This is a repository copy of *Ethics and practice of trials within cohorts: An emerging pragmatic trial design*.

White Rose Research Online URL for this paper:
http://eprints.whiterose.ac.uk/126409/

Version: Accepted Version

Article:
Kim, S.Y., Flory, J. and Relton, C. orcid.org/0000-0001-8530-5011 (2018) Ethics and practice of trials within cohorts: An emerging pragmatic trial design. Clinical Trials, 15 (1). pp. 9-16. ISSN 1740-7745

https://doi.org/10.1177/1740774517746620

Kim SY, Flory J, Relton C. Ethics and practice of Trials within Cohorts: An emerging pragmatic trial design. Clinical Trials. 2018;15(1):9-16. Copyright © 2017 The Authors. DOI: 10.1177/1740774517746620. Article available under the terms of the CC-BY-NC-ND licence (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Reuse
This article is distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs (CC BY-NC-ND) licence. This licence only allows you to download this work and share it with others as long as you credit the authors, but you can't change the article in any way or use it commercially. More information and the full terms of the licence here: https://creativecommons.org/licenses/

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

White Rose
university consortium
Universities of Leeds, Sheffield & York

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk/

Ethics and Practice of Trials within Cohorts (TwiCs):

An Emerging Pragmatic Trial Design

Scott Y. H. Kim, MD, PhD[1], James Flory, MD,[2] Clare Relton, PhD[3]

[1]Department of Bioethics, National Institutes of Health and Adjunct Professor of Psychiatry, University of Michigan.

[2]Memorial Sloan Kettering Cancer Center, New York

[3]University of Sheffield, Sheffield, UK

Correspondence to: Scott Kim, MD, PhD, 10 Center Drive, 1C118, Bethesda, MD 20892, USA
scott.kim@nih.gov

The opinions expressed in this article are the authors' and do not represent the views or policies of the National Institutes of Health, Department of Health and Human Services, or the US government.

There is increasing recognition of the value of pragmatic clinical trials, especially as it relates to the vision of a learning healthcare system that aims to closely integrate the delivery of medical services with clinical research. In such a system, the generation of knowledge would be "embedded into the core of the practice of medicine" leading to "continual improvement in care."[1] The advent of a modern electronic health record system makes it feasible and relatively inexpensive to conduct studies in the context of routine clinical practice.[2] Such a vision provides an opportunity to think creatively about novel trial designs that can fulfill this pragmatic imperative.

In this paper, we describe an emerging pragmatic trial paradigm called 'Trials within Cohorts' (TwiCs) which involves longitudinal cohort studies that provide a platform for randomized clinical trials. To date, studies using the design have obtained research ethics committee approval in 10 countries (Australia, Canada, Finland, France, Germany, Mexico, Netherlands, Spain, UK and the USA) with the most growth in the UK,[3-7] Canada,[8-11] and the Netherlands.[12] The rare disease SPIN (Scleroderma Patient-centered Intervention Network) cohort has obtained IRB approval to recruit to its cohort and conduct four intervention trials using the design in the US, Canada, Mexico, France and Spain.[10]

We will first describe the features of TwiCs, and their strengths and limitations as a pragmatic randomized controlled trial (RCT) design. Because the TwiCs design is novel and unfamiliar to most research ethics committees/institutional review boards—and also because it involves an element of post-randomization consent which has a history of controversy{Flory 2016}—we largely focus on the ethical issues in conducting TwiCs. We place TwiCs within a brief history of RCTs that obtain informed consent after randomization and then provide an

ethical analysis of TwiCs, including a discussion of how it might be regulated by US institutional review boards.

Trials within Cohorts

Randomised controlled trials remain the gold standard to prove effectiveness of interventions and this is no less true when the goal is to show the real-world effectiveness of the intervention in learning healthcare systems. However, the standard approach to RCTs is often complicated by slow recruitment rates, limited generalisability, limited long term follow up, and high costs. The 'Trials within Cohorts' design (formerly referred to as the 'cohort multiple RCT design'[13,14]) was created to address these problems.

