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Should Participants in Clinical Trials Be Able to Withdraw from Passive Follow-Up?

Warren H. Capell, Matthew K. Wynia, Elisa A. Hurley, and Marc P. Bonaca

ABSTRACT A research participant's right to withdraw from all research procedures is widely accepted, but there can be justifiable limits to a participant's exercise of autonomy to withdraw from some procedures. Clinical outcomes trials depend on complete subject follow-up for accurate assessment of the safety and efficacy of investigational therapies. Subjects' refusal to complete follow-up, even through passive medical record review, can cause failure to detect safety signals, inaccurate estimation of efficacy, or lack of acceptance of trial results, which alters the study's benefit-risk ratio. Allowing participant refusal of follow-up data collection therefore creates tension between respect for persons and beneficence. With minimal risk study procedures that can help preserve trial benefit, such as passive data collection, we argue that the importance of upholding the principle of beneficence outweighs individual autonomy concerns. Furthermore, a consent process that prospectively informs participants of mandatory passive follow-up is ethically justified and optimizes the balance between autonomy and beneficence.

KEYWORDS human research ethics, human subjects research, informed consent, passive data collection, respect for persons, autonomy, beneficence, research risks, privacy

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Participants' right to freely withdraw from research procedures dates back to the Nuremberg Code, with increasingly expansive forms of this right found in provisions of U.S. regulations governing research with humans. Today, the right to withdraw from research activities for any reason, without penalty, is generally unquestioned by the research community and research ethics committees worldwide. This broad acceptance of participant withdrawal deserves further consideration, as there are circumstances when a more nuanced position may be important to maximize balance between ethical principles.

Consider this hypothetical scenario:

> *A study coordinator of a large multicenter clinical trial calls a participant to schedule a follow-up visit. The participant states that she stopped taking the study medication "some time ago" because it made her feel poorly, leading to hospitalization. When further questioned about these possible side effects from the study medication, she expresses frustration with having been in the trial and says she no longer wants to participate. When asked if the research team can have continued access to her medical records for follow-up of study outcomes, the participant refuses and states that she wants no further contact with the investigators and no information collected about her for the trial.*

While the participant is within her rights to withdraw from the clinical trial, and her decision to withdraw has effects seemingly limited to her own privacy, withdrawing from the study may actually have broad potential consequences for herself, others in the study, and the general population. We argue that these consequences justify placing limits on her right to withdraw from at least some research activities that pose minimal risk, including passive data collection.

The widely accepted research principle of beneficence calls for minimizing research risks and maximizing the potential benefit-risk ratio. The primary poten-

tial benefit of most research is the development of new, actionable scientific knowledge. In clinical outcome trials, where the primary study results are health consequences to the participants over time, this benefit of actionable knowledge depends on researchers' ability to ascertain the medical outcomes of their participants. Incomplete participant follow-up can threaten a study's benefit in two ways. First, incomplete follow-up results in gaps in the data, which decrease researchers' ability to determine differences in the study intervention's efficacy or safety. Second, and even more concerning, incomplete follow-up can create bias in the trial results, which has been demonstrated in theoretical modeling[1] and in the analysis of existing data sets.[2] Such "attrition bias" may have particularly detrimental effects if individuals having side effects or experiencing no benefit differentially choose to leave the study, making the study intervention look safer or more effective than it actually is.

Because clinical trials are typically powered to detect differences in efficacy but not all potentially relevant safety outcomes, incomplete participant follow-up may be especially problematic for identifying uncommon safety events. In our example case, the participant was hospitalized for a possible study medication side effect that had yet to be documented within the trial. She could still have been at risk of latent drug toxicity, depending on the study medication's properties. Her refusal to allow the researchers to continue monitoring her medical records not only jeopardizes her safety but also risks the researchers' failure to identify important safety signals relevant to the remaining trial participants, regulatory agencies, and the public at large. The drug rimonabant shows an example of inadequate safety signal detection due to participant attrition. A primary concern in the U.S. Food and Drug Administration's (FDA) refusal to approve rimonabant in the United States was the difficulty in assessing the risk of drug-associated suicide due to participant attrition. The drug was approved in Europe but was subsequently withdrawn from the European market mainly due to increased suicide risk.[3] When inferences made from a research study are altered because of attrition bias, due to inaccurate assessment of a treatment's efficacy or safety, the study's benefits are lessened or voided, and the benefit-risk ratio of the research may become unfavorable.

