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REVIEW

Oncology patients were found to understand and accept the Trials within Cohorts design

Danny A. Young-Afat[a,b,*], Roxanne Gal[a,b], Sophie Gerlich[c], Johannes P.M. Burbach[d], Joanne M. van der Velden[c], Desireé H.J.G. van den Bongard[e], Martijn P.W. Intven[c], Nicolien Kasperts[c], Anne M. May[a], Rieke van der Graaf[f], Carla H. van Gils[a,g], Helena M. Verkooijen[b,g]

[a]*Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands*
[b]*Division of Imaging and Oncology, University Medical Center Utrecht, Utrecht, The Netherlands*
[c]*Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands*
[d]*Department of Surgery, University Medical Center, Groningen, The Netherlands*
[e]*Department of Radiation Oncology, Amsterdam University Medical Center, Amsterdam, The Netherlands*
[f]*Department of Medical Humanities, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands*
[g]*Utrecht University, Utrecht, The Netherlands*

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Abstract

Background and Objective: The Trials within Cohorts design aims to reduce recruitment difficulties and disappointment bias in pragmatic trials. On cohort enrollment, broad informed consent for randomization is asked, after which cohort participants can be randomized to interventions or serve as controls without further notification. We evaluated patients' recollection, understanding, and acceptance of broad consent in a clinical oncology setting.

Methods: We surveyed 610 patients with cancer participating in ongoing TwiCs; 482 patients (79%) responded, of which 312 patients shortly after cohort enrollment, 108 patients after randomization to an intervention (12−18 months after cohort enrollment), and a random sample of 62 cohort participants who had not been selected for interventions (1−6 months after cohort enrollment).

Results: Shortly after providing cohort consent, 76% of patients (238/312) adequately remembered whether they had given broad consent for randomization. Of patients randomly offered interventions, 76% (82/108) remembered giving broad consent for randomization; 41% (44/108) understood they were randomly selected, 44% (48/108) were not interested in selection procedures, and 10% (11/108) did not understand selection was random. Among patients not selected for interventions, 42% (26/62) understood selection was random; 89% felt neutral regarding the scenario of "not being selected for an intervention while your data were being used in comparison with patients receiving interventions," 10% felt reassured (6/62) and 2% scared/insecure (2/62).

Preliminary data were presented at the Trials within Cohorts symposium in London, the United Kingdom, in 2016.

Disclosures: Nothing to declare.

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Declaration of interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

* Corresponding author. University Medical Center Utrecht, Utrecht, The Netherlands.
E-mail address: d.a.youngafat@umcutrecht.nl (D.A. Young-Afat).

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Conclusion: Patients adequately remember giving broad consent for randomization shortly after cohort enrollment and after being offered an intervention, but recollection is lower in those never selected for interventions. Patients are acceptant of serving as control without further notifications.

Keywords: Trials within Cohorts; Cohort studies; Randomized controlled trials; Study design; Informed consent

1. Introduction

Randomized controlled trials (RCTs) are essential to evaluate the effectiveness of novel treatment options but are often beset by slow recruitment and limited generalizability. Randomized trials are also hampered by methodological challenges such as contamination of the control arm and disappointment bias (i.e., changes in behavior or perspective of participants because of being disappointed having been allocated to the control arm) [1−3]. Consequently, in the field of oncology, 40% of cancer trials end prematurely [1].

The Trials within Cohorts (TwiCs) design—also known as the cohort multiple RCT (cmRCT) design—is an alternative method to conduct pragmatic trials and was designed to reduce the abovementioned challenges [4]. In the original TwiCs proposal by Relton et al., informed consent for study participation was only obtained from participants who were allocated to the intervention arm but not from those allocated to the standard of care control arm [4]. This approach has led to ethical discussions because patients may then be randomized without their prior consent (i.e., prerandomization). Avoiding prerandomization is desirable when possible because patients might lose trust in physicians when learning that they have participated as research subjects without their explicit consent [5].

In 2013, we created a staged-informed consent procedure for TwiCs that avoids patients being randomized without their prior consent. We subsequently introduced the TwiCs design in a clinical oncology setting using this staged-informed consent model [6]. In this staged-informed consent procedure, on cohort entry, patients provide informed consent for longitudinal data collection in the context of a cohort or registry study. Patients may give additional broad consent for randomization to future interventions. Patients are informed that providing broad consent for randomization entails the possibility of unknowingly serving as controls, meaning that their data can be used comparatively with patients who undergo an experimental intervention, without being notified at the time that this is happening [6]. After randomization, at a later stage, a second informed consent is only obtained from those allocated to an intervention arm. After trials are completed, aggregated results will be shared with cohort participants, including those not randomly selected.

