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Use of altered informed consent in pragmatic clinical research

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Abstract

There are situations in which the requirement to obtain conventional written informed consent can impose significant or even insurmountable barriers to conducting pragmatic clinical research, including some comparative effectiveness studies and cluster-randomized trials. Although certain federal regulations governing research in the United States (45 CFR 46) define circumstances in which any of the required elements may be waived, the same standards apply regardless of whether any single element is to be waived or whether consent is to be waived in its entirety. Using the same threshold for a partial or complete waiver limits the options available to IRBs as they seek to optimize a consent process. In this article, we argue that new standards are necessary in order to enable important pragmatic clinical research while at the same time protecting patients' rights and interests.

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Introduction

According to federal regulations governing most U.S. clinical research,[1] investigators seeking to conduct pragmatic clinical research must submit their proposed research for institutional review board (IRB) review. As part of their IRB applications, investigators propose a procedure for obtaining informed consent from study participants. Depending on the IRB's interpretation of regulations, as part of the consent procedure, investigators may be required to use an informed consent document that includes the eight elements specified by federal regulations in 45 CFR 46.116 (Table 1), plus any additional elements an IRB may deem situationally important.[2]

A uniform requirement for investigators to obtain "traditional" informed consent (i.e., one that contains all eight required elements) can pose a significant barrier to the conduct of pragmatic clinical research, which often entails methods and approaches that create challenges to obtaining individual informed consent.[3,4] The Common Rule affords latitude to investigators and IRBs by defining circumstances in which any of the eight required elements of the informed consent document may be waived,[2] resulting in a consent process we will refer to as an "altered informed consent." In addition, the Secretary's Advisory Committee on Human Research Protections (SACHRP) has provided strategies for omitting required elements from the informed consent document when they are not relevant.[5]

However, investigators and IRBs face a key limitation when attempting to use altered consent: regulations defining when altering or waiving informed consent is permissible (the same standards are used for both situations) can be interpreted in a variety of ways, and if interpreted narrowly can make certain types of studies difficult or even impossible to conduct.[6,7] In some cases, the inability to use an altered consent process may prevent the research from being performed altogether, which has the potential to harm future patients by depriving them and their healthcare providers of the evidence needed to guide care and to support informed clinical decision-making.

In this article, we argue that more flexible interpretations of the current rules can enable important pragmatic clinical research while also protecting patients' rights and interests. We begin with a brief review of terms used and an introduction to pragmatic clinical research.

The Language of Informed Consent

The informed consent *process* is meant to enable a potential research participant to make a sound decision about whether to take part in a study, as well as a decision that is in his or her own best interest. To that end, information about the study, including its putative risks and benefits, should be presented in a fair, balanced, and unbiased manner. For much research, regulations mandate a signed written document[8] and broadly specify its content,[2] thus making the document a tool that constitutes a part of the larger informed consent process.

In this paper, "traditional informed consent" denotes a consent process that incorporates an oral discussion with the potential participant and the use of a consent document incorporating all eight required elements (or more). An "altered informed consent" process uses some form of communication, such as oral discussion, recorded information, electronic

communication, or a written consent document that omits one or more of the eight required elements. Finally, the regulations permit the requirement for written documentation of consent to be waived altogether under certain circumstances, including if "…the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context."[8]

The Nature of Pragmatic Clinical Research

For the purpose of this discussion, pragmatic clinical trials (PCTs) are defined as studies that are characterized by:

> "…(1) an intent to inform decision-makers (patients, clinicians, administrators, and policymakers), as opposed to elucidating a biological or social mechanism; (2) an intent to enroll a population relevant to the decision in practice and representative of the patients/populations and clinical settings for whom the decision is relevant; and (3) either an intent to (a) streamline procedures and data collection so that the trial can focus on adequate power for informing the clinical and policy decisions targeted by the trial or (b) measure a broad range of outcomes."[3]

PCTs typically take place in clinical-care settings and often compare existing and/or approved interventions or therapies, any of which may constitute standard care for a given condition.[9] In addition, many PCTs employ cluster randomization or incorporate design elements that pose challenges for obtaining traditional informed consent, either because doing so could potentially compromise the study's integrity, which in some cases may rely on participants not knowing they are taking part in research, or because of logistical issues. In a cluster-randomized trial, for example, all patients at one center might be assigned to one strategy (such as a care-related checklist, or the same hand-washing soap), while patients at another center would receive an alternative treatment. In such cases, the assignment may need to be complete within one center (e.g., everyone gets a checklist, or everyone does not). In the context of this paper, we will not address waiver or modification of consent for research that takes place in emergency settings because the resulting ethical and regulatory issues are quite distinct.