In the TwiCs design, a cohort of participants with the condition(s) of interest is recruited for a longitudinal cohort study. At the time of recruitment into the cohort, the participants are given information about the process for their potential involvement in future intervention studies (i.e., TwiCs) and consent is obtained for potential future use of their data. As discussed below, there is some variation in how the design is operationalised. Although all obtain permission at the start to use the cohorts' data for future studies, the specificity of information and consent regarding future TwiCs varies among studies. Some have given no information regarding possible trial interventions to the cohort participants prior to any specific TwiC [4,15] while others obtain broad consent at initial recruitment into the cohort regarding future randomization prior to TwiCs and use of data in future TwiCs[12,16] as described further below.

After randomization to any given TwiC, additional consent to receive the intervention is obtained from participants who have been randomly assigned to the new intervention. Those assigned to the treatment as usual control arm do not provide any additional consent after randomization.

The TwiCs design has several advantages over standard RCT design. First, difficulty with recruitment is a common concern in RCTs. The TwiCs design takes advantage of the fact that recruitment into observational cohort studies is often easier and less selective. There is now evidence that recruitment for RCTs within such established cohorts can be highly efficient when compared to recruitment without such cohorts.[17]

Second, disclosure of information and informed consent can be tailored to the needs of the participants (e.g., those not offered the new intervention are not burdened with information about the risks and potential benefits of trial intervention). Thus, the informed consent process is 'patient centered' and 'real world' in its goals—replicating, as much as is ethically feasible, the real world routine health care where clinicians provide patients with the information they need, at the time they need it. As this approach avoids the selection bias introduced when recruitment and consent precedes randomization, it provides information on the acceptability of the intervention in the target population.

Third, the design reduces some problems related to patient preferences in standard RCT designs. For instance, when a condition does not have highly effective interventions, the prospect of trying a new, if unproven, intervention is often an incentive for patients to enrol. In standard RCT designs, this often results in those randomized to the 'treatment as usual' arm dropping out or experiencing disappointment. But this does not occur in the TwiCs design.

Another advantage of embedding an RCT within a cohort is that periodic research data collection that is part of the longitudinal study can provide outcome data in addition to data from medical records.[10] Although the TwiCs design is useful for pragmatic studies, it has some limitations. Apart from identification of potential trial participants, the TwiCs design is not

useful for placebo controlled trials, trials without 'treatment as usual,' or when two commonly used treatments are to be tested in an RCT.

A brief background on RCT designs with consent following randomization

TwiCs is a descendent of a family of older proposals variously known as "Zelen design," "randomized consent," or "pre-randomization" designs.[20] A brief history of these proposals and their implementation illustrates some of the strengths and weaknesses of trial designs that obtain consent for participation in an RCT after randomization. It also helps to clarify how TwiCs is different from earlier proposals.

The original proposal for post-randomization consent, called a "Zelen single-consent design," was the simplest: patients were, without prior consent or knowledge, randomized between "best standard" care (usual care) and an intervention.[20] Subjects assigned to the intervention were then asked for consent, while the others served as control subjects without their knowledge. Two types of advantages were proposed for the single-consent design. First, it reduces the need for patients to confront stressful aspects of research participation, such as knowing that their treatment is going to be randomly chosen and being denied access to an experimental treatment. Second, single-consent designs might increase the efficiency of accrual, in part because patients (assigned to the intervention arm) might be more inclined to enroll knowing that they were guaranteed to receive the intervention.

