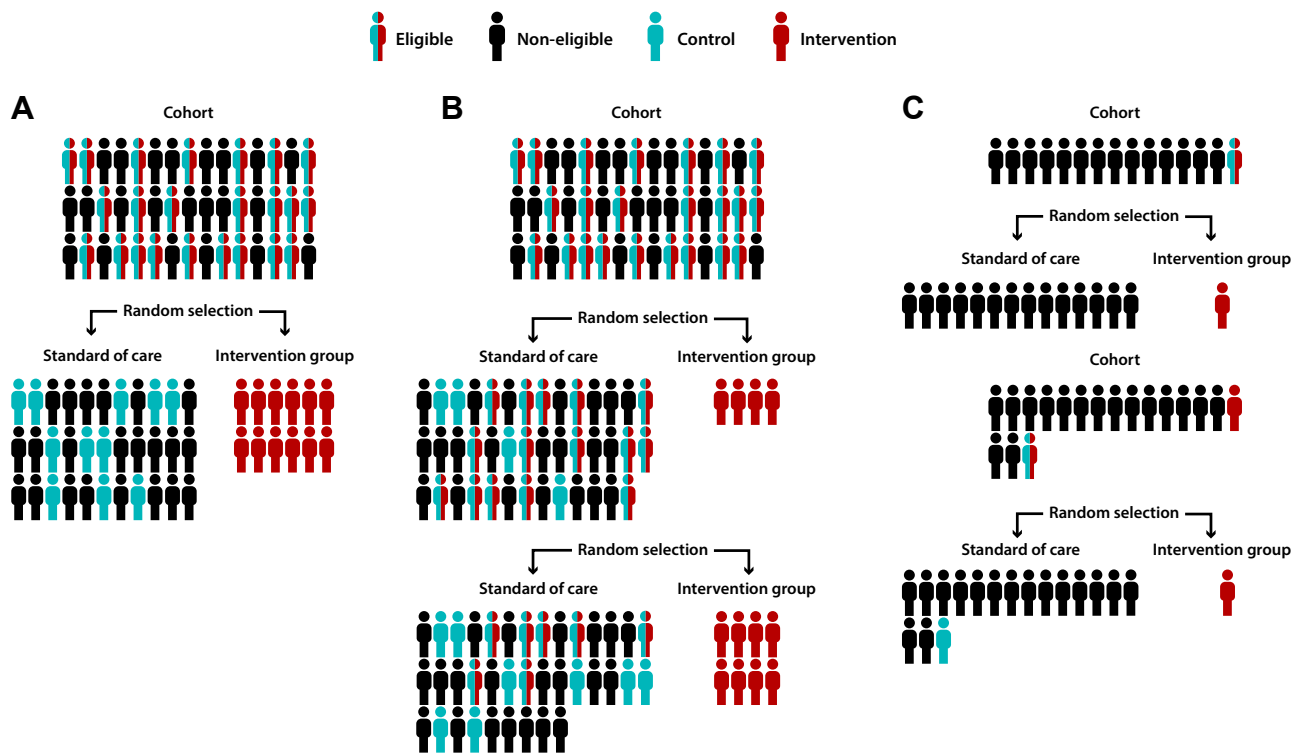
Fig. 1. Timing of randomization in the Trials Within Cohorts (TwiCs) design including batch randomization of all eligible cohort participants (A), batch randomization of a subgroup of eligible cohort participants (B), and randomization of participants directly after cohort enrollment (C).

For some interventions however, both the single and multiple-batch randomization approaches are not feasible. Typically, in clinical settings, screening for trial eligibility and randomization often needs to take place within a short time frame, for example, shortly after diagnosis or after occurrence of a relapse or complication. In these situations, eligible participants should be randomized as they consented, rather than all being randomized at the same time, which means shortly after they become eligible for the intervention (Fig. 1C). In essence, this is comparable with enrollment in a conventional RCT, with the difference being the timing of randomization and the staged-informed consent procedure. This randomization approach often requires a recruiting cohort and can be applied shortly after the start of the cohort study and does not request the availability of a large cohort.

We implemented a TwiCs with direct randomization after cohort enrollment in a clinical radiation oncology setting to study the effect of dose-escalated chemoradiation on complete tumor response in locally advanced rectal cancer (RECTAL-BOOST). The RECTAL-BOOST trial was conducted within a prospective colorectal cancer cohort [13,14]. This study describes the feasibility of patient recruitment and the randomization approach, its implications for recruitment efficiency and sample size, and generalizability of results.

