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Participants' responsibilities in clinical research

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Abstract

Discussions on the ethics and regulation of clinical research have a great deal to say about the responsibilities of investigators, sponsors, research institutions and institutional review boards, but very little about the responsibilities of research participants. In this article, we discuss the responsibilities of participants in clinical research. We argue that competent adult participants are responsible for complying with study requirements and fulfilling other obligations they undertake when they make an informed choice to enrol in a study. These responsibilities are based on duties related to promise-keeping, avoiding harm to one's self or others, beneficence and reciprocity. Investigators and research staff should inform participants about their responsibilities during the consent process, and should stress the importance of fulfilling study requirements. They should address any impediments to compliance, and they may provide participants with financial incentives for meeting study requirements. In very rare cases, coercive measures may be justified to prevent immanent harm to others resulting from non-compliance with study requirements.

INTRODUCTION

Discussions on the ethics and regulation of clinical research have a great deal to say about the responsibilities of investigators, sponsors, research institutions and institutional review boards (IRBs), but very little about the responsibilities of research participants. Investigators are responsible for protecting the rights and welfare of participants, for designing, executing and managing the study, for ensuring the integrity of the data, and for reporting adverse events and unanticipated problems. Sponsors are responsible for providing investigators with financial support, designing the study (except for investigator-initiated research), preparing regulatory and legal documents, monitoring and auditing research, and reporting data, adverse events and unanticipated problems. Institutions are responsible for providing investigators with appropriate staffing, training and resources; ensuring that research has appropriate legal and ethical oversight; auditing research; and reporting adverse events and unanticipated problems. Finally, IRBs are responsible for protecting the rights and welfare of participants, and overseeing and reviewing research. All these different parties are responsible for keeping good records and following written procedures.¹²

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What about participants' responsibilities? The research ethics literature scarcely addresses this question. Published articles on research participants address the duty to participate in research,^{3–6} or the right to withdraw from research,^{7–10} but not the obligations one has as a research participant while taking part in a study. One notable exception is a report from the Institute of Medicine (IOM), *Responsible Research: A Systems Approach to Protecting Human Research Participants*,¹¹ which recommends that: 'Decisionally capable participants should understand their potential role in any study in which they enrol, the rationale underlying that study, and importantly, what is required of them to prevent unanticipated harm to themselves and to maintain the scientific integrity of the study (p. 130).' Though the IOM report acknowledges that participants have important roles and responsibilities, it does not discuss them in detail. In this article, we will consider the responsibilities of participants in greater depth.

ETHICAL ARGUMENTS FOR PARTICIPANT RESPONSIBILITIES

Five ethical arguments support an obligation for competent adult participants to comply with research requirements. (We will focus on competent adults in this essay because very different questions concerning responsibility arise in research on children or mentally disabled adults.)

First, clinical research can be understood as a partnership between investigators (and research staff) and participants.¹² When participants make an informed choice to enrol in research, they agree to follow study requirements, such as taking medications as directed, showing up for appointments, informing investigators or staff about problems, completing surveys and treating investigators and staff with respect. In return, investigators and staff agree to safeguard the rights and welfare of participants, perform study procedures appropriately, provide study medications (if any) and compensate participants for their time and effort (if compensation is offered). These obligations may be explicitly stated in the consent form, educational materials, instructions or other documents, or they may be implied. Participants who do not honour their responsibilities are breaking explicit or implicit promises they have made with investigators and members of the research team. Most ethical theories hold that we should keep our promises, other things being equal.^{13–15}

Second, participants may cause harm to others if they do not comply with study requirements. The duty to avoid causing harm to others is a widely recognised ethical principle.^{13,15} Harm can be direct or indirect. Direct harm to others could occur, for example, if a participant with a highly infectious and dangerous disease, such as tuberculosis (TB), does not take medication as directed or fails to observe certain precautions. The participant could infect people with TB, when he or she comes into contact with them. Direct harm could also occur if a fertile woman, who is participating in a drug study, has been instructed to use an effective means of birth control to avoid pregnancy but fails to do so and becomes pregnant. If the child is born with birth defects due to exposure to the drug prenatally, the woman would be partly responsible. To prevent harm to unborn children, researchers are justified in requiring fertile women to use an effective form of birth control as a condition of participating in a study where there are risks to the foetus. Indirect harm to others could occur, for example, when non-compliance by participants leads to faulty regulatory decisions. If participants fail to report important symptoms to investigators during a drug trial, the drug might be approved on the basis of incomplete safety data. Other types of non-compliance, such as lying about preexisting medical conditions in order to qualify for a study, could also undermine the integrity of the data and cause indirect harm.¹⁶