Zelen seems to have interpreted the US Federal research regulations to say that as long as research subjects received only "established and accepted methods necessary to meet [their] needs," informed consent was not necessary.[21] However, the Office of Protection from Research Risks (OPRR) disagreed. That office reprimanded the investigators of a study of neonates which

used a Zelen single consent design for failing to obtain consent from parents of the control group neonates.[22]

Criticism of the single consent procedure led to greater interest in the 'double-consent Zelen design,' in which both the usual care and intervention arms are approached for consent. In double-consent, in contrast to single-consent, all participants are at least informed that they are participating in research. However, in addition to the obvious difference from a traditional RCT in obtaining consent after treatment assignment, Zelen double consent may include little or no information about the other arm of the trial, or indeed about the fact of randomization.[18]

Trials using Zelen double and single consent designs have remained relatively uncommon—as of 2006, two reviews suggest that approximately 83 unique studies employing Zelen designs had been conducted.[23,24] This relative unpopularity has no definitive explanation, but the experiences of investigators who have used post-randomization consent designs reveal both ethical and logistical problems.

First, Zelen designs have attracted considerable ethical criticism.[25] Even though patients assigned to the control group undergo no material harm, and might actually be spared burdens related to a traditional consent process, they might still reasonably expect to know that a new intervention is being tested for their condition and that they have been randomly assigned not to get the intervention. The perception that information is being withheld has been described as causing an 'outcry' of concern about the ethics of the earliest Zelen proposals, and subsequent modifications have not fully allayed these concerns[26,27]. As we note below, however, despite the 1990 reprimand by the OPRR, pragmatic RCTs are beginning to be conducted in the U.S. with post-randomization single-consent procedures with the apparent knowledge of the Office of Human Research Protections (the successor to the OPRR).[28]

Another problem with post-randomization consent is that it has not always proven to be as efficient as had been hoped. Analysis of a post-randomization study has to be done as intention-to-treat, including patients who declined the intervention, which reduces study power.[26] Post-randomization designs must improve accrual and withdrawal rates sufficiently to make up for this loss of power; these improvements are difficult to predict and are not guaranteed. [21 27,29]

Ethics of informed consent for TwiCs and regulatory implications

As noted above, there are some variations in practice when it comes to the content of the initial consent procedures, at the time of enrolment into the cohort, regarding future embedded RCTs within the cohort. Thus, we will first describe what has been called a "two stage" consent[30] which involves the greatest amount disclosure at the pre-randomization stage. We then discuss other variations.

TwiCs with two stage consent (using pre-randomization broad consent about TwiCs). In some jurisdictions, investigators implementing TwiCs have run into regulatory obstacles; this has led to the development of a 'two-stage' consent model.[30] At the time of recruitment into the cohort, subjects will provide specific consent for the cohort study and also provide broad consent to randomizations for future TwiCs, for future contact if randomized to the intervention arm of TwiCs, and for use of their data in future TwiCs if randomized to the control arm. This is the first stage of consent.

For those whose data will serve as the control arm data, their participation in a TwiC is exhausted by two elements: (a) being randomly selected as a control and (b) use of their data (usually collected from clinical medical records, or in some cases, from measurements that are part of the longitudinal cohort study[10]) in the TwiC. Despite these elements, the entirety of their clinical experience will be decided by what their physicians consider to be the best care for them.

And no additional research measures are needed specifically for TwiCs; thus no additional interactions or interventions of research are involved when these persons' data are used in TwiCs. In sum, persons in the control arm receive usual clinical care and will have given consent to every element of their research participation.

The lack of specificity in broad consent (i.e., broad permission for future use without specific consent for each use) has led to some prominent controversies, such as the much publicized Havasupai case in which the controversy centered around researchers' use of samples and data that went beyond the disease domains of initial focus of the research.[31] The difference in the TwiCs context is that unlike in most biobank-based research, the cohorts are disease-based (or at risk of it) as are the trials within them; thus, given the specificity of the domain of research, there is little risk of violating any subject's non-welfare interests such as their cultural, religious, and moral commitments.[32] For instance, for a person in a diabetes cohort who provides broad consent for use of their electronic health record and other data for evaluation of future diabetes treatments, there is little danger of patients' non-welfare interests (regarding the type of uses to which their data are put) being compromised. (However, it should be noted that if a cohort of interest were a very general one—for example, one encompassing all patients in an integrated health delivery system—conducting TwiCs in such a cohort would require further ethical analysis regarding the content of the initial broad consent.)