The staged-informed consent model avoids prerandomization and ensures that patients are well informed about the study design, goals, and methods of the TwiCs study(design) before agreeing to participate in such a cohort or trial within the cohort. Furthermore, this model aims to keep patients informed and actively engaged throughout study enrollment by providing aggregate disclosure after trials have been completed [6].

Since 2013, we have applied the TwiCs design, and this staged-informed consent procedure to three cohorts enrolling patients with colorectal cancer, bone metastases, and breast cancer [7−9]. Several trials have been completed or are ongoing within these cohorts [10−13]. So far, participation rates (70−90% of patients approached for cohort participation), broad consent rates (80−90% of those who agreed to cohort participation), and longitudinal patient-reported outcome return rates have been high in all three cohorts [5,6,8], indicating patients' willingness to participate in TwiCs in a clinical oncology setting. However, from an ethical point of view, it is also important to evaluate whether patients participating in these studies are adequately informed from a clinical trial standpoint: e.g., do patients, after having participated in the cohorts for some time, remember providing broad consent for randomization?

Therefore, this study aimed to evaluate patients' recollection, understanding, and acceptance of broad consent for randomization within hospital-based TwiCs in a clinical oncology setting.

2. Methods

Between October 2015 and April 2018, a survey was conducted among participants in the colorectal cancer, bone metastases, and breast cancer cohorts at the Department of Radiation Oncology of the University Medical Center Utrecht, the Netherlands.

Since July 2014, all patients with one of these diagnoses receive written information about the cohorts before their first visit to the Department of Radiation Oncology. At the day of their first visit, patients are scheduled to meet a researcher before visiting their radiation oncologist. During this consultation, information about the cohort and the TwiCs design is discussed, and written informed consent is obtained according to the staged-informed consent procedure [6]. In the first stage, patients provide consent for routine care data collection and additional cohort-specific measures (e.g., patient-reported outcomes). At this stage, patients may also provide additional broad consent for future randomization to intervention and control arms of studies. Patients are told that they will not be notified when serving as control. In a second stage, only patients randomized to an intervention

What is new?

Key findings

- In the Trials within Cohorts (TwiCs) design, patients' recollection of providing broad informed consent for randomization seems adequate over time but could be improved in patients who were never selected for interventions. Patients accept the thought of serving as controls in trials without further notice.

What this adds to what was known?

- This is the first evaluation of broad informed consent for randomization for the "Trials within Cohorts" design among patients participating in TwiCs studies and provides valuable insights into what patients do and do not understand of this design. This study also shows that patients have no ethical objections against serving as control without further notice.

What is the implication and what should change now?

- The TwiCs design may be considered more often for pragmatic trials, but extra attention should be paid to keeping all participants aware over time of key elements of TwiCs studies (e.g., the potential of being invited to undergo an experimental intervention after random selection).

arm will be approached to give a second informed consent to accept or decline the intervention they were offered. At a third stage, after trials are completed, all cohort participants receive aggregated study results.

Cohort participants were surveyed with the aim to evaluate patients' recollection, understanding, and acceptance of broad informed consent for randomization. This survey was conducted at several stages of cohort and trial participation. Because no validated questionnaires were available for these purposes, a questionnaire was developed by a local team of researchers, epidemiologists, clinicians, and medical ethicists (Tables 1 and 2).

Five groups of patients received questionnaires at different phases during participation (Fig. 1):

- Group 1: Patients who consented to cohort participation and also provided broad consent for randomization (surveyed within 2 weeks after cohort enrollment).
- Group 2: Patients who consented to cohort participation but declined broad consent for randomization (surveyed within 2 weeks after cohort enrollment).
- Group 3: Cohort participants randomized to an experimental intervention, who accepted the intervention (surveyed directly after accepting the intervention, 12−18 months after cohort enrollment).
- Group 4: Cohort participants randomized to an experimental intervention, who declined the intervention (surveyed directly after declining the intervention, 12−18 months after cohort enrollment).
- Group 5: Random sample of cohort participants who had not been selected for an intervention of ongoing trials at the moment of surveying (surveyed 1−6 months after cohort enrollment). These patients, theoretically, could have been selected for an intervention and may have been serving as a control without their knowledge.

