

ORIGINAL ARTICLE

Most patients reported positively or neutrally of having served as controls in the trials within cohorts design

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Abstract

Objectives: To evaluate patients' experience of having served as controls without a notification at the time of randomization in the context of the trial within cohorts (TwICs) design.

Methods: Patients were asked for their opinion on having served as controls in TwICs, before and after having been provided the trial results. Patients had provided broad consent to randomization at cohort entry and had served as controls in one of two TwICs (an exercise program after breast cancer treatment or radiotherapy dose-escalation for rectal cancer).

Results: Two to 6 years after cohort entry, 15% ($n = 16$) of all patients remembered having provided broad consent to randomization. Before disclosure of trial results, 47% ($n = 52$) of patients thought positively, 45% ($n = 50$) neutrally, and 2% ($n = 2$) negatively of having served as controls in one of the two trials. Seventeen percent ($n = 18$) of patients were positive, 65% ($n = 71$) neutral, and 11% ($n = 12$) negative about not having been notified when serving as controls. The survey results were comparable after disclosure of trial results.

Conclusions: These results support the use of the TwICs design with the staged-informed consent procedure. Keeping patients engaged and aware of the consents provided might further improve patients' experience of serving as controls in TwICs. © 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Keywords: Trials within cohorts; Randomized controlled trials; Informed consent; Broad consent; Patients' experience; Medical ethics

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1. Introduction

Trials within cohorts (TwICs) is a relatively new study design that offers an efficient alternative to classic randomized controlled trials (RCTs) for evaluating effectiveness of interventions [1]. The TwICs design uses a prospective cohort study in which (multiple) pragmatic randomized trials may be embedded. For each trial, eligible patients are identified from the cohort and randomized into the intervention or the control group (Fig. 1). Patients randomized to the intervention group are offered the experimental intervention, which they can accept or decline. Patients in the control group receive care as usual and are not explicitly informed about serving as controls in a trial. Their outcome measurements are routinely collected within the cohort and compared to outcomes of patients allocated to the intervention group.

What is new?

Key findings

- Among cancer patients who had served as controls in two trials following the trials within cohorts (TwICs) design, 93% reported positively or neutrally of having served as controls without a notification at the time of randomization.
- Only 15% of control patients recollected to have provided broad consent to randomization at 2–6 years after cohort entry.

What this adds to what was known?

- Introduction of the TwICs design has led to discussion on the ethics of patients serving as controls without an explicit notification.
- In the staged-informed consent procedure for TwICs, patients are asked for broad consent to randomization upon cohort entry.
- A previous survey showed that 2% of cohort participants would think negatively in the hypothetical situation of their data being used comparatively without their explicit knowledge.
- The current survey evaluated how patients experienced effectively having served as controls without a notification at the time of randomization in two TwICs using the staged-informed consent procedure.

What is the implication and what should change now?

- Our results support the use of the TwICs design with the staged-informed consent procedure.
- Keeping patients engaged and aware of the consents provided might further improve patients' experience of serving as controls in TwICs.

While in TwICs, the intervention is offered to patients after having been randomized to the intervention group, patients in classic RCTs provide consent to receiving the experimental intervention before randomization. Slow recruitment into classic RCTs is a common problem. Reasons why patients decline RCT participation include information overload and an aversion against their treatment being decided by chance [2,3]. Many patients who agree to participate in classic RCTs hope to be allocated to the experimental treatment arm. In these cases, allocation to the control arm may lead to disappointment bias, drop out after randomization, and crossover between study arms. TwICs have been shown to be less susceptible to slow

recruitment, crossover between treatment arms, and drop out after randomization to the control group than classic RCTs [4–8].

Several studies following the TwICs design apply the staged-informed consent procedure (also known as two-stage consent) [9,10]. In the first stage, patients are asked for cohort participation, that is, consent to collection of medical data and study measurements such as patient-reported outcomes (PROs). In addition, patients are asked for broad consent to randomization (Fig. 1). Here, patients consent to (a) randomization to future TwICs, (b) being offered an intervention if selected for the intervention group, and (c) not being notified if selected for the control group. In a later stage, a trial-specific consent is sought from patients randomized to the intervention group of TwICs.