Third, participants may harm their own health if they fail to fulfil some study requirements. Many ethical theories also recognise an obligation not to harm one's self.^{13,15} Failure to

comply with self-administered medication instructions can result in an adverse drug reaction, a dangerous drug interaction (if a contraindicated medication is taken by mistake), or lack of clinical benefit, such as inadequate blood pressure control for a person with hypertension. Failure to follow directions for preparing for a medical procedure may result in physiologic complications. For example, failure to abstain from food and some types of medications prior to a bronchoscopy may lead to excessive bleeding, aspiration of food (which can cause pneumonia), or cardiac arrest.

Fourth, by completing study requirements, participants can benefit others. Beneficence is a widely recognised moral obligation we have, which is to do good for others.¹³¹⁵ Participants who participate in clinical research can help generate data that benefits future patients and society. The data from clinical studies can be useful in evaluating drugs, medical devices or other products useful in diagnosing, preventing or treating various conditions and diseases.

Fifth, complying with research requirements can be regarded as a form of reciprocity: individuals who have benefited from research (or expect to benefit in the future) should comply with research requirements to provide a benefit in return. Reciprocity is different from beneficence, in that reciprocity involves providing a benefit in return for a benefit (or expected benefit), whereas, beneficence is a form of altruism in which no benefits are expected in return.

WHY PARTICIPANT RESPONSIBILITIES ARE DIFFERENT FROM THE OBLIGATION TO PARTICIPATE IN RESEARCH

The ethical arguments for participant responsibilities are similar to, but different from, the arguments for participating in research. The main arguments for an obligation to participate in research are: (1) to benefit society and the research enterprise (ie, beneficence) and (2) to provide something in return for the benefits one has received, or expects to receive, from research (ie, reciprocity).^{3–6} Both these arguments also apply to participant responsibilities, but, as we have seen, there are other arguments for those responsibilities, such as preventing harm to one's self or others, and keeping one's promises and commitments. These other arguments imply that the ethics of complying with research requirements is different from the ethics agreeing to participate in a study.

To illustrate how the ethics of complying with research responsibilities is different from the ethics of participating in research, consider the ethics of providing cardiopulmonary resuscitation (CPR) to a person having a heart attack. The decision about whether to perform CPR is different from the decision about performing CPR correctly, once one has decided to perform it. In deciding whether to perform CPR, one must consider the obligation to help someone in light of the facts at hand as well as other ethical considerations, such as the obligation to avoid causing harm. If one decides to perform CPR, one acquires an obligation to perform it correctly, to the best of one's ability. If one does not perform CPR correctly, one may prevent the person with a heart attack from being saved if there is someone standing by who could perform CPR effectively.

Because failure to adhere to study requirements can lead to direct harm to others in some cases, coercive measures may be justified to ensure compliance. This is one important way that the ethics of participant responsibilities differs from the ethics of deciding to participate in research. We will discuss this implication below.

LIST OF PARTICIPANT RESPONSIBILITIES

Though the specific responsibilities of clinical research participants will vary from study to study, the IOM report¹¹ outlined some general responsibilities. Additionally, some research institutions have developed lists of general responsibilities for participants.^{17–19} *Body Positive*, a magazine that supports HIV/AIDS patients, has also published a brief list of participant responsibilities.²⁰ Some general responsibilities of participants include:

- Respect investigators, research staff and other participants.
- Read the consent form and other documents. Ask questions if they do not understand something about the study, or their rights and responsibilities as a research participant, or need more information.
- Carefully weigh the risks and benefits when deciding whether to participate in the study.
- Refrain from signing the consent document until they believe that they understand its content and feel comfortable with their decision to participate.
- Follow directions for proper use, dosing and storage of self-administered study medications, providing biological samples, and preparing for tests, procedures or examinations.
- Follow directions for abstaining from non-study-related medications, or other contraindicated medications or procedures.
- Know when the study begins and ends. This is particularly important for an intervention trial that has a follow-up period after the intervention is completed.
- Show up at scheduled appointments on time, and inform the staff within a reasonable time if they need to reschedule an appointment.
- Provide truthful answers to questions asked during screening/enrolment and during the study.
- Inform staff if other medical care is needed while on the study.
- Inform the staff if there are questions they would rather not answer.
- Report pain, discomfort, nausea, dizziness and other problems and symptoms they experience during the study.
- Keep information about the study confidential, if asked to do so.
- Keep staff informed when contact information (eg, phone number, address) changes.
- If they decide to withdraw from the study, inform the staff and follow the procedures for withdrawal.

