Recommendations for planning and conducting Trials within Cohorts (TwiCs)

Deliverable 14.2

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The aim of this booklet is to offer a comprehensive overview of the key aspects to consider while planning and conducting trials within cohorts and to provide solutions to the main challenges in developing, implementing and conducting trials within cohorts (or TwiCs).

This booklet has been adapted from ERA4Health's original document D14.2 "Recommendation booklet for investigators and sponsors in multi-country investigator initiated clinical studies". References cited in this document can be found at the original source (1).

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Trial within cohorts (TwiCs)

A Trial within Cohorts (TwiCs) is a trial design where randomised controlled trials are conducted within existing cohorts of individuals.

A research cohort is a group of individuals who share a common characteristic or experience and are studied over a period of time. This type of grouping is commonly used in epidemiology, social sciences, and medical research to observe patterns, causes, and effects of various factors on the group.

The TwiCs design, also recognised as the cohort multiple randomised controlled trial (cmRCT) design, was proposed as an alternative to traditional pragmatic Randomised Clinical Trials (RCT) or intervention seamlessly into an established observational longitudinal cohort (2,3). A TwiCs design incorporates a randomised trial nested within a cohort study. Upon enrolment in the cohort, the participants provide consent for being randomised in future studies. Within this framework, once a RCT is designed, eligible cohort participants are randomly assigned to the trial intervention. Subsequently, they are invited to engage in informed discussions about the intervention, and upon their willingness to proceed, they provide explicit informed consent.

Meanwhile, participants meeting the trial's eligibility criteria but not selected for the trial intervention are not informed about the trial and continue to receive standard of care as part of the cohort study, undergoing regular follow-up activities.

A key tenet of the TwiCs design is that participants are only informed about the trial intervention once they have been selected to receive it, whilst controls are blinded to the existence of the trial.

The TwiCs approach capitalises on the infrastructure and data collection processes already in place within a cohort study.

This allows investigators and healthcare providers to observe how interventions integrate into existing treatment patterns, offering valuable insights into the feasibility and effectiveness of the intervention in real-world settings and therefore representing a more streamlined and cost-effective way for generating evidence on comparative effectiveness of interventions on health systems (4).

Key advantages of TwiCs design include (2, 4-10):

- Efficient Recruitment: The ability to swiftly recruit participants from established cohorts facilitates the rapid and efficient recruitment of a substantial number of participants, streamlining the study process.
- Ethical Considerations: Since TwiCs rely on the use of standard care as the comparator arm, placebo-controlled trials are not possible. Eliminating placebo deception, a common aspect in placebo-controlled trials, contributes to enhanced ethical standards.
- Real World Scenarios: Creating trial conditions that closely resemble the experiences patients would encounter in the routine clinical practice allows for a more realistic assessment of intervention impact in actual clinical settings.
- Patient-Centric Focus: By aligning trial conditions with real clinical practice, TwiCs studies are more likely to capture outcomes that matter for both patients and healthcare providers, fostering a patient-centric approach to research.
- Cost Effectiveness: Represents a cost-effective approach for generating evidence on comparative effectiveness, additionally utilising established cohorts to optimise the use of resources.
- Longitudinal Understanding: Leveraging existing cohorts allows researchers to study the long-term impact of interventions, providing a comprehensive understanding of treatment outcomes over extended periods.
- Addressing Multiple Research Questions: The flexibility of the TwiCs design allows for the possibility of embedding several trials within the same cohort. This enables the assessment of different interventions or the inclusion of participants with different eligibility criteria, facilitating the exploration of multiple research questions within a single study framework.

The TwiCs design has been used in diverse fields such as oncology (5-9), mental health (10-12), and chronic disease (4,13), being particularly useful when studying interventions aligned with the ongoing cohort's objectives. Up to now, the majority of TwiCs studies have focused on evaluating therapies such as physiotherapy, exercise, and radiotherapy rather than investigational medicinal products (IMPs).

An important milestone in the application of the TwiCs design to clinical trials involving IMPs was achieved with the initiation in 2016 of the TILT trial (EudraCT no. 2016-004727-23)(14). The results of all these trials highlight some of the challenges and limitations associated with conducting a full-scale trial within a TwiCs design (6,10,15).

Meanwhile, researchers experienced in the TwiCs approach have established an international network (16) aimed at sharing insights and experiences regarding the design and implementation of practical RCTs using the TwiCs methodology.

Recommendations for TwiCs

Funding & Funding Mechanisms

Developing funding opportunities:

- It is essential to support the creation and maintenance of existing cohorts and to enrich research infrastructure to improve scientific activities. Initiatives such as NIH grants (17) could serve as exemplary models.