When considering whether to approve drugs for marketing in the United States, the FDA convenes an advisory committee of independent scientific experts to provide advice on interpreting the trial data supporting a drug product. Over the past decade, potential attrition bias has continued to be an increasing focus of FDA advisory committees. Even without provable bias, the uncertainty caused by attrition alone can cast doubt on a trial's scientific integrity. For example, a recent cardiovascular trial showed the significant benefit of a low-dose anticoagulation regimen in patients suffering acute coronary syndrome; however, the drug regimen was not approved by the FDA, largely over concerns about bias from incomplete participant follow-up.[4] An expert panel convened by the FDA further concluded that analysis methods could not sufficiently compensate for participant attrition.[5] If concerns over attrition cause a beneficial treatment to be overlooked and prevented from becoming publicly available, the benefits of that research are not realized. Additionally, if study integrity is sufficiently compromised by attrition bias, then all trial participants potentially will have been exposed to risk of harm by participating in a useless trial—that is, a trial that will not lead to benefit in terms of knowledge gained. These factors again may lead to an unfavorable benefit-risk ratio.

> Participants' withdrawal from clinical trial follow-up reduces the study's scientific integrity and may increase risks to other participants, the scientific enterprise, and the public.

BALANCING RESPECT FOR PERSONS AND BENEFICENCE

In our hypothetical case, the research's potential failure to meet the requirements of beneficence derives from an individual research subject's exercise of her right to withdraw from research procedures. In other words, the case reveals a tension between the ethical principle of beneficence and the ethical principle of

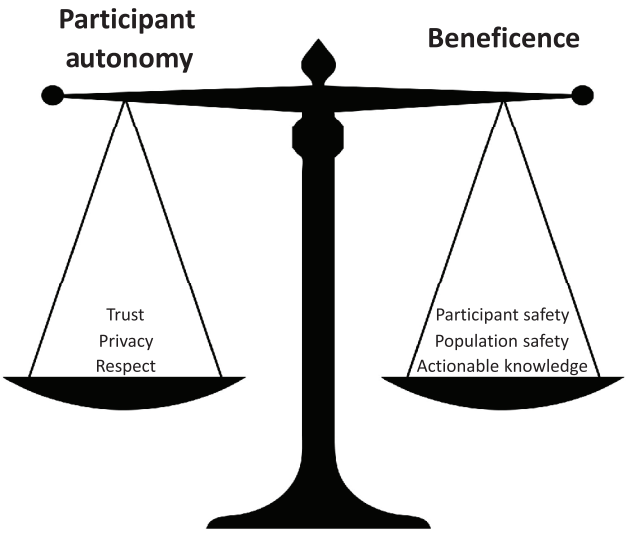
respect for persons. Refusal by just a few participants to allow follow-up data collection might not adversely affect a study's benefits and so might not justify abrogating the study participants' right to withdraw completely. However, it is difficult to predict how many participants will make this decision over the course of a long outcomes study. The riskier the treatment or the more burdened the study population with illness, dependence on others, or socioeconomic stressors, the greater the risk that withdrawing from a study will occur in sufficient numbers to undermine accurate inferences and threaten the trial's benefit-risk ratio. Should respect for each research participant's autonomy always allow for withdrawal, even if it risks harm to others or undermines the potential benefit of research in this way?

For our hypothetical case, failing to support participant autonomy fully would involve overriding the participant's express wishes, with associated potential harms. Though this would incur minimal physical harm or inconvenience to the participant, continued passive data collection against her wishes would create dignitary harm by violating her autonomy, disrespecting her voice, and invading her privacy. Ignoring her directive, and overriding participant wishes as a practice, could cause anger and feelings of injustice and provoke loss of the trust upon which the research enterprise is built.

The ethical principles of respect for persons and participant autonomy clearly take precedence when ongoing research procedures involve significant risks to participants, but when procedures, such as passive data collection, pose only minimal risk, the balance may shift (see figure 1). Research guidance and regulations already acknowledge instances when societal benefits can outweigh individual autonomy. For instance, FDA guidance states that all data collected up to the point of a participant's withdrawal of consent must be retained, limiting the participant's ability to have data already collected withdrawn.[6] Moreover, the U.S. Department of Health and Human Services' research regulations (the "Common Rule") permit institutional review boards to waive or alter the requirement for informed consent when five conditions are met, including when research poses only minimal risk, such as in a medical chart review study.[7] Additional criteria for approval of consent waivers further uphold respect for persons through means other than informed consent, by requiring that the waiver not violate participants' rights and welfare, that notice to participants about the research is provided whenever possible, and that waiving consent is the only practicable way to complete the research. Recent updates to the Common Rule now allow research with private medical records to be exempted from the requirements for informed consent, so long as the data security considerations are adequate.[8] Ironically, these current regulations would allow medical record data collection on the participant in our example, without her consent or knowledge, had she not already been enrolled in the study and then expressed dissent. This discrepancy in how our example participant is treated compared to others who do not actively consent to research regarding medical record review also raises a possible concern with failing to uphold the principle of justice.

