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Characteristics, consent patterns, and challenges of randomized trials using the Trials within Cohorts (TwiCs) design - A scoping review

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Abstract

Objectives: Trials within Cohorts (TwiCs) is a pragmatic design approach that may overcome frequent challenges of traditional randomized trials such as slow recruitment, burdensome consent procedures, or limited external validity. This scoping review aims to identify all randomized controlled trials using the TwiCs design and to summarize their design characteristics, ways to obtain informed consent, output, reported challenges and mitigation strategies.

Study Design and Setting: Systematic search of Medline, Embase, Cochrane, trial registries and citation tracking up to December 2022. TwiCs were defined as randomized trials embedded in a cohort with postrandomization consent for the intervention group and no specific postrandomization consent for the usual care control group. Information from identified TwiCs was extracted in duplicate from protocols, publications, and registry entries. We analyzed the information descriptively and qualitatively to highlight methodological challenges and solutions related to nonuptake of interventions and informed consent procedure.

Results: We identified a total of 46 TwiCs conducted between 2005 and 2022 in 14 different countries by a handful of research groups. The most common medical fields were oncology (11/46; 24%), infectious diseases (8/46; 17%), and mental health (7/46; 15%). A typical TwiCs was investigator-initiated (46/46; 100%), publicly funded (36/46; 78%), and recruited outpatients (27/46; 59%). Excluding eight pilot trials, only 16/38 (42%) TwiCs adjusted their calculated sample size for nonuptake of the intervention, anticipating a median nonuptake of 25% (interquartile range 10%-32%) in the experimental arm. Seventeen TwiCs (45%) planned analyses to adjust effect estimates for nonuptake. Regarding informed consent, we observed three patterns: 1) three separate consents for cohort participation, randomization, and

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intervention (17/46; 37%); 2) combined consent for cohort participation and randomization and a separate intervention consent (10/46; 22%); and 3) consent only for cohort participation and intervention (randomization consent not mentioned; 19/46; 41%).

Conclusion: Existing TwiCs are globally scattered across a few research groups covering a wide range of medical fields and interventions. Despite the potential advantages, the number of TwiCs remains small. The variability in consent procedures and the possibility of substantial nonuptake of the intervention warrants further research to guide the planning, implementation, and analysis of TwiCs.

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Keywords: TwiCs; Trials within cohorts; cmRCT; Randomized clinical trial; Metaresearch; Trial design

1. Introduction

Randomized clinical trials (RCTs) are the gold standard to evaluate interventions in health care [1,2]. However, RCTs can be challenging in terms of slow participant recruitment, limited external validity, burdensome consent procedures, or undesirable study-related behavior of participants ('disappointment effects') when RCTs are designed open label [3−6]. Trials within Cohorts (TwiCs) is a pragmatic design approach [7,8] with the potential to overcome these challenges [9,10]. In TwiCs, participants with the condition of interest are recruited into or are already part of a prospective cohort study. Consent is obtained for regular prospective data collection and for randomization into future trials nested into the cohort. Participants are recontacted only after randomization into the intervention arm of such a future trial and asked whether they accept ('uptake') or decline ('nonuptake') the proposed intervention. As such, the consent procedure mimics usual care, where people are informed about new treatment options but not about treatments they may not receive [11,12].

The consent procedure includes several stages with tailored information provided at each stage, which may raise questions among ethics committees unfamiliar with TwiCs [13]. A further challenge arises from nonuptake of the proposed intervention in the experimental arm, while all control participants continue usual care [14]. This may result in a dilution of the intervention effect [15]. Potential strategies to address this issue include the anticipation of nonuptake in the sample-size calculation and alternative analyses (which have their own challenges), such as the use of Complier Average Causal Effect (CACE) analyses to provide estimates of the treatment effect for participants who adhere to the experimental intervention [16].

Despite growing interest in innovative trial designs, little is known about the number of completed and ongoing TwiCs. To guide future trialists planning TwiCs, our scoping review aims to summarize all available TwiCs regarding their characteristics and output and provide empirical evidence on how others approached consent procedures and low uptake in the planning, conduct, analysis, and reporting of TwiCs.