Introduction of the TwICs design has led to discussions on the ethics of patients serving as controls without an explicit notification [10–12]. In a previous survey among cohort participants, we evaluated the acceptability of hypothetically serving as controls without an explicit notification [13]. Only 2% ($n = 2/62$) of cohort participants stated they would experience negative emotions if their data would be used comparatively without their explicit knowledge. Currently, four TwICs using the staged-informed consent procedure have been completed at the imaging and oncology division of the University Medical Center Utrecht [14–17]. We performed a cross-sectional survey to evaluate how patients experienced effectively having served as controls without a notification at the time of randomization in two of these TwICs.

2. Material and methods

2.1. Study population

This cross-sectional survey was conducted among patients with breast or rectal cancer who had served as controls in two TwICs, that is, the UMBRELLA Fit and the RECTAL-BOOST trial [14,15,18,19]. The UMBRELLA Fit trial included 260 patients from the Utrecht cohort for Multiple BREast cancer intervention studies and Long-term evaluation (UMBRELLA) between October 2015 and February 2018 [20]. Patients treated for breast cancer who had a physically inactive lifestyle as assessed by cohort questionnaires at 12 to 18 months after treatment were randomized 1:1 to either standard follow-up or a 12-week exercise program. The primary end point of UMBRELLA Fit was quality of life (QoL) at 18 or 24 months after cohort enrollment.

The RECTAL-BOOST trial included 128 patients enrolled in the Dutch Prospective ColoRectal Cancer cohort (PLCRC) between September 2014 and July 2018 [21]. Patients with locally advanced rectal cancer were randomized 1:1 to standard neoadjuvant chemoradiation (CRT) (50 Gy

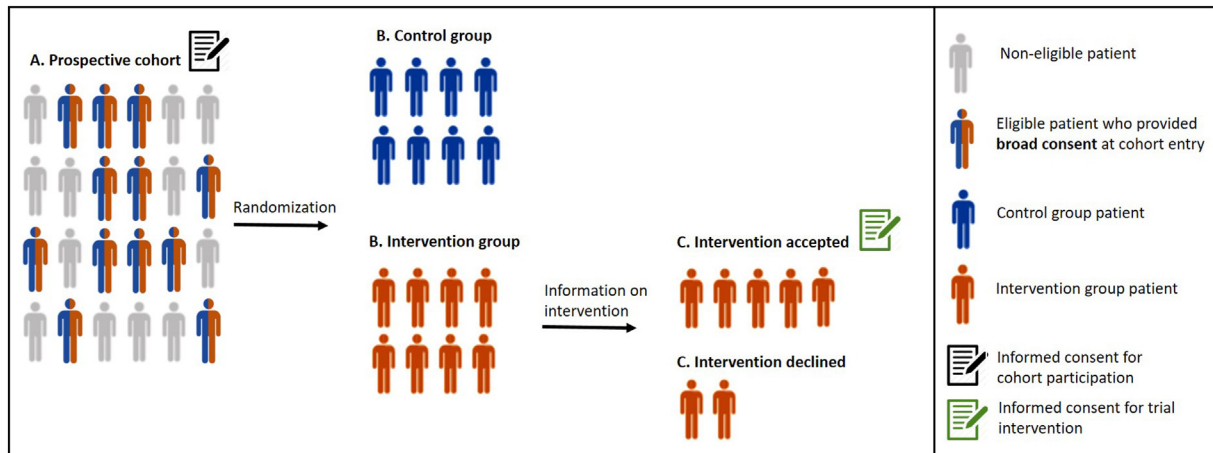


Fig. 1. Trial within cohorts (TwICs) design with the staged-informed consent procedure. Eligible patients who provided a broad consent to randomization are selected from the cohort (A) and randomized into the control or the intervention group (B). Patients of the intervention group who accept the intervention are asked to sign a second trial-specific informed consent (C).

in 25 fractions with concurrent fluorouracil-based chemotherapy) or dose-escalated CRT (standard CRT preceded by a radiotherapy boost of 15 Gy in five fractions). The primary end point was pathological complete response (pCR).