Groups 3 and 4 consisted of patients who were randomly selected from the breast cancer cohort (i.e., UMBRELLA), 12−18 months after initial enrollment, and offered to undergo an exercise intervention in the UMBRELLA FIT trial (i.e., supervised exercise program aiming to improve the quality of life in patients with low physical activity levels) [8,11]. In total, 130 patients were randomly selected and offered the UMBRELLA FIT intervention (i.e., 100% of eligible patients), of which 68 (52%) accepted the intervention.

Because the questionnaires were to be completed anonymously to stimulate the most honest response, no identifiable data were available, and, thus no patient or treatment characteristics, with the exception of tumor site and broad consent status. Data were analyzed and summarized using descriptive statistics. This study was granted a waiver from full ethical review by the Research Ethics Committee of the University Medical Center Utrecht and adhered to the Declaration of Helsinki.

3. Results

In total, 610 patients were invited to participate in the survey, and 482 patients (79%) responded. The study population consisted of 59 patients with colorectal cancer, 121 patients with bone metastases, and 302 patients with breast cancer.

3.1. Recollection of broad informed consent for randomization

3.1.1. Groups 1 and 2 (patients who consented to cohort participation)

Within 2 weeks after enrollment, in the group that provided broad consent for randomization, 76% (188/249) adequately remembered their broad consent decision (i.e., same answer as on signed informed consent form), 16% (40/249) recalled a decision different than the one selected on their informed consent form, and 8% (21/249) selected "I do not remember" (Table 1).

In the group that did not provide broad consent for randomization, 79% (50/63) remembered their broad consent decision correctly, 16% (10/63) recalled a decision different from the one selected on their informed consent form, and 5% did not remember (3/63).

Table 1. Patients' recollection of broad consent in TwiCs

Survey question	%	n/N
Group 1: Broad consent providers: Did you provide consent to receive invitations for (future) experimental interventions? (n = 249)		
I do not remember	8	21/249
Correct recollection[a]	76	188/249
Incorrect recollection	16	40/249
Group 2: Broad consent decliners: Did you provide consent to receive invitations for (future) experimental interventions? (n = 63)		
I do not remember	5	3/63
Correct recollection[a]	79	50/63
Incorrect recollection	16	10/63
Groups 3 + 4: Patients randomized to intervention arm: Do you understand that you have been selected based on your prior choice to potentially receive invitations for experimental interventions? (n = 108)		
No, I cannot remember this	17	18/108
Yes, but I had forgotten about it until being approached for the experimental intervention	38	41/108
Yes, I immediately realized when being approached for the experimental intervention	38	41/108
No answer	7	8/108
Group 3 + 4: Patients randomized to intervention arm: Did you ever think about the possibility of being invited to undergo an intervention? (n = 108)		
No, because I could not have known this	30	32/108
No, never thought about it again although I was aware that it would be possible	63	68/108
Yes, sometimes (at least once a month)	5	5/108
Yes, often (at least once a week)	1	1/108
No answer	2	2/108
Group 5: Random sample of cohort participants not selected for interventions at time of survey: Did you provide consent to receive invitations for (future) experimental interventions? (n = 62)		
I do not remember	29	18/62
Correct answer[a]	42	26/62
Incorrect answer	30	17/62

Group 1 consists of patients who consented to cohort participation and provided broad consent for randomization (surveyed within 2 wk after cohort enrollment).

Group 2 consists of patients who consented to cohort participation but who declined broad consent for randomization (surveyed within 2 wk after cohort enrollment).

Group 3 consists of patients randomized to an experimental intervention who accepted the intervention (surveyed 12–18 months after cohort enrollment).

Group 4 consists of patients randomized to an experimental intervention who declined the intervention (surveyed immediately after declining the intervention, 12–18 months after cohort enrollment).

Group 5 consists of a random sample of cohort participants who had not been selected for an intervention at time of survey (surveyed 1–6 months after cohort enrollment).

Answers may not add up to 100% because of the option to endorse more than one answers or as a result of rounding.

[a] Correct answer means that the patient selected the same answer as on their signed informed consent form.