2. Methods

We followed guidance for conducting and reporting scoping reviews [17,18]. The protocol was prospectively registered on Open Science Framework [19].

For this review, we defined a ''cohort'' as a framework for regular, longitudinal health data collection for observational research purposes with obtained informed consent from the participants. TwiCs were defined as trials that (i) are embedded within a cohort study (obtaining consent from cohort participants for inclusion and regular data collection (''cohort consent'')), and (ii) seek consent from intervention group participants (''intervention consent'') after randomization (postrandomization consent) [12]. We included TwiCs with available protocol or results publication, as well as pilot and feasibility studies.

The systematic search was conducted on December 15, 2022, including Medline and Embase via COVID, and the Cochrane library via Central; trial registries (Clinicaltrials.gov, European Union Drug Regulating Authorities Clinical Trials Database, and International Standard Randomized Controlled Trial Number registry), backward and forward citation tracking using Scopus for all identified TwiCs, the TwiCs global network homepage [20], and an automatic Google scholar alert (detailed search strategy in appendix Text S1). We did not apply any language or date filters in our electronic searches. The search strings for the different databases were developed together with an information specialist. The title and abstract screening and the full text eligibility assessment were performed independently and in duplicate (AA, CMS). Discrepancies were resolved by discussion or by involving a third reviewer (MB). In case of untraceable full texts or protocols, we contacted the research teams via email.

Two researchers independently extracted the data (AA, CMS, BS, JG, JMS, MB). For each TwiC, we extracted various trial characteristics, information about considering nonuptake in the sample size calculation, data analysis, and the interpretation of the primary effect estimates. We performed basic qualitative content analysis for characteristics that required interpretation and categorization (consent procedures and patterns, reporting of the treatment effects, reported rationale, reported challenges). Two reviewers

What is new?

Key findings

- We identified a heterogeneous group of clinical trials using the TwiCs design across a variety of medical fields and interventions.
- We found three different, commonly used, and ethically feasible patterns to informed consent used in TwiCs.
- Low uptake of offered interventions is a common challenge and may lead to a difficult interpretation of the trial results.
- Inflexibility in the data collection imposed by the overarching cohort and the comparison against standard of care are inherent features in TwiCs and need to be considered adequately.

What this adds to what is known?

- A systematic overview about existing TwiCs and their characteristics and challenges are missing.

What is the implication and what should change now?

- Identified methodological challenges of TwiCs such as multistage consent procedures and low uptake of the intervention need further research to guide future trialists using the design.

(AA, CMS) independently highlighted quotes of relevant text passages created labels that best reflected the content, and iteratively discussed and modified categories together with MB until final categories were reached. Regarding consent procedures, we determined the following three consent levels for each TwiCs: i) consent for data collection ('cohort consent'), ii) consent for future randomization ('randomization consent'), and iii) consent to receive a specific intervention, only collected in the intervention group ('intervention consent'). Regarding the conclusiveness of the primary results, we classified each TwiCs as positive (statistically significant result based on reported confidence intervals for the primary outcome), negative (anticipated treatment effect not part of the 95% confidence interval), or inconclusive (anticipated treatment effect part of the 95% confidence interval).

All data were collected in Research Electronic Data Capture [21,22]. We summarized quantitative data as median/interquartile range (IQR) for continuous variables, and frequency/percentage for categorical variables, using R version 4.0.4 (2021-02-15) [23]. Further details about methods are outlined in the protocol [19].

3. Results

We identified a total of 46 [24–40] [41–68] TwiCs (Fig. 1). A list of all included TwiCs is provided in the *appendix* (Table S1). The majority of TwiCs were conducted in Europe, mostly in the United Kingdom (n = 13), France (n = 10) and the Netherlands (n = 9) (Figure S1, *appendix*), often by the same research group in each country (Table S2 and Figure S1, *appendix*).

We found one TwiC published before the seminal paper in 2010 [63], and the remainder published after 2010 with two peaks in 2015 and 2020, each year with eight TwiCs (Figure S2, *appendix*).