2. Methods

2.1. Design and patients

The RECTAL-BOOST was a multicenter, phase 2, pragmatic RCT conducted within the national Prospective Data Collection Initiative on Colorectal Cancer (PLCRC) cohort [13,14]. Patients were recruited at the Departments of Radiation Oncology of the University Medical Center (UMC) Utrecht and in the MAASTRO Clinic/Maastricht University Medical Center (MUMC+). Patient recruitment started in September 2014 in the UMC Utrecht. MAASTRO Clinic/MUMC+ was added as a participating center in March 2017. PLCRC and RECTAL-BOOST were approved by the Medical Research Ethics Committee of the UMC Utrecht and the institutional review board of the MAASTRO Clinic/MUMC+.

In PLCRC, clinical data were prospectively collected, and participants consented to fill in patient-reported outcome (PRO) measures at set time intervals. Furthermore, broad consent for future randomization for experimental interventions within PLCRC was obtained. Cohort participants were informed about the stage-informed consent procedure, that is, that they will not be informed about new interventions in case they are randomized to a control group and that their data may be used comparatively to those who will get the intervention. They were also informed that in case of randomization to the active arm of an experimental study, they were going to be offered the intervention which they could accept or refuse.

2.2. Patient recruitment and randomization

All patients with rectal cancer received information about PLCRC by e-mail before visiting the Department of Radiation Oncology. At their first visit, patients met with a researcher before their intake with the radiation oncologist. Here, they were asked to provide informed consent for cohort (PLCRC) participation. PLCRC participants with locally advanced rectal cancer who were referred for chemoradiation and who met the study-specific inclusion and exclusion criteria as described in the trial protocol were identified eligible for the trial [13]. After signing informed consent for PLCRC, eligible patients were immediately randomized. Centralized randomization was performed at the UMC Utrecht on 1:1 ratio and stratified by the participating center. Patients allocated to the intervention arm were informed about the RECTAL-BOOST by the radiation oncologist and offered the boost intervention. Patients who accepted the offer signed additional informed consent. Patients who refused the offer were planned for standard treatment but remained part of the intervention group for outcome analyses (according to intention to treat). Patients randomized to the control group received treatment as usual (standard chemoradiation). Enrollment was interrupted for 8 months after the first 10 patients in the intervention arm were treated with the boost intervention followed by sphincter-sparing surgery, for safety reasons.

Patients in the intervention arm who accepted the intervention underwent a neoadjuvant external radiotherapy boost before standard neoadjuvant chemoradiation. The extra burden associated with the experimental intervention included five extra days of radiotherapy (i.e., five extra hospital visits). As such, the total treatment duration was 30 days in the intervention arm vs. 25 days in the control arm. Also, patients who accepted the intervention underwent additional imaging. Potential risks for patients in the intervention group included higher acute toxicity, which was estimated to be minimal based on previous studies [15]. Potential benefits of receiving the intervention included a hypothesized higher probability of a complete tumor response.

2.3. Sample size

The estimated sample size was 60 patients per arm, based on a one-sided test, type I error of 15% (as this was an early phase, or screening trial, before a definitive phase three trial) and a power of 80%, and assuming a 20% refusal rate in the intervention arm, as described previously [13]. Because one of the advantages of the TwiCs design is that the sample size can be adapted in case the actual acceptance rate of the intervention deviates from the estimated acceptance rate [16,17], we planned to evaluate the acceptance rate after randomization of the 100th patient to adapt the sample size if needed.

2.4. Generalizability

To evaluate the representativeness of the RECTAL-BOOST population, we compared the baseline characteristics of trial patients with the general rectal cancer population registered in the Dutch National Cancer Registry (provided by the Netherlands Comprehensive Cancer Organisation, IKNL) using descriptive statistics. In this nationwide population-based registry, information on patient and tumor characteristics, diagnosis, and treatment is routinely extracted from medical records by trained registration teams. We selected patients diagnosed with locally advanced rectal cancer between 2008 and 2014, a rectal tumor less than 10 cm from the anus, with complete registration on comorbidity, and who were treated with chemoradiation, yielding 396 patients.