We do not believe that deference to respect for persons should be favored in this situation. Theoretical arguments have been made that the right to withdraw

Figure 1. The Ethical Balance in Participant Withdrawal from Passive Follow-Up in a Clinical Trial



Research participant refusal to allow the minimal risk procedure of medical record follow-up in a clinical outcomes trial requires balancing between respect for persons, preserving individuals' autonomy, and beneficence, with potential impacts on trial benefit, other participants, and society.

from research should not be absolute.[9] Some argue that allowing immediate withdrawal of consent without conditions or exceptions may undermine a research participant's initial exercise of autonomy unless something in the research changes that alters the validity of the original consent.[10] In addition, it is important to consider the real-world consequences that these decisions can have, as we have outlined, when facing this tension between respect for persons and beneficence. Nevertheless, even at the risk of losing the benefits of actionable scientific knowledge from a trial, we expect that research ethics committees would likely have difficulty agreeing to override a participant's expressed wishes in this situation.

PROSPECTIVE CONSENT TO MANDATORY PASSIVE FOLLOW-UP

A more respectful way to uphold respect for persons and lessen the impact of overriding autonomy in such circumstances would be to clarify during the initial informed consent process that participants may freely withdraw from all study procedures *except* continued passive data collection. Called a *Ulysses contract*, such an agreement to limit future rights has been proposed for the federally mandated lifelong surveillance of xenotransplant recipients.[11] The risks of mandatory passive data collection are minimal and are appropriate for potential participants to weigh prospectively in their decision to enroll in a study. Even with a later change of mind about passive data collection, a participant would have consented to participate with a full understanding of their subsequent inability to withdraw from certain study procedures. Respect for persons would not be undermined when researchers follow the limits agreed to in the original consent process.

It has been argued that prospective consent to limit withdrawal might reduce study enrollment rates or damage public trust in the research enterprise.[12] But in our example, highlighting this specific inability to withdraw from passive data collection while explaining that such action could be harmful to oneself and others would also demonstrate a commitment to the welfare of all trial participants and the public. We believe that such transparency would have a negligible effect on enrollment and might serve to enhance public trust in research.

Beauchamp and Childress[13] acknowledge that respect for persons may be overridden by beneficence under the proper conditions, particularly when harms to self or others may be a significant risk. They describe six conditions that constrain the proper balancing of ethical principles: (1) good reasons can be offered to act on the overriding norm rather than on the infringed norm; (2) the moral objective justifying the infringement has a realistic prospect of achievement; (3) no morally preferable alternative actions are available; (4) the lowest level of infringement, commensurate with achieving the primary goal of the action, has been selected; (5) all negative effects of the infringement have been minimized; and (6) all affected parties have been treated impartially. A priori consent to mandatory future passive data collection meets all these criteria regardless of future wishes.

Respect for research participants and their autonomy is critical to the ethical conduct of research; this includes respect for individual participants' decisions to withdraw from research procedures. But it is also critical to acknowledge that the decisions of each person who has agreed to participate in a research study can affect the potential benefits of the research and the other participants who have made the same good-faith agreement to undergo risk to achieve those benefits. Participants' withdrawal from clinical trial follow-up reduces the study's scientific integrity and may increase risks to other participants, the scientific enterprise, and the public at large. A consent process that limits a participant's ability to withdraw from minimal risk follow-up critical to maintaining scientific integrity is ethically justified to preserve study benefits and minimize harm to others. Furthermore, such a consent process is consistent with and acceptable under the Common Rule regulations. Investigators and research ethics committees both have important responsibilities in minimizing threats to the value and integrity of research. In considering limitations on the withdrawal of consent, research ethics committees should thoughtfully evaluate the balance between these different moral imperatives. ♦

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DISCLOSURE

Warren H. Capell is a contracted employee of CPC Clinical Research, an academic research organization affiliated with the University of Colorado Anschutz Medical Campus that receives research grants from various industry sponsors to design and conduct clinical trials.

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