3.1. General TwiCs characteristics

The most common medical fields in TwiCs were oncology (11/46, 23.9%), infectious diseases (8/46, 17.4%, including six COVID-19), and mental health (7/46, 15.2%) (Table 1). TwiCs evaluated diverse types of interventions such as behavioral/counseling/psychological interventions (15/46, 32.6%), drugs (6/46, 13.0%), complementary therapy (4/46, 8.7%), and radiotherapy (4/46, 8.7%). A typical TwiCs recruited participants in an outpatient setting (27/46, 58.7%), included adults (41/46, 89.1%), was investigator-initiated (46/46, 100%), and publicly funded (36/46, 78.3%). Twenty-four TwiCs were completed (24/38, 63.2%), 13 were still ongoing (13/38, 34.2%), and one was discontinued due to slow recruitment (1/38, 2.6%). Out of 25 completed or discontinued TwiCs, 22 had a peer-reviewed results publication (88%).

Reported rationale for the use of the TwiCs design included the reduction of 'disappointment effect' (26/46, 56.5%), improved efficacy of recruitment (24/46, 52.2%), and the availability of a real-life comparator (18/46, 39.1%). The most often reported challenges of the TwiCs design were the low uptake of the assessed intervention in the experimental arm (8/46, 17.4%) and the inflexibility regarding which outcomes can be collected at what timepoints due to the given cohort structure (4/46, 8.7%).

Around half of all TwiCs used patient reported outcome measurements for the primary outcome (21/46, 45.7%). Most trials did not blind outcome assessors (29/38, 76.3%).

The majority of all TwiCs were embedded in a national cohort (40/46, 87.0%). Less than half of the TwiCs used an already existing cohort study (21/46, 45.7%). In the remaining cases, the cohort study was established at the same time as the TwiCs (See Table S4 *appendix*). Seven cohorts hosted more than one and up to five TwiCs (See Table S5 *appendix*).

3.2. Nonuptake of interventions offered in the experimental arm

Eight TwiCs were pilot or feasibility studies, and thus did not outline details about a sample size calculation and statistical analysis of an intervention effect (Table 2).