Those randomized to the intervention arms of TwiCs will have given consent to be approached for enrolment in such trials (in the first stage broad consent). After randomization to a TwiC, they will then provide informed consent for the TwiC (second stage of consent). They would not be enrolled in a TwiC unless they explicitly give consent after they are provided all of usually required elements of informed consent for an RCT. Thus, when both stages of consent

are taken into account, everyone who enrolls in the intervention arm of the TwiCs will have given informed consent to every aspect of their research participation in the TwiC.

TwiCs without pre-randomization broad consent. Some TwiCs do not obtain explicit pre-randomization broad consent (covering the possibility of future randomization, future contact for intervention studies, and use of data specifically for TwiCs) and instead may obtain permission for unspecified future uses of their data (as part of the initial consent for enrolling in the cohort).[4,10,15] The rationale is as follows. For the intervention arm group of a future TwiC, when they are randomized into the intervention arm and then subsequently contacted to be asked if they wish to enroll in the TwiC, it is not that different from someone in a clinic being approached to participate in a traditional RCT. There is no 'cold contact' involved; the subjects are aware that the clinic is a locus of clinical research, and they should not be surprised that they are being asked to consider participation in an RCT.

For the control arm, it might be argued that by enrolling in the cohort study (on, say, diabetes), their permission to the researchers to use their medical records and other data includes a variety of future research uses, such as for comparison purposes in a TwiC testing an intervention to treat diabetes.

It might be objected, however, that none of the study participants agreed to being randomized and thus are being used in a disrespectful way. Is being merely randomized something for which consent is necessary, if one has already agreed to have one's data used in future research projects (as is the case for all who enrolled in the cohort)? Consider a group of people who donate their tissues to a diabetes focused biobank so that the tissues can be used in future diabetes research. At a future date, a researcher selects a subsample sharing some trait, and

then randomizes them into two groups so that she can conduct a controlled laboratory experiment on the stored tissues. In this example, it does not seem that the donors are being disrespected.

There is another potential problem with TwiCs without pre-randomization broad consent. It is possible—indeed probable—that some persons who are enrolled in a cohort who later find out about TwiCs in that cohort may feel that the researchers could easily have obtained their pre-randomization broad consent for future TwiCs and made the researchers' plans for conducting TwiCs in their cohort transparent from the beginning. Some of these participants may feel that the researchers were not as transparent as they could have been, even while recognizing that the lack of transparency has no impact on their welfare (benefits and harms/burdens).

Different people will have different moral intuitions about whether pre-randomization broad consent for future TwiCs is ethically necessary. On one side of the argument is that there is a potential for mistrust due to the lack of transparency such that it may be not only ethically right but prudent to obtain that consent, especially if the burden of obtaining it is low. On the other side is the view that if a consent is not necessary and could cause confusion (since the idea of future randomization with asymmetric consequences for the participants, regarding future unspecified TwiC could be a challenging set of concepts to digest), then it may be better to avoid it. We suspect that a part of the answer will rest on the particular features of the cohort and its TwiCs—the nature of the cohort, the interventions involved, and the setting in which the study is done and the reasonable expectations that researchers might anticipate in the participants.

Implications for US regulations? Although the use of TwiCs is gaining momentum, most of the activity has been in countries outside the United States. Given the potential advantages of the TwiCs design, it may prove useful for US researchers as well. However, the

regulations do differ among different jurisdictions, especially regarding the issue of when it is permissible to deviate from the traditional informed consent procedures.

How might IRBs apply the US research regulations to TwiCs? The task for the IRBs will be different depending on whether cohort studies employ a two-stage consent (using pre-randomization broad consent) for future TwiCs in that cohort. We begin with the assumption that pre-randomization broad consent is used.

