

MEETING ABSTRACTS

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The ethics of 'Trials within Cohorts' (TwICs): 2nd international symposium

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2nd TwiCs symposium summary

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Abstract

On 7-8th November 2016, 60 people with an interest in the 'Trials within Cohorts' (TwICs) approach for randomised controlled trial design met in London. The purpose of this 2nd TwiCs international symposium was to share perspectives and experiences on ethical aspects of the TwiCs design, discuss how TwiCs relate to the current ethical framework, provide a forum in which to discuss and debate ethical issues and identify future directions for conceptual and empirical research. The symposium was supported by the Wellcome Trust and the NIHR CLAHRC Yorkshire and Humber and organised by members of the TwiCs network led by Clare Relton and attended by people from the UK, the Netherlands, Norway, Canada and USA. The two-day symposium enabled an international group to meet and share experiences of the TwiCs design (also known as the 'cohort multiple RCT design'), and to discuss plans for future research. Over the two days, invited plenary talks were interspersed by discussions, posters and mini presentations from bioethicists, trialists and health research regulators. Key findings of the symposium were: (1) It is possible to make a compelling case to ethics committees that TwiCs designs are appropriate and ethical; (2) The importance of wider considerations around the ethics of inefficient trial designs; and (3) some questions about the ethical requirements for content and timing of informed consent for a study using the TwiCs design need to be decided on a case-by-case basis.

Main report

On 7-8th November 2016, 60 people with an interest in the 'Trials within Cohorts' (TwICs) design met in London for the 2nd TwiCs international symposium. The symposium was supported by the Wellcome Trust and NIHR CLAHRC Yorkshire and Humber and organised by members of the TwiCs network led by Clare Relton. As well as UK participants, people came from the Netherlands, Norway, Canada and USA. Over the two days, the invited plenary talks were interspersed by discussions, posters and mini presentations from bioethicists, trialists and health research regulators.

On the first day (7th November, 2016), Jon Nicholl (University of Sheffield, UK) opened the meeting, welcoming all to the symposium. He described how the first international symposium in 2014 brought together trialists using the design for the first time, and led to this, the 2nd symposium which aimed to provide a forum in which to discuss and debate ethical issues including how the TwiCs approach relates to the current ethical framework.

What are TwiCs?

Clare Relton (University of Sheffield, UK) set the scene by outlining the Trials within Cohorts (TwiCs) approach as described in the original article (Fig. 1) in the BMJ in 2010 [1], and the 7 key features of the design:

- (I) Recruitment of a large observational cohort of patients/ people with the condition of interest
- (II) Regular measurement of outcomes for the whole cohort
- (III) Capacity for multiple randomised controlled trials over time. Then for each randomised controlled trial:
- (IV) Identification of all eligible people in the cohort
- (V) Random selection of some individuals from all eligible people in the cohort, who are then offered the trial intervention
- (VI) Comparison of the outcomes in randomly selected people with the outcomes in eligible people not randomly selected; that is, those receiving usual care
- (VII) "Patient centred" informed consent; that is, the process of obtaining information and consent aims to replicate that in routine health care as far as is possible.

Ethics in current use

Clare described how more than 20 studies using the TwiCs design now had ethics board approval from boards in Australia, Canada, Finland, France, Germany, Mexico, Netherlands, Spain, UK, and the USA. These studies were recruiting cohort populations (e.g. early life, children and adolescents, young indigenous, adults, older people) in a variety of settings (e.g., hospital, primary care), in order to facilitate trials in diverse health areas (e.g., attention deficit hyperactivity disorder, breast cancer, colo-rectal cancer, bone metastases, depression, hepatitis C, HIV, hip fracture, falls prevention, long term conditions, severe mental illness, scleroderma). Embedded within these cohorts, there were at least 20 randomised trials testing a wide range of interventions, and various approaches to informed consent were being used in these studies.

Jon Nicholl (University of Sheffield, UK) then gave an example of an emergency medicine research study where it was not possible to obtain informed consent prior to randomisation and have a viable trial, which illustrated that informed consent for participation in a trial is not always required. Jon argued that although all trial participants in TwiCs should receive information about data collection, storage and sharing and all other non-therapeutic research processes, only those in the intervention group need to receive information about the intervention. TwiCs designs randomly select from the cohort and offer the intervention being tested, those unselected are not actually allocated to 'treatment as usual', so there is no ethical obligation to tell those unselected about those who were selected, or about

the treatment they are **not** being offered. Jon offered the analogy of lottery winners who are 'selected', where there is no sense in which ticket holders who don't win are 'allocated' to a losers group. Jon concluded by offering a 'Sheffield' position statement for discussion *"In cohort trials, members of the cohort who are not selected to be offered a new treatment do not need to be told about the trial intervention (s)"*.