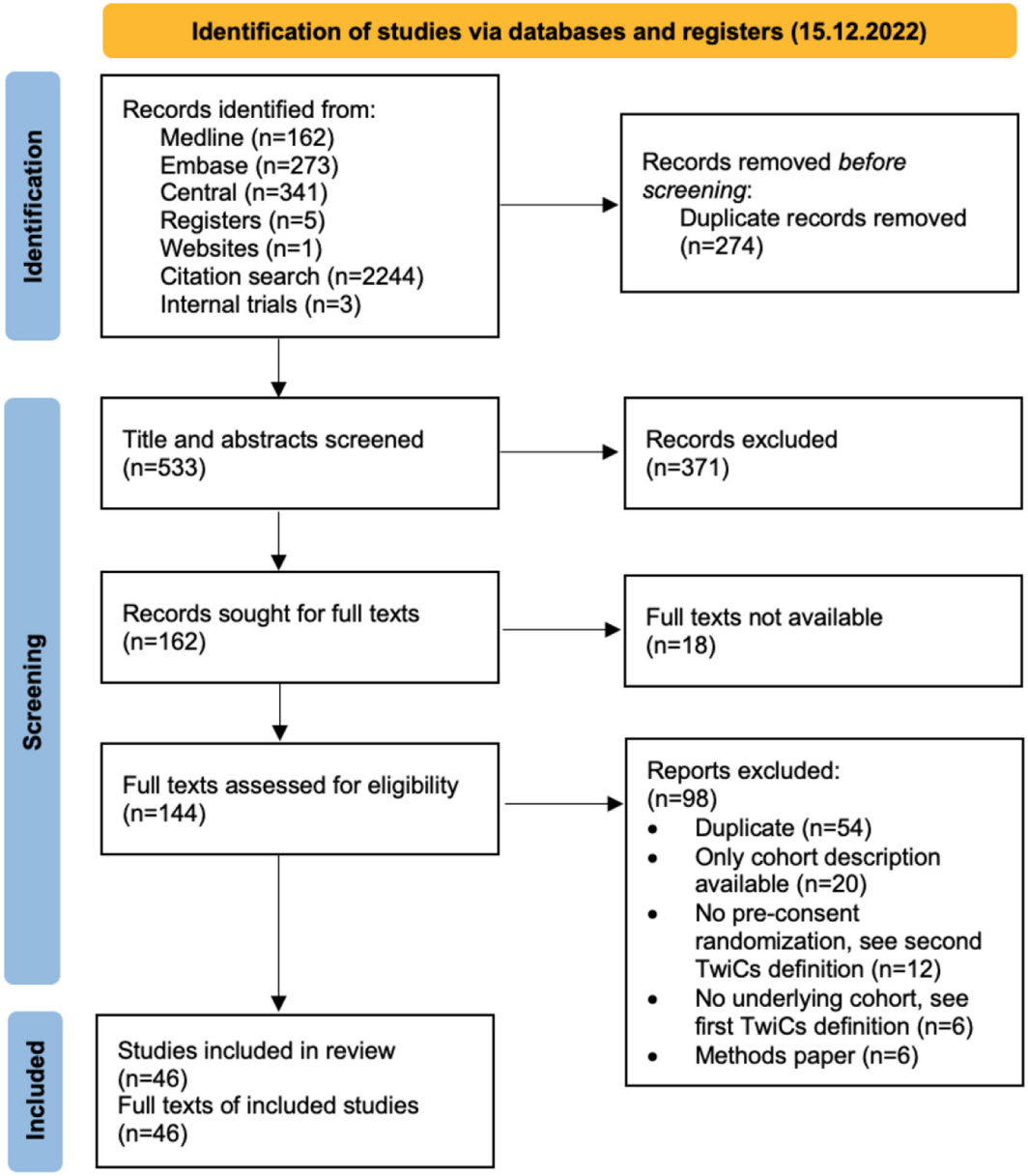

Figure 1. PRISMA flow chart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.(For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Among the 38 remaining trials, ten of the completed TwiCs (10/22, 45.5%) conducted a CACE analysis to adjust for nonuptake, mostly using an instrumental variable method (7/10, 70.0%). One trial used the CACE analysis as the primary analysis [32]. Less than half of TwiCs anticipated the proportion patients who would not adhere to the assessed intervention in their sample size calculation (15/38, 39.5%, median estimated proportion 25%, IQR 10%-32%). Only one group justified their estimate with data from an internal pilot study [70]. Fifteen out of 22TwiCs (71.4%) reported their intention-to-treat result as a direct effect of the intervention on the outcome (*intervention effect*) without considering nonuptake that exceeded 50% in some studies. Seven reported the result as an effect of *offering* the intervention (*offer-of-intervention effect*).

Only one TwiC reported a statistically significant result (based on the reported confidence interval for the primary outcome), while the primary result of nine TwiCs (10/22, 45.5) was inconclusive, meaning the anticipated clinically meaningful treatment effect was part of the 95% confidence interval and the result was not statistically significant (Table S6 appendix).