3.1.2. Groups 3 and 4 (patients randomized to an experimental intervention)

After having been selected and offered an intervention, 76% of patients (82/108) understood that this was because of previously giving broad consent for randomization, and 17% (18/108) did not remember giving broad consent for randomization (Table 1). When asked how often they had thought about potentially being offered experimental interventions, 63% (68/108) stated to have never thought about it again although being aware that it would be possible, and only one patient thought about it frequently (at least once a week).

Table 2. Patients' perspectives and understanding of randomization procedures in TwiCs—Groups 3, 4, and 5

Survey question	%	*n*/N
Groups 3 + 4: Patients randomized to intervention arm: Do you know how you have been selected for the experimental intervention? (n = 108)		
No, but I don't care	44	48/108
No, but I would have liked to know beforehand	5	5/108
Yes, researchers chose me from a large group of patients	8	9/108
Yes, I was selected based on chance from a group of patients who met criteria for this intervention	41	44/108
Yes, all patients in the cohort will be offered this intervention	2	2/108
Group 3: Patient who accepted the offered intervention: What if you had not been offered this experimental intervention, but your data would have been used in comparison with the experimental intervention. How would that make you feel? (n = 63)		
Neutral	97	61/63
Lucky/special	0	0/63
Scared/anxious	0	0/63
Relieved	0	0/63
Reassured	3	2/63
Insecure/worried	0	0/63
Angry	2	1/63
Other	0	0/63
Group 5: Random sample of cohort participants not selected for interventions at time of survey: In this cohort, you could theoretically be selected for experimental interventions. How would you feel if you were not selected for an intervention, but your data would be used in comparison with patients receiving such an intervention? (n = 62)		
Neutral	89	55/62
Lucky/special	0	0/62
Scared/anxious	0	0/62
Relieved	0	0/62
Reassured	10	6/62
Insecure/worried	1	1/62
Angry	1	1/62
Other	0	0/62

Group 3 consists of patients randomized to an experimental intervention who accepted the intervention (surveyed 12–18 months after cohort enrollment).

Group 4 consists of patients randomized to an experimental intervention who declined the intervention (surveyed immediately after declining the intervention, 12–18 months after cohort enrollment).

Group 5 consists of a random sample of cohort participants who had not been selected for an intervention at time of survey (surveyed 1–6 months after cohort enrollment).

Answers may not add up to 100% because of the option to endorse more than one answers or as a result of rounding.

3.1.3. Group 5 (random sample of cohort participants who had not been selected for an intervention at the time of the survey)

In the random sample of cohort participants who had not been selected for an intervention, 29% (18/62) did not remember whether they had agreed to future randomization, 30% (19/62) recalled a decision different than the one selected on their informed consent form, and 42% (26/62) provided the same answer as they had selected on their informed consent form (Table 1).

3.2. Perspectives and understanding of randomization procedures

3.2.1. Groups 3 and 4 (patients randomized to an experimental intervention)

Among the patients randomized to, and offered, the exercise intervention, when asked, "Do you know how you have been selected for the experimental intervention?", 44% (48/108) answered that they were not interested in how they were selected, 41% (44/108) adequately answered