Vital status at the time of the survey was identified through the municipality registry. Patients who had withdrawn consent for cohort participation and/or broad consent to randomization and invitation to future studies were excluded.

The medical ethics committee of the University Medical Center Utrecht approved study protocols for the UMBRELLA cohort, the UMBRELLA Fit trial, the PLCRC cohort, and the RECTAL-BOOST trial and waived the need for an ethical review of the present study.

2.2. Survey

A questionnaire was developed by a local team of epidemiologists, clinicians, and a medical ethicist. Some questions were adapted from a previous survey on understanding and acceptance of the TwICs design, as designed by the same team [13]. Survey responses were not linked to clinical patient characteristics, allowing patients to freely express their honest opinions. The survey consisted of four questions on basic demographics and four questions about the experience of having served as controls in TwICs without a notification at the time of randomization. The latter four questions were answered both before and after the trial results had been disclosed. Because the survey was conducted online, we ensured that patients were only able to read the trial results after having provided their opinion on having served as controls in TwICs.

Control patients of the UMBRELLA Fit trial were informed that women in the intervention group were offered an exercise program, and that the intervention group reported comparable QoL, but less fatigue compared to women in the control arm. Control patients of the

RECTAL-BOOST trial were informed that the boost intervention did not result in an improved pCR rate as compared to standard CRT and that patients treated with a radiation boost group showed increased tumor regression and experienced more mild-moderate acute toxicity, such as transient diarrhea.

A draft survey was first piloted among 10 UMBRELLA Fit and 10 RECTAL-BOOST patients. Pilot patients who provided their contact details were called to gauge their understanding of the survey. Based on the pilot study, a response option was added to the question whether and when patients would appreciate a reminder for the broad consent provided (i.e., one-time reminder 6 months after cohort entry). The definitive survey was then sent out to other eligible control patients. The survey was conducted between October 2020 and January 2021. Patients were first informed of the survey by a postal mail and invited to the online survey in Castor Electronic Data Capture system by an e-mail a week later. An automatic reminder was sent per e-mail if patients did not complete the survey within 1 week, followed by a one-time telephonic reminder within 2 weeks.

2.3. Statistical analysis

Responses to the pilot study were included in the main results. Incompletely filled out surveys were included in the results. Responses to the survey were presented using descriptive statistics. Free text comments provided with the online survey were categorized post hoc. SPSS, version 25 and R language, version 3.6.0 were used for a statistical analysis.

3. Results

Of the 130 breast cancer patients who had served as controls in the UMBRELLA Fit trial, 1.5% ($n = 2$) were

deceased and 25% ($n = 32$) had withdrawn cohort consent. The remaining 96 patients were invited to participate in this survey, 76% ($n = 73$) of whom responded and 73% ($n = 70$) fully completed the questionnaire. Of the 64 rectal cancer patients who had served as controls in the RECTAL-BOOST trial, 14% ($n = 9$) had deceased, 7.8% ($n = 5$) had withdrawn cohort consent, and 1.6% ($n = 1$) was lost to follow-up. The remaining 49 patients were invited to participate, 76% ($n = 37$) of whom responded and completed the questionnaire.

All UMBRELLA Fit patients were female (Table 1). The median age was 62 years (interquartile range [IQR]: 56–67). Fifty five percent ($n = 40$) received higher vocational education or went to university. In the RECTAL-BOOST group, 70% ($n = 26$) were male and the median age was 68 years (IQR: 61–75). Forty one percent ($n = 15$) received higher vocational education or went to university.