Merrick Zwarenstein (Western University, Ontario, Canada) set the context for the design by clarifying how pragmatic trials provide evidence to inform decision making and explanatory trials test whether or not an intervention causes an outcome. Merrick suggested that the PRagmatic Explanatory Continuum Indicator Summary -2 (PRECIS-2) framework could help designers of TwiCs trials match their design to their intentions. James Flory (Memorial Sloan Kettering Cancer Centre, New York, USA) outlined his review [2] of proposals for randomised controlled trials (RCTs) where randomisation occurred without prior information being given that interventions would be allocated at random (Randomisation without Consent). He described 6 different approaches found in the literature including emergency medicine research, Zelen designs and TwiCs designs.

The morning session concluded with two researchers reporting their practical experiences with the TwiCs design and the ethical questions that were generated and/or resolved through the use of the design. Rudolf Uher (Dalhousie University, Canada) described the FORBOW cohort of youth at high risk of severe mental illness and the first RCT (Skills for Wellness) embedded within this cohort. He described the advantages of using the design in a situation where most children at risk were not seeking help. No concerns had been raised about the TwiCs design during institutional review board process for FORBOW. Then Anne May (University Medical Centre, Utrecht, Netherlands) described the exercise-based FIT trial which is embedded within the hospital-based breast cancer 'UMBRELLA' cohort which uses the staged consent version of the TwiCs design [3]. She highlighted the possible pros (fast recruitment, no contamination) and cons (non-acceptance in the intervention group) using the TwiCs design.

Ethical perspectives

The afternoon session began with bioethicist Scott Kim (National Institute for Health, USA) who provided an overview of the ethical questions that pragmatic RCTs raise and an ethical analysis of two variations of TwiCs designs, those where information about (and consent for) future RCTs (i.e. the possibility of being randomised to the offer of a therapeutic intervention) was provided at enrolment to the cohort, and those where this information was only provided after randomisation to those in the intervention group. He concluded with system level ethical questions for broad population based TwiCs cohorts and learning healthcare systems. This was followed by Shaun Treweek (University of Aberdeen, Scotland) who focussed on the wider ethical question of the ethics of inefficiency, describing the lack of evidence to inform trial process decisions (e.g. 'opt out' vs 'opt in' for recruitment), and highlighting the potential waste of resources and participant goodwill. He argued that inefficiency is an ethical problem and how methodologists must generate evidence to support their decisions about trial processes. Tjeerd van Staa (University of Manchester, UK) described how TwiCs designs are suited for pragmatic trials in the era of big and ubiquitous data collection, but highlighted that refusal of treatment in the intervention arm could result in bias and loss of power. Andrew Vickers (Memorial Sloan Kettering Cancer Centre, USA) emphasised the benefits of integrating patient reported outcomes into routine clinical practice for optimizing clinical care, reusing these data for observational and experimental research such as TwiCs, and improving response rates.

Towards the end of the day, Kirsty Wydenbach from the MHRA (Medicines & Healthcare products Regulatory Authority) in the UK, emphasised that they were familiar with the TwiCs design and that their main concern was to ensure that participants in TwiCs were aware that they could withdraw at any time and that the requirements for safety monitoring were in place. Day one concluded with a speaker panel discussion on the ethics of whether or not to inform potential trial participants about interventions that they are not then subsequently offered if they are in the control (treatment as usual) group.

Day Two (November 8th, 2016) began with an overview of key findings of the previous day by Helena Verkooijen (University Medical Centre, Utrecht, Netherlands): including how a case can be made to ethics committees that TwiCs designs are appropriate and ethical; the importance of wider considerations around the ethics of inefficiency; and the range of perspectives on whether upfront information on randomisation to future interventions should be given at enrolment to the cohort. She summarised the discussion as *'If we don't need to, why should we?' Versus 'And if we can do it, why shouldn't we?'*

Regulators perspective

Clive Collett, Ethics Guidance & Strategy Manager at the UK Health Research Authority (HRA) argued that the methods and procedures used and the information provided should be proportionate to the nature and the complexity of the research, and the risks, burdens and potential benefits (to the participants and/or society) and the ethical issues at stake. He suggested that the closer the research is to standard clinical practice, the less need there is to provide patients and service users with detailed and lengthy information. The legal requirements for non-drug trials are that information must be provided regarding the broad nature and purpose of the research, the material and significant risks and benefits and alternatives, but that written evidence of consent was not legally required. He outlined forthcoming HRA guidance on applying a proportionate approach to the process of seeking consent which will allow the consent process to take place at the consultation using brief information sheets that promote genuine understanding.