3. Results

3.1. Recruitment and sample size adaptation

Between September 2014 and July 2018, 288 consecutive patients with locally advanced rectal cancer were referred for chemoradiation to the two radiotherapy centers (Fig. 2). Seventy-eight patients did not meet the inclusion and exclusion criteria, and 10 patients were not eligible because of a stop for patients undergoing sphincter-sparing surgery (an inclusion stop of 8 months was applied after the first 10 patients treated with dose-escalated chemoradiation followed by a low anterior resection, to compare anastomotic leakages between the boost and control group). Of the 200 patients who remained potentially eligible for the RECTAL-BOOST, 10 were not invited to participate in PLCRC because of logistic reasons. One hundred ninety eligible RECTAL-BOOST
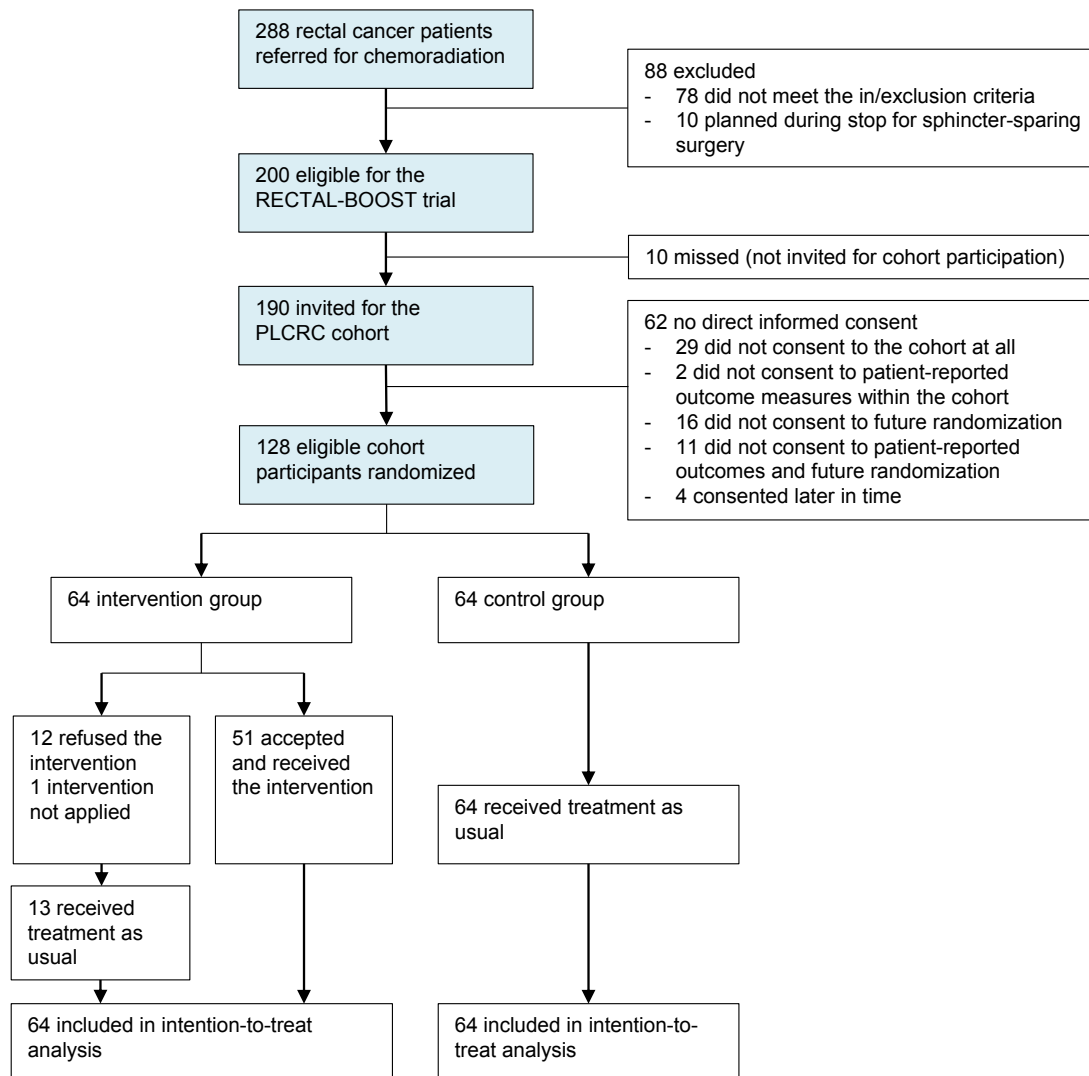

Fig. 2. Flowchart of screened and eligible patients for the RECTAL-BOOST within the Prospective Data Collection Initiative on Colorectal Cancer (PLCRC) cohort.

patients were asked for PLCRC, of whom 62 (34%, 95% confidence interval (CI): 26−39%) patients did not consent (directly) to cohort participation. Of these non-participants, 29 (47%) patients did not consent to PLCRC at all, 2 (3%) patients did not consent to PROs within PLCRC, 16 (26%) patients did not consent to future randomization within PLCRC, 11 (18%) patients did not consent to PROs and future randomization, and 4 (7%) patients consented later in time (i.e., after the moment that randomization was feasible).