First, unlike recent debates in US in which the focus has been on whether traditional informed consent is necessary for pragmatic trials in learning health systems,[33,34] TwiCs does not need to rely on waivers or alterations of informed consent. As noted above, the intervention arm participants, before consenting, would receive all of the information that persons enrolling in traditional RCTs would receive. The only difference is that the information is given (and specific consent for TwiC obtained) after randomization while consent for the randomization would have been given separately at the time of enrolment into the cohort.

The control arm participants' consent would not be waived or altered either. They would have provided informed consent for the cohort study, and also given broad consent for randomization and for the use of their data for TwiCs. As already noted above, the pre-randomization broad consent is ethically more robust than currently accepted consent standards for biobank research. Since those are all of the 'research participation' elements that control groups are part of, and since they will have given consent to each element, there is no need to invoke the criteria for waiver or alteration of consent in the Common Rule.

What about TwiCs that are proposed without a substantive pre-randomization broad consent? The regulatory situation could involve the IRBs requiring the investigator to show that the waiver or alteration criteria in the US regulations are met. As we saw above, the intuition

concerning the need for pre-randomization broad consent varies, and will likely vary among IRBs. It is quite possible that some IRBs will in fact see the lack of transparency regarding randomization and future TwiCs as implying at least an alteration of informed consent, and therefore will require that such a proposal meet the several regulatory criteria for waiver or alteration of informed consent in 45CFR46.116: (a) the research must be minimal risk; (b) the research would be impracticable to conduct without the waiver or alteration; (c) the participants' rights or welfare would not be adversely affected by the waiver or alteration. (d) The fourth condition of debriefing after the fact (which will not be further discussed here).

How might these criteria apply to studies that forgo substantive pre-randomization broad consent? Although some TwiCs will be minimal risk, many will not be minimal risk; whether an IRB would or should analyze the risk-benefit issue separately for the intervention and the control arms is not clear. In terms of the practicability of research criterion, it would be difficult to argue that a TwiC is impracticable if pre-randomization broad consent is used—especially since there are examples of cohorts with TwiCs that are being successfully conducted with pre-randomization broad consent. And we have already noted that some people may see the lack of transparency about randomization into TwiCs as something that goes against their legitimate expectations—this could be interpreted by some as at odds with the condition that waiver or alteration not adversely affect subjects' rights and welfare.[35] Thus, some IRBs could require the use of substantive pre-randomization broad consent for TwiCs.

It is, however, possible that the specific circumstances of a cohort and a TwiC within it, may make the forgoing of pre-randomization broad consent justifiable under the criteria and therefore a case by case is still necessary. Of particular interest in this context is a pragmatic clinical trial in the US involving approximately 20,000 subjects comparing care management,

skills training, and treatment as usual for the prevention of suicide attempts among outpatients who endorse suicidal thoughts on a routine clinical measure.[28] According to the investigators, this study uses a modified Zelen design (control arm patients are unaware of the RCT; subjects in the intervention arms provide clinical consent to the interventions) that has been approved by IRBs of multiple institutions, and the investigators report having held "extensive discussions" with the Office of Human Research Protections. Thus, it appears that the study is deemed to pose no more than minimal incremental risk and also that it would have been impracticable to conduct without the waiver and alteration of consent, despite what amounts to a single-consent Zelen design.

Conclusion

For conditions in which longitudinal cohort studies can be valuable (which likely includes most chronic conditions), recruiting and conducting multiple randomized trials within such cohorts provide significant scientific and ethical advantages over both traditional and stand-alone Zelen designs. With the increasing emphasis on pragmatic trials,[14,36] investigators from many countries are now using this design. One of the main obstacles to its use is the concern over the ethics of obtaining informed consent for the TwiC after randomizing the subjects and obtaining it only from the intervention arm. Pre-randomization consent to cohort participation as well as, in some cases, to more explicit broad consent to elements of future TwiCs (including for randomization, and use of data specifically for TwiCs) mitigates this ethical concern. However, regulatory policies vary among jurisdictions and interpretations of those policies vary among research ethics committees. Investigators who hope to benefit from the scientific and practical advantages of the TwiCs design will need to clearly articulate its ethical and scientific strengths and limitations.