Amanda Hunn, Joint Head of Policy and Public Affairs at the HRA sketched plans for a survey of Research Ethics Committee (REC) members in England to explore their appetite for five different study designs where there was randomisation without prior information being given that interventions would be allocated at random. Sophie Welch (Independent Ethics Consultant) emphasised the importance of dialogue with ethics boards, and suggested that researchers should not avoid the design on the assumption that it would not secure ethical approval.

Sophie then detailed 5 different questions that ethics committee members are likely to consider during ethical review: 1) does the proposed research respect the rights, autonomy, dignity, and well-being of the participant?, 2) is there a sound ethical basis for this research design?, 3) based on my experience, what do I think to this approach?, 4) what are the views of other committee members, and what guidance and/or regulation can we draw on?, and 5) have similar research designs already received ethical approval?

Bioethicist Søren Holm (University of Manchester, UK) explored why and when control groups should consent and whether ethical considerations relating to harm, burden, rights and reasonable expectations help us to answer this question. He concluded his talk with an exploration of what might be the reasonable expectations from the ordinary understanding of the patient-healthcare provider relationship.

Engagement with ethics committees

The morning session concluded with two researchers describing their experiences of using the TwiCs design and the ethical questions that were generated and/or resolved through use of the design. Linda Kwakkenbos (McGill University, Canada), reported that the Scleroderma Patient-centered Intervention Network (SPIN) Steering Committee and Patient Advisory Board liked that the TwiCs design was providing a sustainable framework for multiple trials of interventions for the rare disease scleroderma, and that the design did not engender disappointment for those patients not receiving intervention. Since the start of enrolment in the SPIN Cohort more than 1500 patients with the rare disease scleroderma had been enrolled from 39 centres in 5 countries after obtaining approval from the local ethics board for each centre.

Sophie Gerlich (University Medical Centre, Utrecht, Netherlands) discussed preliminary results of her study of patient understanding and opinions regarding informed consent with data drawn from questionnaires to patients who had either agreed or declined to participate in three cohorts using the TwiCs design – colorectal cancer, breast cancer and bone metastases.

After the lunchtime poster presentations, Danny Young-Afat (University Medical Centre, Utrecht) introduced the afternoon session which was devoted to 8 mini talks on future directions for empirical and conceptual research in relation to the TwiCs design. The session began with Joanne van der Velden (University Medical Centre, Utrecht) discussing the interim results regarding recruitment and randomisation for their ongoing Vertical RCT embedded in the PRESENT bone metastases cohort. She noted that these compared favourably to a classic multi-centre RCT in the same patient population which is running simultaneously in the Netherlands.

Future research

The remaining sessions explored future plans relating to the TwiCs design with a focus on ethical aspects. Petter Viksveen (University of Stavanger, Norway) outlined early plans to set up a mental health cohort for adolescents in Norway. Joanne Zakrewska (Pain Management Centre, UCLH NHS Foundation Trust, London, UK) argued for the need for a cohort study using the TwiCs design to facilitate the testing of surgical and pharmacological interventions for patients suffering from Trigeminal Neuralgia. Amanda Hunn (Health Research Authority (HRA), UK) described HRA plans to set up a special panel to give endorsement for registries that recruit patients into research (this includes 'consent for consent' and 'consent to be approached' registries such as the Yorkshire Health Study and Health Wise Wales). Panel endorsement of registries would mean that a study using an endorsed register/cohort to recruit would not require the ethics board to look at the recruitment process again as it would already have been endorsed by the HRA. Andrew Vickers (Memorial Sloan Kettering Cancer Center, USA) discussed the overzealous approach to autonomy of standard informed consent procedures and the harm which often arose from information overload for those patients randomised to usual care. He illustrated this with an example of a trial where late stage cancer patients make heart wrenching decisions about whether to risk possible side-effects for uncertain harms and then for 50% of the patients then randomised to usual care, this agonizing consent process makes no difference to their care and they could have been spared considerable anxiety and decisional burden. He argued for empirical research to document any consent-related distress and how this might be ameliorated by alternative approaches such as the TwiCs patient centred approach to informed consent.