Before the trial results were disclosed, 71% ($n = 52$) of UMBRELLA Fit and 54% ($n = 20$) of RECTAL-BOOST patients answered they did not remember that they had previously provided a broad consent to randomization (Table 2); 8.2% ($n = 6$) respectively 30% ($n = 11$) said they remembered a part of the broad consent and 16% ($n = 12$) respectively 11% ($n = 4$) fully remembered having provided a broad consent. Only 5.5% ($n = 6$) of all patients indicated they sometimes had thought about the possibility of serving as controls without an explicit notification. Ten patients commented in the free text “I never understood the possibility of serving as control without explicit notification” and seven patients explained “I forgot about the broad consent provided at cohort entry, because I was occupied with my rectal/breast cancer treatment at the moment consent was asked” (Table 3).

Of all patients, 47% ($n = 52$) reported positively, 45% ($n = 50$) neutrally, and 1.8% ($n = 2$) negatively of having served as controls in TwiCs (Table 2). Seventeen percent ($n = 18$) were positive, 65% ($n = 71$) were neutral, and 11% ($n = 12$) were negative about not having received a notification at the time of randomization. Positive opinions were accompanied by free text comments such as “I appreciate that research on rectal/breast cancer treatment is performed” in 17 patients, “I’m happy to have contributed to the treatment of future rectal/breast cancer patients” in 13 patients, and “I trust that researchers have their reasons for not notifying me when serving as control” in three patients (Table 3). Negative opinions were illustrated by comments such as “I’m disappointed/I dislike that I was not notified [at the time of randomization] of serving as control” in six patients.

After disclosure of the trial results, 53% ($n = 57$) of all patients thought positively, 41% ($n = 44$) neutrally, and 0.9% ($n = 1$) negatively of having served as controls in the UMBRELLA Fit or RECTAL-BOOST trials (Table 2). Forty three percent ($n = 36$) were positive, 50% ($n = 54$) neutral, and 1.9% ($n = 2$) negative about

being selected for the control group by randomization. Twenty two percent ($n = 23$) thought positively, 62% ($n = 66$) neutrally, and 6.5% ($n = 7$) negatively about not having received a notification when serving as controls in these TwiCs. Positive opinions were supported by comments such as “I understand the scientific reasons for not notifying patients [at the time of randomization] of serving as control” in seven patients and “I think it’s good that I was not notified [at the time of randomization] of serving as control in a trial, because I was not selected for receiving the experimental treatment either way” in three patients. On the contrary, nine patients wrote “I would rather have been notified [at the time of randomization] of serving as control”.

Fifty five percent ($n = 59$) of patients indicated that a reminder for the broad consent provided at cohort entry would have been appreciated (Table 2). This reminder would preferably be received once at 6 months after cohort enrollment by 19% ($n = 20$), each year by 30% ($n = 32$), and every 6 months by 6.5% ($n = 7$). Free text comments were “I would have liked to know about the possibility of serving as control without explicit notification” in five patients, “I would have liked to be reminded of the broad consent provided at cohort entry, because my opinion might have changed in the meantime” in three patients, and “If I had remembered providing broad consent to randomization at cohort entry, I would not have indicated a negative opinion [on serving as control without notification]” in one patient.

4. Discussion

This cross-sectional survey demonstrated that a large majority of breast and rectal cancer patients reported positively or neutrally of having served as controls without an explicit notification in TwiCs. After being informed about the trial results, only 1% reported a negative attitude toward having served as controls and 7% towards not having received a notification when serving as controls. Responses did not vary by the type of intervention, by cancer site, or by knowledge about trial results. Recollection of having given broad consent to randomization was poor (15%). A small majority of patients (55%) noted that they would have appreciated being reminded of having provided broad consent to randomization, including a reminder of the possibility that they might act as controls without an explicit notification.