Table 1. Characteristics of included TwiCs

Characteristics	Included TwiCs (n = 46)
Age group (%)	
Adults	41 (89.1)
Children/adolescents (below 18 years)	3 (6.5)
Both	2 (4.3)
Medical field (%)	
Oncology	11 (23.9)
Infectious diseases/COVID-19	8 (17.4)
Mental health	7 (15.2)
Primary care/public health	5 (10.9)
Rheumatology	4 (8.7)
Other[a]	11 (23.9)
Type of intervention (%)	
Behavioral/counseling/psychological/life-style intervention	18 (39.1)
Drug	6 (13.0)
Complementary therapy	4 (8.7)
Radiotherapy	4 (8.7)
eHealth supported care by lay health workers	3 (6.5)
Surgical/invasive procedure	2 (4.3)
Physical/manual therapy	2 (4.3)
Other[b]	7 (15.2)
Primary outcome (%)	
Patient reported outcome[c]	21 (45.7)
Survival or disease progression[d]	9 (19.6)
Feasibility outcome	6 (13.0)
Biomarker outcome	6 (13.0)
Other[e]	4 (8.7)
Setting of recruitment (%)	
Outpatient[f]	27 (58.7)
Community	13 (28.3)
Hospital ward or emergency room	6 (13.0)
Recruiting sites (%)	
Multicenter, national	19 (41.3)
Multicenter, international	5 (10.9)
Single center	22 (47.8)
Sponsorship, investigator-initiated [69] (%)	46 (100.0)
Funding (%)	
Only public	36 (78.3)
Public and industry funding	10 (21.7)
Unit of randomization (%)	
Individual participant	43 (93.5)
Cluster (villages)	3 (6.5)
Trial registry entry available (%)	45 (97.8)
Pilot or feasibility study (%)	8 (17.4)
Hypothesis (%)[g]	
Superiority	37 (97.4)
Noninferiority	1 (2.6)
Planned sample size (median [IQR])[g]	200 [122, 622]
Duration of participant recruitment in days (median [IQR])[g]	491 [150, 1164]
Trial status (%)[g]	
Completed as planned	24 (63.2)
Ongoing (recruitment or/and follow-up)	13 (34.2)
Discontinued (i.e., less than 80% of planned sample size achieved)	1 (2.6)
Results publication available (%)[h]	
As peer-reviewed publication	22 (88.0)
No	3 (12.0)
Terminology used by authors (%)	
TwiCs	20 (43.5)
cmRCT	12 (26.1)
Zelen	6 (13.0)
Cohort embedded RCT	3 (6.5)
Cohort RCT	2 (4.3)
Other[i]	3 (6.5)
Reported rationale for using the TwiCs design (%)[j]	
Reduce 'disappointment effect'	26 (56.5)
Efficient recruitment	24 (52.2)
Real life comparator	18 (39.1)
Perform multiple RCTs	10 (21.7)
Staged consent closer to clinical routine	6 (13.0)
Other[k]	19 (41.3)
No design rationale reported	9 (19.6)
Reported challenges using the TwiCs design[j]	
Low uptake of intervention	8 (17.4)
Inflexibility of cohort structure	4 (8.7)
Other[l]	6 (13.0)
Primary method of outcome collection (%)[g]	
In-person site visits	23 (60.5)
Postal or online survey (± calling and electronic health record) linkage)	11 (28.9)
In-person home visits	3 (7.9)
Electronic health record linkage only	1 (2.6)
Blinding of outcome assessor (%)[g]	
No[m]	29 (76.3)
Yes	7 (18.4)
Unclear	2 (5.3)

(*Continued*)

[a] Geriatrics (n = 3), Orthopedics (n = 2), Complementary medicine (n = 2), General surgery (n = 1), Urology (n = 1), Nephrology (n = 1), Gynecology (n = 1).

[b] *Artemisia afra* tea (n = 1), Plasma (n = 1), offer of screening test + drug if screened positive (n = 1), Placebo (n = 1), Radiotherapy and Surgery (n = 1), Device (n = 1), Screening (n = 1).

[c] Symptom severity (n = 7), Pain (n = 5), Depression (n = 4), Quality of life (n = 3), Number of falls (n = 2).

[d] n = 1 trial used a composite endpoint (survival or cardiovascular event), all others survival only.

[e] Length of hospital stay (n = 1), Complete tumor response (n = 1), Cognitive development (n = 1), Behavior change (n = 1).

[f] Outpatient and Community (n = 3).

[g] We used 38 as denominator (8 pilot and feasibility trials excluded).

[h] We used 25 as denominator (including 24 completed and 1 discontinued trial).

[i] Platform trial ($n = 1$), Trial nested within a cohort ($n = 1$), Two-stage consent design ($n = 1$).

[j] Multiple selection possible.

[k] Possibility to conduct long-term follow-ups easily ($n = 5$), Possibility to assess uptake of intervention in detail ($n = 4$), Improved generalizability of the results ($n = 3$), Reduction of crossovers ($n = 3$), Lower costs ($n = 2$), Efficient data collection through existing cohort infrastructure ($n = 2$).

[l] Ethical concerns from physicians ($n = 2$), No possibility for placebo ($n = 2$), Prolonged ethical approval ($n = 1$), Contamination bias (participants sitting in the same waiting area) ($n = 1$).