UNDERSTANDING PARTICIPANT IRRESPONSIBILITY

Sometimes participants fail to fulfil their responsibilities in clinical research. One of the main reasons for this failure is that they view participation in a study as a potential medical benefit, and they want to make sure that they qualify for the study.²¹²² They may not answer questions concerning eligibility criteria truthfully during the enrolment process (so they can qualify for the study), or they may fail to report symptoms and other problems during the study (so they will not be withdrawn). The temptation to lie about excluding conditions and symptoms/problems may be especially great when participants have a serious illness, such as cancer or HIV/AIDS, and they are strongly motivated to enter a clinical trial to obtain

treatment.^{23,24} Evidence shows that one of the main reasons why participants enrol in studies is that they hope to derive medical benefits from participation.^{24,25} Patients may take this attitude toward research participation even when investigators stress that the main purpose of the study is to advance scientific knowledge, and that participants may not benefit. Participants may view studies as designed to provide them with personal benefits because they fall prey to therapeutic misconception.²⁶

Participants may also have financial motivations for dishonesty. One of the main reasons why healthy volunteers enrol in Phase I drug safety research is to earn money.²⁷ Participants may lie about their age or preexisting medical conditions in order to qualify for a study. In some cases, they have failed to disclose concurrent or recent enrolment in another clinical study. Participants may also have financial motivations to lie about the symptoms or problems they are experiencing in order to avoid being dropped from a study.²⁸

Participants may fail to take medications, as directed, for a variety of reasons, including complexity of the drug regimen, inconvenience and side effects. Evidence shows that rates of medication non-compliance are greater than 25% in clinical trials of antiretroviral drugs used to treat HIV/AIDS.²⁹ Mental illness, substance abuse and socioeconomic factors, such as race and education, also influence medication compliance.^{29–31}

There are a variety of other reasons why participants may fail to follow study requirements, including difficulties with transportation or phone service, relocation, miscommunication, negative interactions with research staff, mental illness, substance abuse, excessive study length and competing commitments, such as work or childcare responsibilities.³² Since there has been very little empirical research on participants' non-compliance with clinical research requirements, additional research could help investigators to better understand this problem and take effective measures to address it.

PROMOTING PARTICIPANT RESPONSIBILITY

There are several ways that investigators and staff can promote participant responsibility in clinical research. First, they can inform participants about study requirements during the consent process, stressing the importance of following instructions and answering questions honestly. A list of participant rights and responsibilities can be spelt out in a separate document if necessary. Investigators and staff can also remind participants of the crucial role that they play in research, and that they may harm themselves or others (in some cases) if they fail to follow instructions. They can also ask participants if they think they may find it difficult to meet or fulfil some of their responsibilities. They should encourage potential participants not to enrol in a study if they think they will not be able to meet all the requirements. Since consent is an ongoing process, not just signing a document, investigators and staff should continue to communicate with participants about their responsibilities.

Second, investigators and staff should address potential impediments to participant compliance with study requirements, such as transportation issues, phone service, competing commitments and drug side effects. Potential obstacles to completing study requirements may be discovered during enrolment, initial consent discussions, or later on in the study. When impediments are identified, it may be necessary to take some steps to promote compliance with study requirements, such as helping a participant obtain transportation or childcare.

Third, investigators and staff should maintain good relationships with participants. Participants are more likely to fulfil their obligations if they identify with the research and

feel that they are being treated respectfully, because they will have some personal investment in the study.

Fourth, if participants fail to fulfil some of their responsibilities, research staff can remind them of the importance of meeting study requirements and try to persuade them to honour their obligations. They can also inform participants that they may be withdrawn from the study if their non-compliance undermines the integrity of the data or results in other problems.