After the 100th randomization, 50 patients had been allocated to the intervention group and the acceptance rate was 78% (39 patients accepted to undergo the intervention). However, of the last 13 patients allocated to the intervention group, only 6 (46%) had accepted the offer. Extrapolating this trend, the final acceptance rate would become 73%, which was lower than the anticipated acceptance rate of 80%, and which would have reduced the power of the study. We therefore calculated a new sample size based on observed new acceptance rate of 73% resulting in 71 patients per arm. However, after the 128th randomization, 64 patients had been allocated to the intervention arm, of whom 52 patients (81%) accepted to undergo the intervention. At this point, we stopped trial recruitment based on the original sample size.

In total, 128 of the 200 (63%, 95% CI 57−71%) eligible patients were randomized in a total of 48 months. This corresponds with a recruitment rate of 2.7 patients/month (not corrected for the 8-month recruitment pause for patients planned for low anterior resection); 2.4 patients/month in the UMC Utrecht (116 patients in 48 months), and 0.7 patient/month in MAASTRO Clinic/MUMC+ (12 patients in 17 months). Of the 64 patients in the intervention group, 52 (81%, 95% CI 72−91%) accepted the offer and 51 (80%) received the boost intervention. In one patient, the intervention could not be administered because the tumor was too close to the small bowel. All 13 patients who did not receive the boost intervention underwent standard chemoradiation. In the control group, all patients received standard chemoradiation and no cross-over was observed.

3.2. Generalizability

Of all 128 randomized patients, the median age was 64 years [IQR 55−70], 95 (74%) were male, 45 (35%) had presence of one comorbid condition, and 26 (20%) had two or more (Table 1). Most patients had a clinical T3 tumor stage ($N = 90$, 70%) or a T4 stage ($N = 31$, 24%) and were diagnosed with regional lymph node metastases ($N = 144$, 89%). In terms of age, comorbidities, and disease stage, trial patients were comparable with the general rectal cancer population. The RECTAL-BOOST, however, included fewer female patients (26% vs. 39% in the general rectal cancer population).

4. Discussion

In this article, we evaluated our experiences of a TwiCs on dose-escalated chemoradiation in patients with rectal cancer embedded within a colorectal cancer cohort using randomization directly after cohort enrollment. We showed that this trial design resulted in efficient patient recruitment indicated by the high percentage of actually randomized patients out of all theoretically eligible patients. Patients in the RECTAL-BOOST were fairly comparable with a sample from the national rectal cancer registry in terms of age, comorbidities, and disease stage, indicating a representative study population. This suggests that the results obtained from the trial are likely generalizable. Also, the sample size was easily adapted (and readapted) when the acceptance rate dropped to pursue optimal statistical power.

We experienced a high accrual rate of 44% (128/288) and a high patient participation rate of 64% (128/200) in the RECTAL-BOOST, despite the sample size adjustment because of temporary lower acceptance rate. Literature on accrual in patients with cancer shows much lower rates of 5−14% [18−20]. In a prospective study on trial recruitment of 1022 new patients with cancer, only 16% of the eligible patients participated in a trial [20]. Low accrual and participation is partly related to the lack of clinical trials appropriate for the type and stage of cancer, strict inclusion criteria of trials, and to refusal of the patients because of preferences or logistical reasons [19].

Efficiency in a TwiCs is mostly influenced by cohort enrollment and randomization, and the acceptance rate of the intervention [7]. The latter mostly depends on the participant's perception of harms and benefits of trial participation. The boost intervention had a potential benefit for the patient with a relatively low risk of toxicity. The 20% noncompliance in the intervention arm was due to patient preference for standard treatment, except for one patient who did not receive the intervention for technical/clinical reasons (dose constraints). The acceptance rate among published TwiCs varies [8,10,21,22]. In a TwiCs on depression treated by homeopaths, 95 of the 185 (51%) patients in the intervention group accepted the offer of treatment [10]. In a TwiCs evaluating the effect of telephone-based health coaching (6 monthly 20 minute calls) on self-management and quality of life, 100 of the 252 (40%) patients in the intervention group consented to receive the intervention [8]. Larger sample sizes are needed in case of a high rate of noncompliance to account for dilution of the treatment effect in TwiCs studies [11].