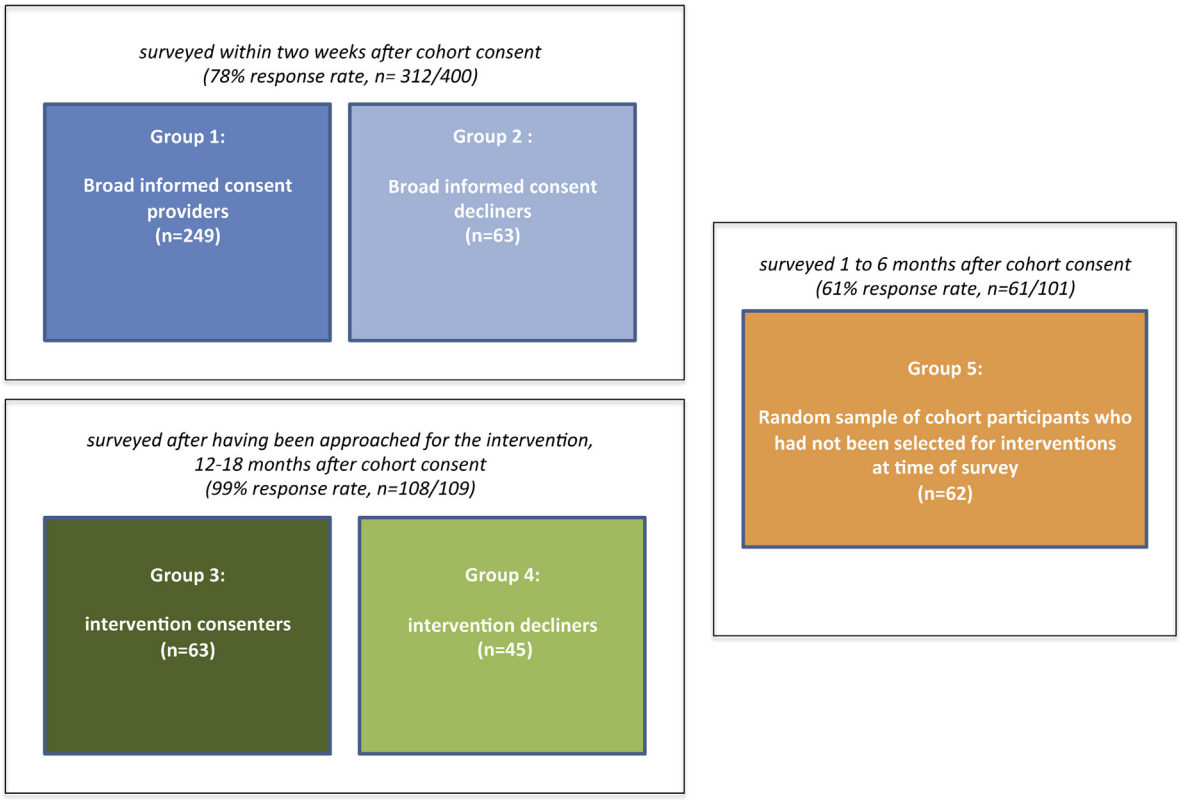

Fig. 1. Overview of survey participants.

that this was based on chance, 10% (11/108) thought it was based on reasons other than chance, and 2% (2/108) selected that they did not know how they were selected but would like to have known (Table 2).

Patients who accepted the intervention were also asked how they would feel if they had not been offered the intervention but if their data were being used comparatively without their knowledge. Here, 97% (61/63) stated they would feel neutral, 3% (2/63) would feel reassured, and one patient would feel angry.

3.2.2. Group 5 (random sample of cohort participants who had not been selected for an intervention at the time of the survey)

Patients in the random cohort sample were also asked how they would feel if their data were being used comparatively with those of patients who had been offered an experimental intervention. Here, 89% (55/62) indicated they would feel "neutral," 10% would feel reassured (6/62), one patient would feel angry, and one patient would feel insecure (Table 2).

4. Discussion

This study provides the first evaluation of broad informed consent for randomization for the "TwiCs" design, among patients participating in TwiCs studies, and was conducted within a clinical oncology setting. Recollection of broad consent for randomization was adequate shortly after enrollment and after having been randomized and offered to undergo an intervention. However, recollection was poor (42%) in patients who had not been selected for interventions 1–6 months after providing informed consent. Of patients randomly selected and offered to undergo an intervention, 41% understood that this was based on chance, 10% did not understand that selection was based on chance, and 44% stated not to care how they had been selected. Patients were acceptant of the thought of serving as control without further notice (only 2% stated they would experience negative emotions from serving as control without being notified).

Our study was performed at a clinical department where TwiCs cohorts have been implemented in routine care as of 2013. Here, patients with specific cancer diagnoses (i.e., colorectal cancer, bone metastasis, breast cancer, and recently also brain metastases and oligo metastases) are systematically invited to participate in TwiCs cohorts, and the staged-informed consent procedure is applied [6]. Data collection mainly consists of routine care data. Jagsi et al. surveyed 875 patients with cancer to evaluate their views on informed consent when using routinely collected data for research purposes. They found that 71% of patients felt that consent should be obtained at least once before using