Informed Consent Regulations and their Application to Pragmatic Clinical Research

When clinical research involves comparisons between widely used therapeutic approaches that are considered standard care, there are situations in which it might be preferable for the potential research participant's decision-making to use an altered consent process. Although the regulations offer various options for the informed consent process, making use of altered informed consent will require IRBs to interpret those regulations broadly. Note that for PCTs that include the testing of products that are subject to FDA jurisdiction, except for permitting a waiver of documentation of certain research that is found to hold no more that minimal risk of harm and where consent would not otherwise be obtained (21 CFR 56.109(c)(1),[9] FDA regulations do not otherwise allow for waiver or alteration of consent except in the case of emergency use of a test product (21 CFR 50.23)[10] or planned emergency research (21 CFR 50.24).[11]

At present, an investigator wishing to use an altered consent procedure must meet the same requirements as someone seeking to waive consent altogether. According to 45 CFR 46.116(d),[2] an IRB can approve a waiver of consent or altered form of informed consent only if *all* of the following conditions are met:

1. The research involves no more than minimal risk to subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of subjects;
3. The research could not practicably be carried out without the waiver or alteration; and
4. When appropriate, the subjects will be provided with additional pertinent information after participation.

Below, we consider each of these four conditions in turn, and evaluate how an IRB might interpret the standard in order to allow or forbid an alternative consent process utilizing either complete waiver of consent or elimination of some elements.

Interpreting the Standard for "No More than Minimal Risk"

In order to meet the standard of "no more than minimal risk," researchers must be able to show that the "…the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[12]

Federal regulations do not otherwise describe "daily life" or specify whether the basis for determining minimal risk should be the relative standard of a comparable patient or the absolute standard of a completely healthy individual. This indeterminacy has resulted in a high degree of variability in how IRBs interpret minimal risk.[13–16] Accordingly, IRBs could interpret the Common Rule in such a way that permits (or does not permit) modified informed consent procedures, particularly in the setting of pragmatic clinical research.[17]

Some IRBs apply an absolute standard of a healthy person engaged in non-risky activities as the benchmark for "minimal risk," which presents several concerns. First, it could imply that almost any participation in clinical research necessarily involves greater than minimal risk, because there are few interventions that do not result in changes to a person's baseline state to at least some minor degree. However, it seems highly unlikely that there would be a Common Rule provision permitting waiver or alteration of informed consent if IRBs were expected to interpret that provision so strictly as to render such discretion impossible to exercise. Second, the "absolute" standard implicitly invokes a nebulous, unquantifiable standard: activities common to "daily life," including driving a car, riding a bicycle, or playing contact sports all entail differing degrees of risk.[18] Finally and most importantly, the Common Rule itself makes clear that the appropriate benchmark for assessing minimal risk is the degree of *incremental* risk added by participation in the study:

> *In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).*[17]

With this last point in mind, we believe that a reasonable interpretation of the regulations is that minimal risk determinations should be made by assessing the degree of risk introduced by study participation over and above the risk that characterizes the person's life if he or she were not participating in the study.

Research participants' rights and welfare

The second condition that must be addressed with regard to 45 CFR 46.116(d) is that a waiver or alteration of informed consent cannot adversely affect the rights and welfare of research subjects.[2] This issue of welfare relates to the discussion of minimal risk above. If there is no additional risk incurred by participation (other than being assigned to what turns out to be the less successful arm in the research), then the research subject's welfare should not be harmed.

The question of rights is less clear, depending upon which rights one feels are relevant. Those typically associated with respect for autonomy include the right to choose between therapeutic options, the right to choose whether to participate in research, and the right to be informed. A full exposition of these issues is beyond the scope of this paper, but we offer several general observations. First, there is some debate about the extent to which the standard of disclosure and consent for clinical care should be used as the standard of disclosure and consent for PCTs.[19] In usual clinical-care settings (where PCTs are typically conducted), patients may or may not be offered choices about their treatment. In essence, waiver of consent in pragmatic research involving standard therapies can be viewed as consistent with everyday medical practice in many cases. It is, however, reasonable to argue that an individual's right to decide about their care is absolute, and if patients are unaware of a choice to be made or that a choice has already been made for them, their rights have been adversely affected by the waiver of consent. On the other hand, some have suggested that not all medical choices engage an autonomy interest for patients, such that waiving consent involving some aspects of care would not adversely affect the patient's rights.[4] This is an evolving area of discussion among bioethicists and policy makers.

