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Commentary: Innovative approaches to informed consent for randomized clinical trials - Identifying the ethical challenges

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At least since issuance of the Nuremberg Code in 1947,¹ there has been debate over the ethics of informed consent for clinical research. When do participants need to consent and what do they need to consent to? Many guidelines, policies, and commentators attempt to answer these questions by comparing clinical research to clinical care and mandating informed consent for the differences. This approach, like comparisons more generally, has the potential to illuminate important differences, and also to exaggerate them. It has illuminated the importance of disclosing to potential participants that enrollment in research involves contributing to a project to help others. It has also encouraged the view that the many differences between research and care are necessarily contrary to participants' clinical interests, hence, they all must be disclosed to potential participants. The result: consent for clinical research has become complicated and burdensome.

The present two proposals, Just-in-Time consent² and Trials within Cohorts,³ aim to simplify the consent process by leveraging the fact that clinical trials often include standard of care arms. The statistician, Marvin Zelen, famously started with the same thought and proposed to randomize participants first and then obtain their consent for the option to which they had been randomized.⁴ Individuals randomized to the experimental arm would provide consent for research, while those randomized to the control arm would provide standard clinical consent. [Zelen briefly considered obtaining research consent from both arms, but this proposal has received much less attention.] Zelen's proposal was met with skepticism. Research methodologists expressed concern that a significantly higher percentage of those who are randomized to the experimental arm, and undergo research consent, might decline to participate.⁵ Research ethicists expressed two additional objections.⁶ First, participants in the control arm are never informed that they are enrolled in research.⁷ Second, it is thought unethical to randomize patients as part of a study before they have given consent to participate in research.⁸

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The present proposals modify the Zelen approach in hopes of retaining its virtues while addressing these concerns. The central innovation in both proposals is to create pools of potential participants for randomized trials that compare experimental interventions to the standard of care. These pools might be established from individuals who are members of the same insurance plan, patients at a particular hospital, individuals in a given community, or patients with a specific diagnosis. The pools can provide participants for a single study or a range of studies, and they might serve as reservoirs of potential participants only or they might double as longitudinal studies, collecting data from members over time.

Creation of these pools allows researchers to split the informed consent process into stages. In the first stage, individuals consent to being placed in the pool, with the understanding that they might be evaluated for one or more clinical trials, and information from their medical records might be used for research. This step addresses the first ethical objection to Zelen's proposal (individuals randomized to the standard of care arm contribute to research without ever consenting to it). Once the pool is established, members who are found to be eligible for a comparative trial are randomized. The second stage of consent occurs after randomization, when participants assigned to the experimental arm are asked for research consent, while those assigned to the control arm provide standard clinical consent. This approach avoids the need to obtain in-depth research consent for up to half of the participants. It thereby avoids the need to describe the experimental treatment to them and avoids any disappointment they might otherwise experience at not receiving it.

These two proposals are intended to promote several goals related to informed consent for randomized clinical trials: increasing recruitment, decreasing burdens on researchers and participants, and improving participant understanding and satisfaction. To what extent they succeed is, as the authors note, a matter for future research. For example, it will be important to assess whether the use of different consent processes for the experimental and control arms leads to significantly different rates at which individuals agree to participate. In the meantime, because both proposals address the first ethical objections to Zelen's proposal, analysis is likely to focus on the second ethical objection: handling consent for randomization appropriately.

One version of the Trials within Cohorts approach informs participants who are offered the experimental treatment, but not participants who are offered the standard of care, that a random process was used to make this decision. Just-in-Time consent informs all those who agree to be included in the potential participant pool that they might be randomized in the future. However, those who are offered the standard of care rather than the experimental treatment are not informed that this choice was made by a random process. Critics might object to both approaches on the grounds that all research participants should prospectively consent to being randomized. And all participants should be informed that the specific treatments they are offered were chosen by a random process. These objections are based on the common assumption that obtaining prospective consent for randomization is critical to ensuring ethical research. To assess whether this assumption holds in the present setting, consider an alternative way to implement these two approaches.

Rather than randomly *assigning* all of the eligible individuals in the pool to the experimental arm or the control arm, imagine that investigators randomly *sample* a percentage of the eligible individuals and offer them the experimental treatment. The remaining eligible individuals are offered standard treatment, and the outcomes in the two groups are compared.⁹¹⁰ For example, the investigators might sample half of the eligible individuals and offer them the experimental treatment, while the remaining half are offered standard treatment. In this case, it seems that the participants who are not sampled do not need to provide prospective consent for the sampling process and they do not need to be informed of its use when they are offered standard treatment. If this is right, it suggests that consent for random *assignment* is not important in these cases either. And, if that is right, it suggests that ethical analyses of innovative approaches to informed consent for randomized trials in this setting should focus on other issues. To see why this follows, consider a different type of research.

Imagine that a researcher is interested in collecting preliminary data on the impact of mindfulness. She proposes to set her phone to vibrate every seven minutes and approach the next person who enters a hospital emergency room. Those who consent will be offered \$50 to listen to a mindfulness tape and allow the researcher to access their records after the visit to document their blood pressure. The individuals in the emergency room who are *not* sampled do not contribute to the research and it does not affect their care in any way. This explains why the researcher does not need to inform them that a random process resulted in their not being invited to participate in research, even though they could have benefitted from listening to the tape and earning \$50.

