CASE STUDY

TRIALS WITHIN COHORTS (TWICS)



TRIALS WITHIN COHORTS (TWICS): A NOVEL DESIGN TO EFFICIENTLY EMBED PRAGMATIC RANDOMISED TRIALS INTO COHORT STUDIES

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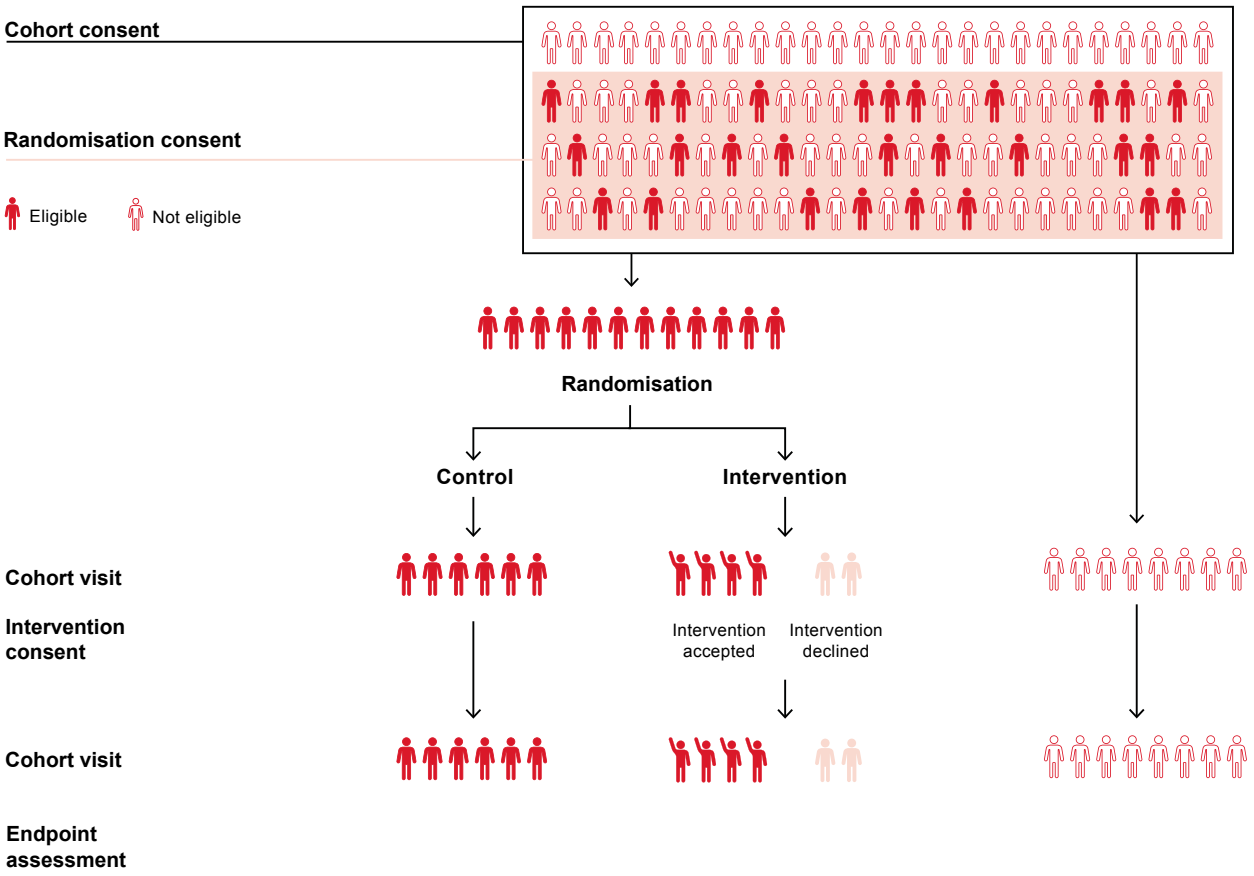
Trials within cohorts (**TwiCs**) is a novel trial design that promises to overcome frequent challenges of traditional randomised clinical trials, such as high cost, slow recruitment, and a limited generalisability of results. In studies with a TwiCs approach, a randomised comparison is nested into an observational cohort by design in order to use synergies in infrastructure for recruitment and data collection. The TwiCs design has been applied to the assessment of interventions in different medical fields in several countries using three different consent patterns. In Switzerland, the Swiss HIV Cohort Study is taking a pioneering role as the first cohort in the country to implement the TwiCs design.