Second, an altered form of consent clearly affords greater protections of rights than a waiver of consent. With altered consent, potential participants would have the opportunity to choose whether to participate. They would still be provided information about the research and their various options, although the amount of information provided would generally be focused on what they need to make a reasoned and informed choice. It is critical that consent processes convey the appropriate type and amount of information and the best mode of delivery to enable informed decision-making. Further research and policy work is required to understand whether more or less information should be disclosed for different types of PCTs.

Finally, while rights are often described in terms of autonomy interests, there is a broader debate about how exactly autonomy interests should be interpreted in the context of consent for research[20–23] and, relatedly, how respect for persons can be achieved through institutional structures and processes in addition to or instead of an informed consent process.[24]

Practicability

The next condition concerns the question of whether research could be *practicably* carried out without the waiver or alteration of consent. The word "practicably" offers IRBs a flexible criterion spanning definitions ranging from "impossible" to "inconvenient" when choosing whether to allow waiver or alteration of consent. In 2008, SACHRP proposed that "Practicability should not be determined solely by considerations of convenience, cost, or speed."[25] We agree that none of those factors should be the sole criterion of practicability, but we do think that each of them may be relevant to an IRB's determination of whether it is practicable to obtain consent. When the risk of a study is low, issues of expense and convenience should be considered in deciding whether the consent process may be altered.

The question of whether research is rendered impracticable by requiring a traditional consent process can be viewed from at least three perspectives. The first is that of scientific feasibility: i.e., can the scientific question be answered if research participants are aware of the experiment's purpose? For example, research evaluating the effect of wall paint color on mood could not be done in an unbiased manner if subjects knew the purpose of the experiment beforehand. While relevant to research that might require deception, this notion of practicability is perhaps less relevant for PCTs. The second view of practicability is logistical feasibility: for example, obtaining consent from each individual would be extremely difficult in some large studies of a minor intervention (e.g., one that examined whether the rate of false positive results from blood cultures is decreased more by the use of alcohol or betadine to clean the skin prior to sampling). The third concerns situations in which it is feasible to obtain individual prospective consent, but at the expense of scientific validity (by introducing bias) and/or in terms of the resources required. This type of effect of the consent process was reported in the SUPPORT study, in which a long prenatal consent process favored enrollment by wealthier white women (and infants) rather than poor African American women, despite the higher incidence of premature births among the latter group.[26] This third aspect of practicability was also part of the rationale advanced by the investigators of the NIH Health Care Systems Research Collaboratory's Time to Reduce Mortality in End-Stage Renal Disease (TiME) trial, whose proposal for the use of an altered consent process was approved by the IRB. The investigators reasoned that in a cluster-randomized trial such as TiME, randomized group assignments would be known to participants prior to enrollment; therefore, requiring traditional informed consent would likely result in imbalances in participant characteristics across the treatment groups and compromise the validity of the findings.[27]

Provision of information

The last condition for waiver or alteration of consent—that subjects be provided with additional pertinent information after participation—does not actually limit whether a waiver or alteration can be allowed. Rather, it requires that information be provided to the participant after the study, and establishes that, where appropriate, researchers will need to know which patients they have included so that they can contact them and provide relevant information. This specification was initially intended to address situations where deception was used in research in order for it to be possible. Thus, the field would benefit from greater

discussion about whether this condition is appropriate for PCTs and in situations of altered consent where some degree of informing does take place.

Alternatives to Traditional Written Informed Consent

Alternatives to obtaining full informed consent available under federal regulations comprise a broad spectrum of options. Below and in Table 2 we describe these alternatives, as well as highlighting two nontraditional methods for documenting consent—short forms and electronic consent. Additional consideration within the field is required to understand what information should be conveyed for different types of PCTs and different processes/formats for altered consent.