Our study gives the answer to an important question regarding the TwiCs design: how do patients experience serving as controls without an explicit notification [9–12]? Following the staged-informed consent procedure, patients provide consent for each research procedure they (may) experience, and control patients have provided consent for the use of their medical data comparatively without an explicit notification at cohort entry [10,11]. It has been

Table 1. Self-reported baseline characteristics of breast and rectal cancer patients in the UMBRELLA Fit and RECTAL-BOOST trials within cohorts (TwICs)

Characteristic	UMBRELLA Fit (<i>n</i> = 73)	RECTAL-BOOST (<i>n</i> = 37)
Male	0	26 (70.3)
Age (median [IQR])	62 [56, 67]	68 [61, 75]
Year of cohort inclusion		
2014	25 (34)	0
2015	16 (22)	7 (19)
2016	16 (22)	12 (32)
2017	4 (5.5)	9 (24)
2018	0	8 (22)
I do not remember	12 (16)	1 (2.7)
Highest completed education level		
Primary, secondary, or lower vocational education	33 (45)	22 (59)
Higher vocational education or university	40 (55)	15 (41)

Abbreviations: IQR, interquartile range.

Data are presented as frequencies (percentage) unless stated otherwise.

argued that the broad consent provided at cohort entry may be considered ethically problematic because cohort participants do not know the aims of the TwICs in which they may serve as controls [12]. Our results show that the great majority of patients thought positively or neutrally of having served as controls without an explicit notification in TwICs. In the free text comments, control patients often indicated altruistic motivations, for instance that they were happy to have contributed to the future of other patients with breast/rectal cancer. Patients seem to value contributing to research on their condition more than providing explicit consent for each TwICs design in which their data are used comparatively.

In our survey, 1% reported negatively of having served as controls and 7% reported a negative attitude toward not having received a notification when serving as controls. This small group of patients expressed feelings of disappointment and the wish to have been notified of serving as controls. Some respondents suggested that a negative experience could have been prevented by (regular) reminders during cohort participation of having provided broad consent to randomization. Nonetheless, it remains inherent to the TwICs design that patients are not informed on the experimental intervention when randomized to the control group.

Correct recollection of having given broad consent to randomization was reported by only 17% of breast cancer and 11% of rectal cancer patients at 2–6 years after cohort enrollment. In our previous survey among cohort participants, 76% remembered having provided broad consent to randomization at 2 weeks after cohort enrollment, which dropped to 42% at 1–6 months after cohort enrollment [13]. The recollection of the broad consent provided decreases over time. The ethical acceptability of randomizing

patients to the control group without further notice seems questionable when broad consent is not recollected.

In the PLCRC and UMBRELLA cohorts, patients are provided both written and oral information on the TwICs design upon cohort entry. In the UMBRELLA cohort, breast cancer patients are reminded of the TwICs design by annual newsletters and annual research participant days. The recollection rates were slightly higher in the UMBRELLA cohort, but still insufficient. A solution for the poor recollection could be found in a dynamic informed consent model. Dynamic informed consent is a concept wherein patients are actively involved in research by regular (digital) updates on the studies which use their data, together with the option to continue to participate in the study, or to opt out of the consents provided [22]. Along these lines, three patients indicated that they would have liked to be reminded of having provided broad consent at cohort entry because their opinion could have changed in the meantime. Regarding the potential use of a dynamic informed consent model, patients in two previous focus group studies reacted mostly positive [23,24]. They thought that such a model could enhance autonomous choice of research participation, improve patient engagement, and trust in researchers. Dynamic informed consent could potentially further improve recollection of having provided broad consent to randomization and patients' experience of participating in studies following the TwICs design.

Patients' experience of serving as controls without an explicit notification might be influenced by the stakes of a trial, that is, the potential benefit of the experimental intervention given the patients' current condition. Control patients might feel more strongly to have missed an opportunity when they are informed of having served as controls

Table 2. Survey responses of breast ($n = 73$) and rectal cancer patients ($n = 37$) on having served as controls in the UMBRELLA Fit respectively RECTAL-BOOST trials within cohorts (TwICs), before (question 1–4) and after (question 5–8) having been provided the trial results