Acknowledgements

The authors thank …

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

Funding

This research is supported in part by the Intramural Research Program at the National Institutes of Health (SK). CR was funded and supported by the Wellcome Trust and the NIHR Collaboration for Leadership in Applied Health Research and Care Yorkshire and Humber (NIHR CLAHRC YH) www.clahrc-yh.nihr.ac.uk and her views expressed in this paper are not necessarily those of the NHS, the NIHR or the Department of Health.

1. Olsen L, Aisner D, McGinnis J. *The Learning Healthcare System.* Washington, DC: Insitute of Medicine of the National Academies;2007.

2. Califf RM, Platt R. EMbedding cardiovascular research into practice. *JAMA.* 2013;310(19):2037-2038.

3. Mitchell N, Hewitt C, Adamson J, et al. A randomised evaluation of CollAborative care and active surveillance for Screen-Positive EldeRs with sub-threshold depression (CASPER): study protocol for a randomized controlled trial. *Trials.* Oct 11 2011;12:225.

4. Relton C, Bissell P, Smith C, et al. South Yorkshire Cohort: a 'cohort trials facility' study of health and weight - Protocol for the recruitment phase. *BMC Public Health.* 2011// 2011;11(1):1-10.

5. Clegg A, Relton C, Young J, Witham M. Improving recruitment of older people to clinical trials: use of the cohort multiple randomised controlled trial design. *Age and ageing.* Jul 2015;44(4):547-550.

6. Cockayne S, Adamson J, Corbacho Martin B, et al. The REFORM study protocol: a cohort randomised controlled trial of a multifaceted podiatry intervention for the prevention of falls in older people. *BMJ Open.* Dec 17 2014;4(12):e006977.

7. Dickerson J, Bird PK, McEachan RR, et al. Born in Bradford's Better Start: an experimental birth cohort study to evaluate the impact of early life interventions. *BMC Public Health.* Aug 04 2016;15:711.

8. Johnson JA, Al Sayah F, Wozniak L, et al. Controlled trial of a collaborative primary care team model for patients with diabetes and depression: rationale and design for a comprehensive evaluation. *BMC health services research.* Aug 16 2012;12:258.

9. Jongbloed K, Friedman AJ, Pearce ME, et al. The Cedar Project WelTel mHealth intervention for HIV prevention in young Indigenous people who use illicit drugs: study protocol for a randomized controlled trial. *Trials.* Mar 09 2016;17(1):128.

10. Kwakkenbos L, Jewett LR, Baron M, et al. The Scleroderma Patient-centered Intervention Network (SPIN) Cohort: protocol for a cohort multiple randomised controlled trial (cmRCT) design to support trials of psychosocial and rehabilitation interventions in a rare disease context. *BMJ Open.* 2013;3(8).

11. Mayo NE, Brouillette MJ, Fellows LK, Positive Brain Health Now I. Understanding and optimizing brain health in HIV now: protocol for a longitudinal cohort study with multiple randomized controlled trials. *BMC neurology.* Jan 14 2016;16:8.

12. Burbach JPM, Kurk SA, Coebergh van den Braak RRJ, et al. Prospective Dutch colorectal cancer cohort: an infrastructure for long-term observational, prognostic, predictive and (randomized) intervention research. *Acta Oncologica.* 2016:1-8.

13. Relton C, Torgerson D, O'Cathain A, Nicholl J. Rethinking pragmatic randomised controlled trials: introducing the "cohort multiple randomised controlled trial" design. *BMJ.* 2010;340.

14. Ford I, Norrie J. Pragmatic Trials. *New England Journal of Medicine.* 2016;375(5):454-463.

15. Uher R, Cumby J, MacKenzie LE, et al. A familial risk enriched cohort as a platform for testing early interventions to prevent severe mental illness. *BMC psychiatry.* 12/02

10/06/received
11/19/accepted 2014;14:344.