[m] $n = 16$ of these TwiCs had a patient reported primary outcome.

3.3. Approaches to informed consent procedure in TwiCs

We identified three different consent patterns (Fig 2). Pattern 1 (Dutch pattern; as seen in all nine TwiCs conducted in the Netherlands) requires three separate consent steps: for being part of the observational cohort, for being randomized in future trials, and for receiving the TwiCs intervention. Pattern 2, UK pattern was the most common pattern (19/46; 41.3%). In this pattern there was no explicit consent for being randomized/randomly selected. Pattern 3, French, the least common pattern was found in 10 (21.7%) TwiCs. In this pattern consent for being part of the observational cohort and for being randomized was combined thus it was not possible to be part of the cohort without agreeing to be randomized in a future TwiC in the French pattern. Higher risk interventions such as radiotherapy or surgery were only tested in TwiCs with explicit randomization consent (Dutch and French patterns, Table S7).

Table 2. Items related to nonuptake of offered intervention in the experimental arm

Category	Overall ($n = 38$)
Primary analysis as reported by trial team (%)	
Intention to treat	31 (81.6)
Modified intention to treat	3 (7.9)
Complier Average Causal Effect (CACE)	1 (2.6)
Unclear	3 (7.9)
CACE planned (%)	17 (44.7)
CACE conducted (%)[a]	
No	12 (31.6)
Yes, using instrumental variable	7 (18.4)
Yes, using propensity score matching	1 (2.6)
Yes, using both Instrumental variable and propensity score matching	1 (2.6)
Yes, method unclear	1 (2.6)
No results published yet	16 (42.1)
Nonuptake estimated in sample size calculation (%)	16 (42.1)
If included, estimated nonuptake in percent (median [IQR])	25 [10, 32]
If included, any justification provided	
No	15
Yes	1
Effect reported as (%)	
Offer-of-intervention effect	7 (18.4)
Intervention effect	15 (39.5)
Not applicable as no result publication available	16 (42.1)

[a] One trial conducted CACE as primary analysis.

4. Discussion

This scoping review of existing TwiCs highlights the diversity in populations, interventions, and applied methodology. The review provides evidence that different multistage strategies for obtaining informed consent are possible and that the trial design may be associated with low risk for recruitment failure (affected only one trial). However, nonuptake of the offered intervention was a frequent challenge. Investigators often did not consider nonuptake in their sample size calculations, rarely accounted for it in the analysis, and frequently interpreted the effect estimates as direct *intervention* effects and not as *offer-of-intervention* effects.

The variety of existing consent patterns and terminologies reflects an evolutionary process (Figure S2, *appendix*). Postrandomization consent, where participants are randomized before giving consent to the intervention, is a distinctive feature of TwiCs. First described by Marvin Zelen in 1979 [71], Relton and colleagues embedded the preconsent randomization into cohort studies and named it the ''cohort multiple RCT'' design [10]. Driven by ethical concerns from regulatory authorities that the control participants are only informed about the trial after its conduct, Dutch researchers added an additional explicit consent level (randomization consent), named it ''staged-informed consent'' procedure [12]. The staged-informed consent procedure (Dutch pattern) was often used to test higher risk interventions in an oncology setting. While it increases the administrative burden on the one hand, it may strengthen the rights and autonomy of trial participants on the other. However, most TwiCs in our sample omitted an explicit randomization consent (UK pattern), were more heterogeneous regarding medical fields and types of interventions, and typically assess low risk interventions (in terms of potential harm for participants). The third pattern (French pattern) was prominently used in quickly built-up cohorts for the conduct of TwiCs, investigating drugs during the COVID-19 pandemic in France. All consent patterns aim to mimic clinical practice to gain real-world comparative effectiveness evidence [72]. The decision about the type of consent procedure in a TwiC appears to be strongly influenced on the ethical assessment of local regulatory