their data for research [14]. They also found that 35% of patients with cancer found it necessary to obtain consent each time their data were being used for research. Dal Ré et al. also evaluated patients' beliefs regarding informed consent for low-risk pragmatic trials [15]. They found that 74% endorsed obtaining informed consent, with a clear preference for written informed consent over verbal consent. The findings from both these studies support the use of our staged-informed consent approach, as written consent is obtained for all relevant study activities at least once on enrollment (e.g., collection of routine care clinical data and patient-reported outcomes, consent for randomization, and serving as control), and additional written informed consent is obtained each time patients actively needs to do something other than what is part of routine care (e.g., consenting to accept an experimental treatment). Although there is an ongoing ethical discussion about the need to disclose or ask informed consent for randomization in (low-risk) pragmatic RCTs, and about the need to clearly demarcate the difference between research and clinical practice in pragmatic RCTs, our staged-informed consent model does not challenge any of this and adheres to traditional ethical guidelines for informed consent [16−19]. Our model would allow for future adaptations if ethical guidelines further relax their recommendation regarding informed consent in a way that would be relevant to TwiC-related studies.

In our survey, after having been selected for an intervention, 76% of patients understood that this was because of previously providing broad consent for randomization. This number is in contrast to the poor recollection of providing broad consent among patients who had not been approached for interventions 1−6 months after enrollment. This is an important finding that needs further exploration to understand and improve.

Understanding of the random selection process was far from optimal, as only 41% of patients who were randomly selected and approached for an experimental intervention understood that this selection was based on chance. Interestingly, 44% stated that they were not interested in how they were selected. An optimistic explanation for this would be that patients made a well-informed decision with a good understanding of the study design upon enrollment, after which they no longer cared about fully understanding the design later in time. A less favorable explanation is that these patients never fully understood the design on enrollment and do not want to understand the design after they were selected because the design is too complex for them to understand. If the latter were true, this would suggest that informed consent may not have been as effective as we were hoping for. Other studies have shown that understanding of randomization is poor in general. Kodish et al. explored understanding of randomization in childhood leukemia classic RCTs and found that 50% of parents (68/137) did not understand the randomization procedure shortly after enrollment/informed consent procedure [20]. Furthermore, a literature review by Flory et al. on informed consent also found that in most other studies, fewer than half of the participants understood randomization [21]. This review showed that the most effective way to improve understanding is by applying a face-to-face informed consent process, with the opportunity for a dialog and interaction with a qualified person [21]. In our setting, despite providing written information, face-to-face information, and a face-to-face informed consent process with opportunity to ask questions to a qualified person, still only 41% of patients understood that selection was based on chance. Understanding of randomization should be improved for all study designs that use some form of randomization. Unfortunately, it remains unclear how this can best be achieved; thus, additional studies are required, potentially from psychological fields, to inform researchers about the best ways to improve patients' understanding. In the meantime, for TwiCs, more attention should be paid during informed consent discussion to explaining that selection for all trials within the cohort will be based on chance instead of the physician's or patient's preference and that—unlike classic RCTs—patients will not be informed when allocated to receiving standard of care but only when allocated to being offered an intervention (after which they will have a choice to accept or decline this offer).

At present, patients who are participating in the TwiCs cohorts at our center are informed once or twice per year about aggregated study results and cohort participation rates through meetings and newsletters. A solution for the poor recollection may be to add general reminders in such newsletters explaining that the receiver of the newsletter is actively enrolled in a cohort study, with the possibility of being offered interventions or serving as controls without being notified. A solution for the poor understanding of randomization may be to add information about the study design—and that selection was done based on chance instead of the physician's or patient's preference—when providing study results for trials performed within the cohorts. Adding such information to the newsletters may stimulate more adequate recollection of informed consent choices for all cohort participants, irrespective of whether they have been offered interventions within the cohorts, and may improve understanding that selection for trials within the cohort is based on chance. Furthermore, discussing completed trial results and cohort measurements with patients during clinical follow-up may further improve recollection.

The main concern of opponents of the TwiCs design is that patients might experience distrust toward the scientific community or their caregivers when finding out that they were randomized without their prior knowledge or their explicit consent for randomization [22]. The staged-informed consent approach for TwiCs aims to avoid this situation by asking patients to provide broad consent for future randomization, before randomization is applied, and by informing patients beforehand that this potentially

entails serving as controls without their knowledge. This approach was well accepted by patients, as only 2% of patients not selected for interventions stated they would feel negative about the idea of not being selected for interventions while their data are being used in comparison without further notice.

In conclusion, recollection of broad consent for randomization is adequate shortly after enrollment and after being randomly selected but could be improved in patients who were never selected for interventions. Future studies are required to explain this difference; frequent reminders of the possibility of being approached for interventions may ensure to keep all broad consent providers aware and informed.

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