The session concluded with three proposals for further research from Clare Relton (SchARR, University of Sheffield). The first suggestion was to compare the efficiency and acceptability of two different Informed Consent pathways (Standard vs Tailored) for effectiveness trials with 'usual care' comparators. Efficiency would be measured using the ratios of numbers analysed, to the numbers: (i) approached, (ii) randomised, (iii) allocated to the intervention, (iv) accepting their allocation; as well as the representativeness of the population recruited, and the time taken and cost incurred. The second suggestion was to introduce an 'Information and Consent' extension to the CONSORT flow diagram and/or statement, and the third was to explore the potential of the TwiCs approach to transform healthcare systems into learning healthcare environments – linking up existing cohorts or even building a UK NHS based national cohort.

Day two concluded with a lively and wide ranging panel discussion with many contributions from the audience including the announcement that £1.1mn NIHR funding had just been obtained for a TwiCs designed study which was trialling a range of investigational medicinal products. The panel acknowledged that it was clearly possible to make a compelling case to ethics committees that TwiCs designs were appropriate and ethical; the importance of wider considerations around the ethics of inefficient trial designs; that there was broad consensus from those attending the symposium that there were no hard and fast rules regarding the informed consent processes relating to therapeutic processes (interventions, randomisation), and that some key ethical questions about the content and timing of informed consent for a TwiCs may need to be decided on a case-by-case basis.

The slides and films from the TwiCs Ethics symposium can be viewed at <https://www.twics.global/ethics-symposium-2016>

Declaration

-Competing interests

The authors have no competing interests

-Funding

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-Authors' contributions

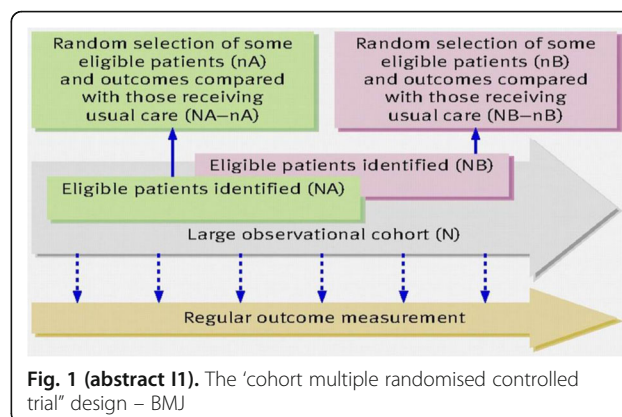
CR wrote the first draft and subsequent drafts with contributions from all authors.

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References

1. Relton C, Torgerson D, O'Cathain, Nicholl J. Rethinking pragmatic randomised controlled trials: Introducing the 'cohort multiple randomised controlled trial' design. *BMJ* 2010; 340: c1066–c1066.
2. Flory JH, Mushlin AI, Goodman ZI. Proposals to Conduct Randomized Controlled Trials Without Informed Consent: a Narrative Review. *Journal of general internal medicine*. 2016 Dec 1;31(12):1511-8.
3. Young-Afat DA, Verkooijen HA, van Gils CH, van der Velden JM, Burbach JP, Elias SG, van Delden JJ, Relton C, van Vulpen M, van der Graaf R. Brief Report: Staged-informed Consent in the Cohort Multiple Randomized Controlled Trial Design. *Epidemiology*. 2016 May 1;27(3):389-92.



ABSTRACTS

Topic 1: Context

A1

TwiCs RCTs can be explanatory, pragmatic or in-between

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Randomised controlled trials (RCTs) using the TwiCs design streamline patient recruitment by tailoring and staging consent, allow for testing of multiple interventions against a common control group, and integrate evaluation into the natural flow of care. Are they pragmatic?

Schwartz and Lellouch [1] identified two opposite attitudes or purposes to RCT design: to provide evidence which supports a clinical, service delivery or health policy decision (the "pragmatic" attitude) or to explore a mechanism of action of the intervention under study (by testing whether or not it causes an outcome – the "explanatory" attitude).

These attitudes are not dichotomous, but represent opposite ends of a spectrum. The Pragmatic Explanatory Continuum Indicator Summary second generation tool (PRECIS-2) [2] operationalises the pragmatic/explanatory spectrum as 9 domains (Table 1), each reflecting an aspect of RCT design, each rated on a 5 point scale for similarity to usual care, as ordinarily provided in the clinical settings in which the intervention is intended to be used after evaluation in the planned RCT.