1. Do you remember that you provided broad consent for future randomization to clinical trials within PLCRC/UMBRELLA without a notification if selected for the control group?		
	UMBRELLA Fit ($n = 73$)	RECTAL-BOOST ($n = 37$)
No, I do not remember	52 (71)	20 (54)
I do not remember a consent for randomization, but I do remember that I would not be notified if selected for a control group	4 (5.5)	6 (16)
I do remember a consent for randomization, but I do not remember that I would not be notified if selected for a control group	2 (2.7)	5 (14)
Yes, I remember	12 (16)	4 (11)
Other, namely...	3 (4.1)	2 (5.4)
2. Was it on our mind that you might be selected for a control group of a clinical trial within PLCRC/UMBRELLA without a notification?		
	UMBRELLA Fit ($n = 73$)	RECTAL-BOOST ($n = 37$)
No, because I did not remember providing a broad consent for future randomization	47 (64)	20 (54)
No, never thought about it however I did know that it might happen	20 (27)	14 (38)
Yes, sometimes (less than once a month)	4 (5.5)	2 (5.4)
Other, namely...	2 (2.7)	1 (2.7)
3. How do you think about having served as control in a clinical trial within PLCRC/UMBRELLA?		
	UMBRELLA Fit ($n = 73$)	RECTAL-BOOST ($n = 37$)
Negative	1 (1.4)	1 (2.7)
Neutral	34 (47)	16 (43)
Positive	33 (45)	19 (51)
Other, namely...	5 (6.8)	1 (2.7)
4. How do you think about serving as control in a clinical trial within PLCRC/UMBRELLA without being notified?		
	UMBRELLA Fit ($n = 72$)	RECTAL-BOOST ($n = 37$)
Negative	7 (9.7)	5 (14)
Neutral	48 (67)	23 (62)
Positive	10 (14)	8 (22)
Other, namely...	7 (9.7)	1 (2.7)
5. Now you know the trial results, how do you think about having served as control in the RECTAL-BOOST/UMBRELLA Fit trial?		
	UMBRELLA Fit ($n = 71$)	RECTAL-BOOST ($n = 37$)
Negative	1 (1.4)	0
Neutral	28 (39)	16 (43)
Positive	36 (51)	21 (57)
Other, namely...	6 (8.5)	0
6. Now you know the trial results, how do you think about being selected by randomization for the control group of the RECTAL-BOOST/UMBRELLA Fit trial?		
	UMBRELLA Fit ($n = 70$)	RECTAL-BOOST ($n = 37$)
Negative	1 (1.4)	1 (2.7)
Neutral	34 (49)	20 (54)

(Continued)

Table 2. Continued

Positive	30 (43)	16 (43)
Other, namely...	5 (7.1)	0
7. Now you know the trial results, how do you think about serving as control without being notified in the RECTAL-BOOST/UMBRELLA Fit trial?		
	UMBRELLA Fit (n = 70)	RECTAL-BOOST (n = 37)
Negative	3 (4.3)	4 (11)
Neutral	42 (60)	24 (65)
Positive	17 (24)	7 (19)
Other, namely...	8 (11)	2 (5.4)
8. Do you think we should remind PLCRC/UMBRELLA participants of the broad consent provided for future randomization to trials within the cohort?		
	UMBRELLA Fit (n = 70)	RECTAL-BOOST (n = 37)
No	29 (41)	11 (30)
Yes, one time reminder half a year after cohort enrollment	14 (20)	6 (16)
Yes, each year	17 (24)	15 (41)
Yes, each half year	4 (5.7)	3 (8.1)
Other, namely...	6 (8.6)	2 (5.4)

Free text comments that could be provided if patients ticked the option “other, namely...” or other answer options were categorized post hoc and are displayed in [Table 3](#).

in a high stakes trial. A survey among 2,004 healthy individuals from the United States showed that slightly more participants would be fine with being randomized without further notice in a low stakes trial as compared to a high stakes trial [25].