Fifth, investigators can use financial incentives to motivate participants to comply with study requirements. Participants can be paid for completing particular parts of the study, such as providing biological samples or filling out surveys. They can also receive a bonus for completing the entire study. As long as the incentives are not so high that they compromise rational decision making, they will not constitute an undue inducement to continue participating.³³

Finally, in some cases, coercive measures may be justified to ensure compliance with study requirements. Coercive measures would be justified only to prevent immanent harm to others. A widely recognised ethical rule known as the harm principle, implies that it is acceptable to restrict a person's freedom to prevent harm to others.³⁴ In the hypothetical TB study mentioned above, coercive measures would be justified. For example, direct observed therapy (DOT) is a widely accepted public health practice for TB treatment in which a healthcare professional observes a person taking TB medication. DOT is sometimes used in TB clinical trials.³⁵ DOT is more coercive than simply allowing the patient to take drugs unobserved, because observation by a health professional poses a potential threat to the patient. If the person refuses treatment, and they have infectious TB that poses a risk to others, they can be arrested for violating public health laws and forced to take the treatment. Arresting a non-compliant TB patient is an extreme measure of last resort. Though used infrequently, it is a legal option in many jurisdictions.^{36,37}

In a TB clinical trial, DOT could be used to ensure compliance.³⁵ If a participant refuses to take the study medication, they could be withdrawn from the study and asked to take another medication to treat their TB. If they refuse this medication, then they could be arrested to protect public health.

Although we think that coercive measures are sometimes justified in research to ensure compliance with study requirements, we would like to stress that this is a very rare situation, and that for most studies, non-coercive measures, such as education and persuasion, are more appropriate. Coercion would not be justified to ensure that a fertile woman in a drug study uses an effective method of birth control, because this would interfere with her legal and moral right to make reproductive choices. If investigators discover that a fertile woman in a drug trial is not using an effective method of birth control, the best option would be to withdraw her from the study.

The legitimacy of coercive measures in some cases illustrates an important difference between the ethics of participant responsibilities and the ethics of deciding to participate in a study. Though some authors³ have defended coercive measures, such as conscription, to compel individuals to participate in research, this recommendation is controversial.⁶ One reason why some writers who defend an ethical duty to participate in research do not endorse coercion is that they view the right to refuse to participate in research as fundamental, since research participation often involves significant risks, invasion of one's body and loss of privacy.⁶ The situation is very different, however, when one's refusal to comply with study requirements poses a risk of immanent harm to others. Coercive

measures that are justified in order to prevent harm to others may not be justified in order to promote social goods.

OBJECTIONS AND REPLIES

Before concluding this article, we would like to consider some potential objections to our view. First, one could object to our endorsement of coercive measures in some rare cases. One might argue that coercion undermines the autonomy of participants, and that autonomy should be respected. While we agree that respect for autonomy is a foundational principle in bioethics, we think that it can be overridden, or constrained, to prevent harm to others. Other writers have argued, convincingly we think, that coercive measures, such as isolation, quarantine and forced treatment, are sometimes justified to prevent harm to public health.³⁸³⁹ Our argument for using coercive measures stands on similar footing.

Second, one might object that some of the other measures for ensuring compliance we have defended, such as reminding participants about their responsibilities, stressing the importance of fulfilling study requirements, and financial incentives are potentially coercive and, therefore, may undermine participants' autonomy. Participants who enrol in studies should still be free to decide whether to comply with study requirements without facing coercive pressure from investigators or staff.

While we understand the importance of not placing undue pressure on participants, we do not think that these other measures we discuss are coercive. Coercion involves threatening to harm a person.³³ Investigators and staff can discuss responsibilities with participants in a non-threatening way, and can stress that some of the study procedures actually help assure safety for the participant. They can use persuasion and financial incentives appropriately without engaging in coercion.

CONCLUSION

Competent adult participants in clinical research are responsible for complying with study requirements and fulfilling other obligations they undertake when they make an informed choice to enrol in a study. These responsibilities are based on duties related to promise-keeping, avoiding harm to one's self or others, beneficence and reciprocity. Investigators and research staff should inform participants about their responsibilities during the consent process and should stress the importance of fulfilling these requirements. They should also address any impediments to compliance, and they can also provide participants with financial incentives for meeting study requirements. In very rare cases, coercive measures may be justified to prevent immanent harm to others resulting from non-compliance with study requirements. Additional research should be conducted on participants' non-compliance with clinical research requirements, so that investigators can better understand this problem and take effective measures to address it.

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