Now imagine that the researcher obtains additional funds which allow her to expand the study to include as controls the individuals who are not sampled. How should this change affect the consent process? Because the individuals who are not sampled are now contributing to the study, the researcher should obtain consent at the end of the visit to document their blood pressure and use it for research. In contrast, the research still does not affect the care of those who are not sampled. Hence, the researcher does not need to obtain their prospective consent to use the random selection process, nor does she need to explain at the end of the visit that they might have been chosen for the mindfulness activity, but weren't.

What implications does this example have for the random *sampling* version of Just-in-Time consent and Trials within Cohorts? The fact that individuals who are not sampled contribute to the research provides a reason for the researchers to briefly explain the study and obtain consent to use their information for research purposes. But, as in the mindfulness study, the random sampling process does not affect the care of the controls. As a result, there is no need to obtain their prospective consent to use the random sampling process, nor is there a need to explain this process when they consent to having their data used for research. This example thus suggests that any objections to the two proposals on the grounds that they do not obtain appropriate consent for randomization could be met by using random sampling rather than random assignment. More importantly, random sampling is almost identical to random assignment. The primary difference, indistinguishable from participants' point of view, is whether some participants are offered standard treatment because their names are

not chosen, or because their names are chosen and they are assigned to that option. This similarity between the two approaches suggests that ethical analysis of them should not be dramatically different. If individuals do not need to consent prospectively to the use of random *sampling*, they do not need to consent prospectively to the use of random *assignment*. And if individuals do not need to be informed that they are being offered standard treatment because they were not *sampled*, they do not need to be informed that they are being offered standard treatment because they were randomly *assigned* to that option.

One could support this conclusion by pointing out that the individuals who are randomly assigned to the standard of care previously consented to contribute to research when they entered the participant pool. In addition, the use of randomization does not increase the risks they face,¹¹¹² nor does it change the treatments they receive. Critics might respond that the use of randomization still affects participants in the sense that which treatment they are offered is determined by randomization. Hence, mandating consent for randomization in these cases, critics might argue, upholds the principle of respect for persons by ensuring that individuals are not affected by research without their consent. Although this understanding of the principle of respect for persons sounds reasonable, it is, strictly speaking, impossible to satisfy. Essentially all participants are affected by research in a number of ways prior to consent. At the theoretical extreme, approval of a randomized trial itself affects potential participants in the sense of increasing the number of options available to them. And, in practice, potential participants must be approached prior to consent to see whether they are even willing to hear about a study. These unconsented research-related activities are ethically acceptable because they involve minimal impact on individuals' lives, suggesting that the implication of the principle of respect for persons is not: "Individuals should not be affected by research in any way without their consent." Instead, it implies: "Research should not affect individuals in meaningful ways without their consent."

We have seen that randomization does not affect in a meaningful way those who are offered the standard of care that they would otherwise have been offered absent the research. Hence, it is not ethically important to obtain their prospective consent to be randomized. This conclusion leaves the challenge of determining which aspects of research do affect individuals in meaningful ways, and how consent should be obtained for them. The fact individuals contribute data to a study provides a reason to obtain their consent, even when the study does not change their care in any way. This consent is typically obtained just before individuals enroll in a study. As a result, current approaches to consent for randomized trials tend to combine three things: individuals agreeing to contribute to the research; individuals knowing at the time that they are involved in research; and individuals knowing that they have participated in research. By dividing the consent process into stages and obtaining consent for some procedures (randomization, assessment of records to determine trial eligibility, collection of data) at the time of inclusion in the potential participant pool, the present proposals disaggregate these considerations.

Consider an institution that implements the present proposals by asking potential participants, at the time of enrollment in the pool, to consent to providing up to 5 ml of extra blood during a clinically indicated procedure if needed to evaluate their research eligibility. Potential participants also consent to having their data used for research purposes. This

consent provides permission for the screening procedures and for the possibility of contributing to research. However, the participants may never learn whether any extra blood was taken and, if it was, during which procedure it was obtained. The participants also may never learn whether they contributed to research. Separating the consent process into phases thus raises important questions regarding when participants need to consent and what they need to consent to. In addition to giving consent to the *possibility* of contributing to research, is it important for individuals to know that they have contributed to research? Is it important for them to know, at the time, that they are involved in research? To take another example, we typically do not think it is important for clinicians to explain to their *patients* why a particular treatment was chosen, even when the existing data equally support other treatment options. Is it important, in the same setting, for research participants to know that the specific treatment they are offered was chosen by a research protocol?¹³

In summary, the consent process for clinical research has become complicated and burdensome, and it is nonetheless associated with inadequate understanding. We need more proposals for innovative approaches to address these concerns.¹⁴ And we need more conceptual and empirical research to assess them.¹⁵ Ethical analyses are likely to focus a good deal of attention on how innovative approaches to consent for clinical trials handle randomization. Yet, the similarity between random sampling and random assignment, together with the fact that consent is not needed for random sampling, suggests that consent for random assignment is not important in these cases either. More important for assessing the ethical acceptability of innovative approaches to informed consent for randomized trials is to determine which aspects of the research process individuals need to consent to, and when they need to consent to them. Is there a point at which Just-in-Time consent become Too Long Ago consent?

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