TWICS: WHY AND HOW?

Randomised clinical trials are the gold standard for causal inference in medical research. However, randomised clinical trials often face various challenges, including high costs, slow participant recruitment, limited generalisability, burdensome consent procedures, and a disappointment bias that may occur in open-label trials if participants and providers change their behaviour when participants are not allocated to their preferred group.[1-3]

In recent years, trials within cohorts (**TwiCs**) has emerged as a pragmatic trial design with the potential to overcome these challenges.[4-9] Studies with the TwiCs design involve recruiting participants with a condition of interest into a prospective cohort. At enrolment, not only is consent obtained for regular prospective data collection, but participants are also informed about randomisation into future trials nested within the cohort. In a future trial using the TwiCs design, participants are approached only if they are randomised to the intervention group and are then given the option to accept or decline the proposed intervention. The participants randomised to the control group are not informed about the intervention being offered to other cohort participants but continue usual care and regular data collection as part of the cohort (see **Figure 1**). This consent procedure mimics usual care in that individuals are informed about new treatment options but not about treatments they may not receive. Additionally, the TwiCs design offers a comparison to a real-life control group, allows researchers to recruit efficiently from a well-described cohort, and embeds outcome collection efficiently within the cohort's follow-up structure.

Figure 1: Trials within cohorts (TwiCs) design according to the *Dutch* consent pattern



Cohort participants can agree to be randomised in future TwiCs (randomisation consent) for which they might be eligible. Participants who are then randomised to receive an intervention are asked to accept or decline the intervention (intervention consent). Participants randomised to the control group are not informed about the intervention and receive usual care according to the cohort's procedure. Participants who decline the intervention remain in the intervention group for analysis according to the intention-to-treat principle.

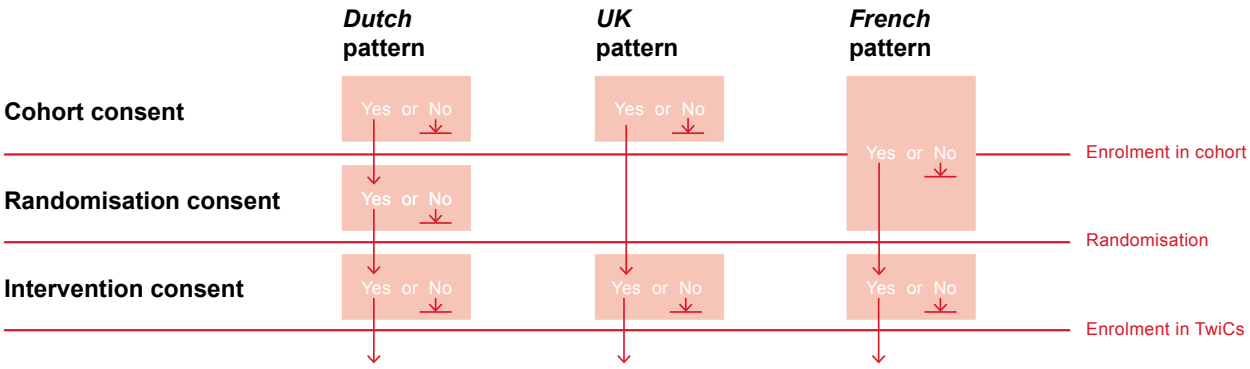
Source: Adapted from figure provided by the Division of Clinical Epidemiology at the University of Basel

TWICS: WHAT DO WE KNOW?

In a recent scoping review, Amstutz, Schönenberger, Gerber, et al. identified 46 trials in 14 different countries that were conducted with a TwiCs design up to December 2022.[10] The most common medical fields in which the design was applied were oncology (24%), infectious diseases (17%), and mental health (15%). A typical trial with a TwiCs design was investigator-initiated, was publicly funded, and recruited outpatients. The TwiCs in the review evaluated various types of interventions – mostly behavioural, psychological, or complementary interventions (42%) – as well as drugs (13%) and radiotherapy (9%).

Based on how ethics committees in three different countries guided trialists who implemented the TwiCs design, three major consent patterns have emerged (see **Figure 2**). In the *Dutch* pattern, there are three separate consent steps for cohort participation, randomisation, and intervention; in the *French* pattern, there is combined consent for cohort participation and randomisation and separate intervention consent; and in the *UK* pattern, there is consent only for cohort participation and intervention (randomisation consent is not mentioned). Among the 46 trials with the TwiCs design, the *UK* pattern was the most common (41%), followed by the *Dutch* pattern (37%) and the *French* pattern (22%).