Planning appropriate allocation of research costs:

- Pay careful attention to ensure accurate allocation of research costs and adherence to funders' expectations for grant utilisation.
- Justify the inclusion of costs associated with control participants in the funding application for the TwiCs, despite their designation as cohort participants rather than trial participants; these individuals contribute directly to the analysis of trial outcomes rather than serving solely cohort-specific purposes (18).

Regulatory and ethical considerations

Favouring the use of a staged informed consent model (8,13, 16, 18-21):

- 1st stage: participants grant initial consent during cohort enrolment, encompassing agreement for random selection in future trials and utilisation of their data as control data if not selected, without requiring additional notification.
- 2nd stage, participants selected for the intervention are asked to provide a second consent specifically related to the trial.
- This model demands detailed education of healthcare professionals involved in the trial, since it is crucial to ensure that eligible trial participants are not informed about the trial prematurely.
- Patients generally have not raise ethical objections to serving as controls without additional notice (20,24).

Dividing randomisation process into two phases (19,22):

- The 1st phase allows assessment of basic clinical inclusion criteria and allows randomisation to one of the study arms.
- The 2nd phase occurs after the comprehensive baseline assessment, including trial consent. In this phase the study team must confirm the randomisation to ensure that all inclusion/exclusion criteria are met before participants proceed to the study-mandated treatment.

Protocol design or methodological considerations

Evaluating the appropriateness of TwiCs:

- TwiCs methodology is well-suited for pragmatic trials, which focus on real-world effectiveness, and that frequently use standard of care as a comparator arm. The appropriateness of TwiCs methodology should be carefully evaluated based on the research question and the specific goals of the trial (2,4,18).

Addressing feasibility:

- Conducting a pilot study before adopting the TwiCs design to assess whether thorough eligibility screening can be effectively executed using the routinely collected data within the existing cohort (6). Addressing the non-compliance within the intervention group through:

1) Pilot Study (6,8):

- Provides valuable insights into estimating intervention refusal, non-compliance, and understanding participant behaviours.
- Allows for small protocol adjustments to optimise participant engagement and minimise non-compliance.

2) Sample Size Calculations (22,23):

- Including expected non-compliance rate in sample size calculations accounts for potential dilution of treatment effect in a TwiCs.
- Incorporating realistic scenarios during planning ensures study is adequately powered to detect meaningful treatment effects despite non-compliance.

Aligning of Trial and Cohort Assessment Schedules (18):

- Harmonising timing and frequency of data collection between the trial and cohort activities is crucial.
- Synchronisation optimises data collection efficiency and maintains participant engagement throughout the study.
- Introducing flexibility into the cohort study protocols in future to allow for potential adjustments to the follow-up regimen based on clinical or research requirements. This flexibility should be explicitly communicated to participants through the participant information sheet for the cohort study.

Choosing the appropriate randomisation approach (6,8,9):

Single-Batch Sampling Approach:

- Cohort participants are randomised to either the control or the intervention arm at a single point in time. This is feasible in closed or recruiting cohorts.

Multiple-Batch Sampling Approach:

- A subgroup of eligible cohort participants is randomised at one specific moment in time. Additional randomisation occurs over multiple rounds to reach the intended sample size.
- This method offers efficient patient recruitment but is not suitable for situations requiring rapid screening and randomisation shortly after diagnosis, progression, or relapse.
- Multiple-batch randomisation approaches may not be feasible in situations where prompt intervention is required after diagnosis. Eligible patients should be randomised immediately or shortly after cohort enrollment, instead of all being randomised simultaneously.

Patient recruitment and retention considerations

Choosing the right recruiting and retention strategy:

- The requirement for patient unawareness and blinding of controls demands detailed education of healthcare professionals and limits typical publicity methods.
- Engaging multiple stakeholders, including patient representatives, is crucial in discussing recruitment strategies. Involving patients ensures their perspectives, needs, and concerns are considered in developing patient-centred and ethical recruitment strategies.
- Innovative and alternative recruitment strategies are needed to engage eligible participants while maintaining blinding and confidentiality.

Data management

- Use a single database for both the cohort and TwiCs to ensure efficiency and streamlined data management.
- Implementing secondary identification numbers (IDs) within the database is recommended. These secondary IDs facilitate the identification of trial and control participants for data extraction and monitoring purposes (18).

Dissemination of results

Sharing trial results:
In TwiCs design, it is advisable to share trial results with all cohort participants, regardless of their specific trial participation (19,20):

- Sharing results promotes openness and inclusivity in research and contributes to the overall trust and credibility of the research endeavour.
- Providing trial results to all participants acknowledges their importance and keeps them engaged in the research process.
- Even non-participants benefit from being informed, fostering a sense of involvement and trust.
- Extending trial results to all participants reflects a commitment to their well-being and respects their contribution to the study.

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