16. van der Velden JM, Verkooijen HM, Seravalli E, et al. Comparing conVEntional RadioTherapy with stereotactIC body radiotherapy in patients with spinAL metastases: study protocol for an randomized controlled trial following the cohort multiple randomized controlled trial design. *BMC cancer.* Nov 21 2016;16(1):909.

17. *cmRCT in a Fragile Patient Population. Presentation at the International symposium on the ethics of 'Trials within Cohorts' (TwiCs). https://www.twics.global/ethics-symposium-2016. Accessed January 16, 2017.* 2016.

18. Flory JH, Mushlin AI, Goodman ZI. Proposals to Conduct Randomized Controlled Trials Without Informed Consent: a Narrative Review. *J. Gen. Intern. Med.* 2016:1-8.

19. Relton C, Thomas K, Nicholl J, Uher R. Review of an innovative approach to practical trials: the 'cohort multiple RCT' design. *Trials.* 11/16 2015;16(Suppl 2):P114-P114.

20. Zelen M. A New Design for Randomized Clinical Trials. *New England Journal of Medicine.* 1979;300(22):1242-1245.

21. Zelen M. Randomized consent designs for clinical trials: An update. *Statistics in Medicine.* 1990;9(6):645-656.

22. Marwick C. NIH 'Research Risks Office' Reprimands Hospital Institutional Review Board. *JAMA.* 1990;263(18):2420-2420.

23. Schellings R, Kessels AG, ter Riet G, Knottnerus JA, Sturmans F. Randomized consent designs in randomized controlled trials: systematic literature search. *Contemp Clin Trials.* Aug 2006;27(4):320-332.

24. Adamson J, Cockayne S, Puffer S, Torgerson DJ. Review of randomised trials using the post-randomised consent (Zelen's) design. *Contemporary Clinical Trials.* 8// 2006;27(4):305-319.

25. Hawkins JS. The ethics of Zelen consent. *Journal of Thrombosis and Haemostasis.* 2004;2(6):882-883.

26. Ellenberg SS. Informed consent: protection or obstacle? Some emerging issues. *Control Clin Trials.* Dec 1997;18(6):628-636; discussion 661-626.

27. Velthuis MJ, May AM, Monninkhof EM, van der Wall E, Peeters PH. Alternatives for randomization in lifestyle intervention studies in cancer patients were not better than conventional randomization. *Journal of clinical epidemiology.* Mar 2012;65(3):288-292.

28. Simon GE, Beck A, Rossom R, et al. Population-based outreach versus care as usual to prevent suicide attempt: study protocol for a randomized controlled trial. *Trials.* 2016;17(1):452.

29. Ellenberg SS. Randomization designs in comparative clinical trials. *N Engl J Med.* May 24 1984;310(21):1404-1408.

30. Young-Afat DA, Verkooijen HM, Van Gils CH, et al. Staged-informed consent in the cohort multiple randomized controlled trial design. *Epidemiology (Cambridge, Mass.).* Jan 6 2016.

31. Mello MM, Wolf LE. The Havasupai Indian tribe case--lessons for research involving stored biologic samples. *N Engl J Med.* Jul 15 2010;363(3):204-207.

32. Tomlinson T. Respecting Donors to Biobank Research. *Hastings Center Report.* 2013;43(1):41-47.

33. Platt R, Kass NE, McGraw D. Ethics, regulation, and comparative effectiveness research: Time for a change. *JAMA.* 2014;311(15):1497-1498.

34. Kim SYH, Miller FG. Varieties of standard-of-care treatment randomized trials: Ethical implications. *JAMA.* Mar 3 2015;313(9):895-896.

35. Kim S, Miller F. Waivers and Alterations to Consent in Pragmatic Clinical Trials: Respecting the Principle of Respect for Persons. *IRB: Ethics & Human Research.* 2016;38(1):1-5.

36. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ.* May 08 2015;350:h2147.