Sample size considerations in TwiCs remain a critical issue because of potential selective noncompliance, that is, selective refusal of the allocated treatment [7]. When the noncompliance is higher than expected, sample size adaptation during patient recruitment should be considered [16]. A pilot study may be of guidance to evaluate the acceptance rate for a certain intervention. In a TwiCs where the control group consists of all eligible cohort participants

Table 1. Baseline characteristics of the RECTAL-BOOST study population (arms combined) and selected patients with rectal cancer within the Dutch National Cancer Registry

Characteristics	RECTAL-BOOST (n = 128)	Sample of general population with rectal cancer (n = 396)[a]
Age, median years (IQR)	64 (55—70)	65 (57—70)
Sex		
Male	95 (74%)	240 (61%)
Female	33 (26%)	156 (39%)
Comorbidities		
None	57 (45%)	174 (44%)
One	45 (35%)	113 (29%)
Two or more	26 (20%)	109 (28%)
Tumor stage		
cT2	7 (6%)	28 (7%)
cT3	90 (70%)	251 (63%)
cT4	31 (24%)	117 (30%)
Nodal stage[b]		
cN0	14 (11%)	37 (9%)
cN1-2	144 (89%)	342 (86%)

Abbreviation: IQR, interquartile range.

[a] Selected patients of the National Cancer Registry with locally advanced rectal cancer referred for chemoradiation between 2008 and 2014, with a rectal tumor lower than 10 cm from the anus and with complete registration on comorbidity.

[b] Numbers and percentages in the general population group do not add up because of 17 missing values on nodal stage.

(as depicted in Fig. 1A), sample size adaptation may become difficult especially when performed within a closed cohort (i.e., the total number of available participants is fixed). For example, in the TwiCs on the efficacy of a telephone-based health coaching on self-management and quality of life, the sample size needed to be expanded because of a lower acceptance rate than expected [11]. However, all remaining eligible cohort participants were already assigned as controls. Expanding the sample size with controls was not considered a valid option because part of these did not meet the trial criteria anymore. New eligible patients in the previously ineligible cohort were therefore identified. Nevertheless, these patients may have been more likely to refuse the intervention. In a TwiCs using batch randomization of a subgroup of eligible cohort participants or randomization directly after cohort enrollment, the sample size is easily increased because the cohort contains more eligible patients. Furthermore, randomization directly after cohort enrollment allows monitoring of the acceptance rate after each randomization. The sample size can be adapted, if needed, until the acceptance rate is achieved. In this way, sample size extension in TwiCs becomes flexible. This is not problematic because sample size adaptation is based only on the acceptance rate, and independent of the outcome. In the initial trial protocol of a TwiCs, one can choose to incorporate the option for sample size adaptation including various scenarios of different acceptance rates.

In the RECTAL-BOOST, we obtained a representative study population as shown by the comparison with the data of population-based data on patients with rectal cancer. According to a literature review on the representativeness of RCTs, real-world patients with cancer are often older, more likely to be female, and have a poor performance status and worse disease prognosis than patients in RCTs [23]. In the RECTAL-BOOST, a lower proportion of female patients was included as compared with the general population with rectal cancer. This is, at least partly, explained by the RECTAL-BOOST exclusion criterion of female patients with a ventral tumor in the rectal wall in close proximity of the uterus and vagina due to boost treatment planning constraints. This exclusion criterion was removed in December 2015 via amendment approved by the ethics committee of the UMCU after which the proportion of female patients increased to 30% of the randomized patients. Still, this proportion is lower than observed in the national cancer registry.

A TwiCs in a clinical setting has some downsides. The staged-informed consent procedure demands detailed education of health care professionals who are involved in the trial as it is crucial not to inform eligible trial participants about the trial before randomization. Also, patients in the active arm may talk about their trial participation on patient platforms, social media, or in the waiting room. In case a patient has heard of the trial before randomization, the benefit of TwiCs regarding the avoidance of disappointment bias in the control group is diminished. Also, doctors may find it (ethically) difficult not to explain the trial to patients allocated to the control group especially when patients ask about on-going trials or the specific trial of interest. For this, we think it is highly important to clarify the staged-informed consent procedure for patients at time of cohort enrollment and to inform health care professionals in detail about the TwiCs design.

5. Conclusions

In the example of the RECTAL-BOOST, the TwiCs design with randomization of patients directly after cohort enrollment in a clinical oncology setting resulted in a high proportion of randomizable patients, with positive impact on trial efficiency and generalizability of results.

CRediT authorship contribution statement

Alice M. Couwenberg: Conceptualization, Methodology, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Johannes P.M. Burbach:** Conceptualization, Methodology, Writing - review & editing. **Anne M. May:** Conceptualization, Methodology, Writing - review & editing. **Maaike Berbee:** Methodology,

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