As for the stakes of our TwiCs, the UMBRELLA Fit trial showed that an exercise program after breast cancer treatment did not improve QoL but did improve patient-reported fatigue. Since control patients, after being informed of these results, still have the possibility to follow an exercise program to improve fatigue, UMBRELLA Fit can be considered a low stakes trial with positive results. The RECTAL-BOOST trial demonstrated that dose-escalated CRT did not improve pCR, which is a surrogate marker for disease-free and overall survival in rectal cancer [26]. A complete response also indicates eligibility for nonoperative management [27]. The RECTAL-BOOST could therefore be considered a high stakes trial with negative results. Other than in the survey mentioned above, the differences in stakes did not lead to differences in the experience of control patients of the UMBRELLA Fit vs. the RECTAL-BOOST trial. Based on our current findings, we see no reason to stop conducting (high stakes) TwiCs. When a high stakes TwiCs trial with positive results has been finished, the experience of the control patients should be evaluated.

The response rate of this survey was reasonably high (76%). Patients who responded to the questionnaire were comparable to the original trial population in terms of age and gender [14,15]. However, women of the UMBRELLA Fit control group who had a higher level of

education seemed more likely to respond to this questionnaire. It remains possible that the reason why some patients did not respond to the questionnaire is correlated to a specific opinion or understanding of the TwiCs design (nonresponse bias).

In this study, 25% of UMBRELLA patients had withdrawn consent for cohort participation at 2–5 years after inclusion. As a reason for cohort withdrawal, patients often indicate that they dislike to be regularly reminded of having had breast cancer. We do not think that withdrawal of consent for participation in UMBRELLA is related to patients' opinion on having served as controls in TwiCs.

5. Conclusion

Our results support use of the TwiCs design with a staged-informed consent procedure. Keeping patients engaged and aware of the consents provided could further improve patients' experience of serving as controls in TwiCs.

CRedit authorship contribution statement

Maaïke E. Verweij: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, visualization, and writing—original draft. **Roxanne Gal:** Conceptualization, methodology, and writing—review and editing. **J.P. Maarten Burbach:** Conceptualization, methodology, and writing—review and

Table 3. Post hoc categorized free text comments by breast and rectal cancer patients on their experience of having served as controls in the trials within cohorts (TwICs) design

N = 17	"I appreciate that research on rectal/breast cancer treatment is performed"
N = 13	"I am happy to have contributed to the treatment of future rectal/breast cancer patients"
N = 10	"I never understood the possibility of serving as control without explicit notification"
N = 9	"I would rather have been notified [at the time of randomization] of serving as control"
N = 7	"I forgot about the broad consent provided at cohort entry, because I was occupied with my rectal/breast cancer treatment at the moment consent was asked"
N = 7	"I understand that randomization is necessary in clinical trials"
N = 7	"I am okay with not having been notified of serving as control [at the time of randomization]"
N = 7	"I understand the scientific reasons for not notifying patients [at the time of randomization] of serving as control"
N = 6	"I am disappointed/I dislike that I was not notified [at the time of randomization] of serving as control"
N = 5	"I would have liked to know about the possibility of serving as control without explicit notification"
N = 4	"I cannot be bothered that I did not receive a notification when my data were used comparatively"
N = 3	"I trust that researchers have their reasons for not notifying me when serving as control"
N = 3	"I would have liked to be reminded of the broad consent provided at cohort entry, because my opinion might have changed in the meantime"
N = 3	"I think it's good that I was not notified [at the time of randomization] of serving as control in a trial, because I was not selected for receiving the experimental treatment either way"
N = 1	"If I had remembered providing a broad consent to randomization at cohort entry, I would not have indicated a negative opinion [on serving as control without notification]"

editing. **Danny A. Young-Afat:** Writing—review and editing. **Joanne M. van der Velden:** Writing—review and editing. **Rieke van der Graaf:** Conceptualization, methodology, and writing—review and editing. **Anne M. May:** Conceptualization, methodology, and writing—review and editing. **Clare Relton:** Writing—review and editing. **Martijn P.W. Intven:** Conceptualization, methodology, supervision, and writing—review and editing. **Helena M. Verkooijen:** Conceptualization, funding acquisition, methodology, supervision, and writing—review and editing.

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