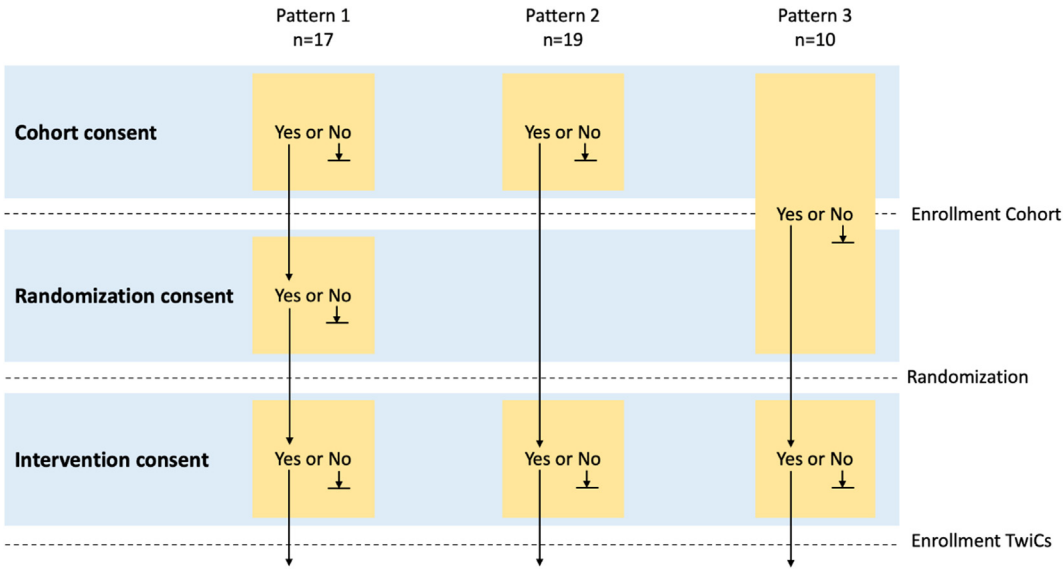

Figure 2. Identified consent patterns. The horizontal axis displays the different consent patterns (Pattern 1 = Dutch pattern, Pattern 2 = UK pattern, Pattern 3 = French pattern) and corresponding number of TwiCs these are used in. On the vertical axis three different levels of consent (cohort consent, randomization consent, intervention consent) are shown. The dotted lines indicate enrollment in the cohort and the TwiCs (randomized trial), the arrows indicate the consent decisions of the participants. In pattern 1 = Dutch pattern, there are three separate consent steps. In pattern 2 = UK pattern an explicit consent for randomization is missing. In pattern 3 = French consent, the consent for being part of the cohort and for the randomization is combined. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

authorities. Evidence on the participants' experience in TwiCs is limited and the rationale that the inclusion process in TwiCs is less burdensome for participants than in traditional RCTs needs to be further investigated [66,73,74].

TwiCs introduce some challenges by design. First, a classic placebo-controlled trial is not possible with this design since the control group is provided with standard of care. As such, as in every pragmatic open-label trial, participants and care providers may modify their behavior, because they are aware of what care they receive. This is often an acceptable feature (''real-life behavior'') in pragmatic trials [75] and might even be closer to reality in a TwiCs design where the randomized groups do not know from each other (masked allocation). Importantly, as a mitigation strategy, one may choose clinical endpoints that are hard to modify (eg, survival) and blinded outcome assessors [76]. However, we found a substantial number of TwiCs using patient reported outcome measures without blinding of outcome assessors.

Second, TwiCs are embedded in a cohort and the data collection is usually dictated by the type and frequency of the routine cohort follow-up visits. Since the control group remains unaware of the trial, additional assessments and visits are difficult to implement. Despite this lack of flexibility, we found a substantial number of TwiCs that examined drugs, radiotherapy, or invasive procedures, interventions which typically require closer monitoring and more detailed outcome collection. However, if the cohort is built up simultaneously with the first TwiCs in this cohort, as it is the case for more than 50% of the TwiCs in our sample, then the follow-up can be tailored to meet the necessary data collection frequency and endpoints − as demonstrated with the radiotherapy TwiCs conducted at University Medical Center Utrecht [50] or the COVID-19 drug treatment TwiCs [33−36,77].