Figure 2: Consent patterns in trials with a TwiCs design



The vertical axis shows three different stages of consent (cohort consent, randomisation consent, and intervention consent). In the *Dutch* pattern, there are three separate consent steps. In the *UK* pattern, there is no explicit consent for randomisation. In the *French* pattern, consent for being part of the cohort and for randomisation are combined.

Source: Adapted from Amstutz, Schönenberger, Gerber, et al. (2024), Figure 2[10]

TWICS: WHAT ARE THE DESIGN'S LIMITATIONS AND MITIGATION STRATEGIES?

The TwiCs design presents several challenges and limitations. First, the consent procedure involves multiple stages with tailored information provided at each stage, which requires training the participating sites and carefully communicating consent information when initially implementing the TwiCs design. Nevertheless, once cohort consent and randomisation consent are part of routine cohort enrolment procedures, participants will only be asked for intervention consent in all future TwiCs. Because intervention consent is closer to routine clinical decision-making, the consent process in these trials promises to be less burdensome, less complex, and less distressful than the consent process in traditional trials.[11–13]

Second, the control group in a TwiCs study is, by design, always receiving usual cohort care. Consequently, a placebo-controlled comparison is not possible, and participants and providers are aware of the intervention received/provided. In most pragmatic trials, however, a usual care comparator is the option of choice. Therefore, the TwiCs design may even offer a comparison group that is closer to reality since the randomised groups do not know there are other groups (masked allocation). To mitigate undesired open-label effects, researchers may choose clinical endpoints that are hard to modify (e.g. survival) or blinded outcome assessors.

Third, trials with a TwiCs design are embedded in a cohort, and data collection is strictly dictated by the type and frequency of the routine follow-up visits in the overarching cohort. Since the control group remains unaware of the trial, additional assessments and visits are generally not possible. However, if the cohort is built up with the first TwiCs study in mind, as was the case for more than 50% of the trials with a TwiCs design reviewed by Amstutz, Schönenberger, Gerber, et al., the follow-up can be tailored to meet the necessary data collection frequency and endpoints. This was demonstrated in some radiotherapy TwiCs conducted in Utrecht and some COVID-19 drug TwiCs conducted in Paris.[14–19]

Fourth, while in the control group all eligible participants are included by design, some eligible participants will decline the proposed intervention (non-uptake), resulting in an imbalance of uptake across the groups. Across all the trials with a TwiCs design that were reviewed, non-uptake was highly variable, ranging from 0% to 75%. If non-uptake is high, the intention-to-treat estimand will not reflect a direct *intervention* effect but merely an *offer-of-intervention* effect. Moreover, non-uptake should be accounted for in the sample size calculation, which only 37% of TwiCs in the review did.[10] While an intention-to-treat estimand is of interest to policymakers, it may have limited value for participants and treating physicians.[20] Instrumental variable and inverse probability weighting can be applied to estimate per protocol estimands accounting for non-uptake, but they depend on the data available and the type of non-uptake (time-varying versus one-time) and require careful consideration of the underlying assumptions of such observational causal inference approaches.[21-27]

TWICS: HAS THE DESIGN BEEN USED IN SWITZERLAND?

The Swiss HIV Cohort Study (**SHCS**) is the first Swiss cohort – and, notably, the first HIV cohort worldwide – to implement the TwiCs design. Over a ten-month period with various stakeholder meetings, the SHCS worked closely with patient representatives to adapt the cohort protocol to reflect the *Dutch* consent pattern. The SHCS obtained ethics approval for the amended protocol, and in August 2024 it started rolling out randomisation consent across its sites in order to prepare for the implementation of future trials using the TwiCs design. The first such trial is to be started by the end of 2024 and will test the effect of a preference-based choice of different nicotine replacement products on smoking cessation in people living with HIV in Switzerland. The TwiCs design may enable researchers to efficiently generate high-quality, randomised evidence using existing cohort infrastructure in Switzerland and elsewhere. Early insights from the pioneering roll-out of the design and the first TwiCs study in the SHCS will determine if the anticipated benefits of the TwiCs design – such as a more realistic comparator, less burdensome consent procedures, and improved recruitment efficiency – outweigh its limitations.

To follow developments related to the TwiCs design or receive information about and support with the approach, researchers may visit the TwiCs network's website (www.twics.global).

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