Third, while in the control group all eligible participants are included (without additional consent) and are not experiencing any disappointment of not receiving the intervention, a certain percentage of eligible participants in the intervention will decline the proposed intervention (''nonuptake'') [13]. Reported observed nonuptake was highly variable in TwiCs, ranging from 0% to 75% (Table S6 appendix). Reasons for this are probably multifactorial (intervention offered, medical field, patient characteristics, etc.). Ninety percent of the TwiCs followed the principle of intent to treat (ITT) in their primary analysis. However, if nonuptake is large, the estimated effect must be interpreted as an *offer-of-intervention* effect as the traditional ITT effect, interpreted as a direct *intervention* effect, might be prone to significant dilution effects. Importantly, nonuptake should be accounted in the sample size calculation for proper assumption on the effect size [15]. Only 37% of TwiCs accounted for the nonuptake in their sample size calculation and only one reported on which data they base their nonuptake estimates on. Nearly half prespecified a CACE analysis that estimates the effect among the adherent study population, using an instrumental variable approach. However, the underlying main assumptions (monotonicity,

exchangeability, exclusion restriction) for such an instrumental variable analysis need to be reviewed and carefully verified [78−81].

Among 21 TwiCs with a primary result available, only one had a statistically significant result. This is in line with similar findings from a meta-analysis of traditional pragmatic RCTs [82]. It would be interesting to see if more TwiCs reported significant results if the assumptions made when planning the sample size included a better consideration of the nonuptake issue.

Half of the TwiCs mentioned more efficient recruitment of participants as part of their rationale for using the TwiCs design. This argument is supported by case studies from a pioneer Dutch TwiCs group focusing on oncology trials reporting efficient recruitment [83,84]. We found only one trial prematurely discontinued for recruitment failure. Therefore, the TwiCs design approach may help overcome recruitment problems prevalent in traditional RCTs [6].

To our knowledge, this is the first review systematically searching and summarizing available TwiCs. A recently published review also included TwiCs but had a much broader scope with the objective to examine the range of use of cohorts for RCTs in general and the employed terminology and concepts [85]. Our search strategy was developed with an information specialist and experts from the TwiCs global network [20]. We used state-of-the-art review methodology and prospectively published our study protocol.

Our study has several limitations. First, the level of detail of the available information depended on the available sources (protocol, results publication, registry entry, etc.). If the level of detail was insufficient, we reached out to the investigators for clarification. Second, the relatively small number of completed TwiCs prevents firm conclusions regarding quantitative questions such as risk of recruitment failure.

5. Conclusion

We identified a heterogeneous group of clinical trials using the TwiCs design across a variety of medical fields and interventions. We found three common patterns of informed consent procedures.

Low uptake of the offered intervention remains a challenge that needs to be considered in sample size calculations and interpretation of the results and should be addressed in more comprehensive guidance.

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Ethical statement

Ethical approval was not required for this metaresearch study.

Patient and Public Involvement

We did not involve patients or public in this metaresearch study.

CRediT authorship contribution statement

Alain Amstutz: Writing − review & editing, Writing − original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Christof M. Schönenberger:** Writing − original draft, Visualization, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Benjamin Speich:** Writing − review & editing, Data curation. **Alexandra Griessbach:** Writing − review & editing. **Johannes M. Schwenke:** Writing − review & editing, Data curation. **Jan Glasstetter:** Data curation. **Sophie James:** Writing − review & editing. **Helena M. Verkooijen:** Investigation. **Beverley Nickolls:** Writing − review & editing. **Clare Relton:** Writing − review & editing, Investigation. **Lars G. Hemkens:** Writing − review & editing, Investigation. **Frédérique Chammartin:** Writing − review & editing. **Felix Gerber:** Writing − review & editing, Investigation. **Niklaus D. Labhardt:** Writing − review & editing. **Stefan Schandelmaier:** Writing − review & editing, Methodology, Investigation. **Matthias Briel:** Writing − review & editing, Supervision, Methodology, Conceptualization.

Data availability

AA and CMS affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Declaration of competing interest

Several coauthors (AA, CMS, HMV, CR, FC, FG, NDL, MB) are using the TwiCs design or are part of the academic TwiCs global network (https://www.twics.global). We declare no financial conflict of interest. There are no competing interests for any other author.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2024.111469.

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