Waiver of consent

Complete waiver of consent means there is no decision-making on the part of participants with respect to research participation because they are not prospectively made aware of their involvement in research. Although there are circumstances where this is appropriate, the imperative to respect the autonomy interests of research participants requires that this approach be limited to cases in which the risks of participation are low and where more engaged consent options are unworkable.

“Broadcast” notification

The “broadcast” approach, wherein notices are placed in prominent locations, informs patients that they could be part of research, allows them to ask questions about their participation, and if the research is completely systematic (i.e., there is no option for non-participation at that institution/system) they can decide to seek care elsewhere. This approach honors individual decisional rights to some extent but does not provide an individualized approach to disclosure of information and consent. If used, the type and amount of messaging should be tailored to the study; for some categories of research, such as cluster-randomized trials, a general notice could be appropriate.

Integrated consent

Kim and Miller[33] recently proposed an approach that integrates clinical and research consent within the same clinical encounter. With the assent of the IRB, the prescribing physician (in the case of a drug trial) would discuss the treatment’s rationale, alternatives to the treatment, the use of randomization, and potential benefits and harms of the treatment. The physician would then either seek the patient’s approval (opt-in; with or without a written consent form) or provide an opportunity for the patient to decline (opt-out). Finally, the physician would document the conversation and its result in the patient’s medical record. This integrated approach places the decision to participate in research on a similar plane as the decision to accept a therapeutic strategy using standard clinical consent.[33] Because integrated consent does necessarily involve the use of a standard written consent form with the eight required elements, it may be appropriate for situations in which the traditional research consent process would exaggerate the decision’s importance and make it difficult or impossible to conduct the research. To our knowledge, the integrated approach has yet to be used in a PCT, and so there is much to learn about its implementation and effects.

Whether to ask participants to opt in or out of research and whether to obtain written or oral consent are decisions to be based on the nature of the study and the differences between study arms, among other considerations.

Short form consent

An alternative method of documenting consent, rather than an alteration of consent itself, is the use of a "short form" documenting that the contents of a full eight-element informed consent process (and usually, document) have been reviewed orally with a potential research subject in the presence of a witness.[8] An IRB-approved written summary of what was presented orally is also required. The short form is signed by the research subject, the witness signs the both the short form and a copy of the summary, and the person obtaining consent also signs the summary. One particular use of this approach noted by OHRP[32] is for potential research subjects who do not speak English, although the preferred solution to this problem is a consent document translated into that person's language.

Electronic consent

Another alternative means of documenting consent involves the use of electronic methods. Because electronic consent processes (vs. paper-based ones) are relatively novel, the rules governing electronic consent are currently evolving.[34] An electronic form could be created to closely mimic current paper consent documents in format and length. Alternatively, an electronic consent could take advantage of newer communication methods: for example, providing a video description of the research that is consistent, clear, and more easily assimilated than the standard written consent form.[35] The FDA has recently offered draft guidance regarding the acceptable use of e-consent as a form of informed consent process.[34] In essence, the same information should be provided as in a full consent procedure, but the mode of delivery can be electronic (on a tablet, for example), and it need not be written materials on screens, although that remains a legitimate format. The Office for Human Research Protections (OHRP) has also offered suggestions regarding the use of electronic signatures.[36] Consistent with such guidance, an approach to using electronic consent was explored in a pilot study undertaken through the NIH HCS Collaboratory (the BPMedTime study[37]). However, the approach was constrained by the same expectations of multiple required elements that pertain to standard paper-based informed consent processes. Although an electronic version of the full consent document may be desirable, particularly for studies with significant risks where a consistent presentation of information would be helpful, the regulatory framework currently being applied to electronic consent seems better suited for a paper-based process. For less risky studies, electronic consent forms that provided appropriate and focused information could be very desirable. For example, Houston et al. reported a minimal-risk study of smoking cessation in which the electronic consent process was clearly designed as a decisional aid.[38,39] However, best practices for electronic consent processes remain to be defined.

The Need for Appropriate Interpretations and Modified Regulations

An IRB's decision regarding whether or not to approve a waiver or altered consent hinges on the IRB's interpretation of "minimal risk" and "practicability." Both of these standards

are interpreted variably by IRBs; this variability has significant ramifications, particularly for multicenter research protocols. It would be useful, therefore, to have either more concrete guidance, or a change to the regulations. As we move into new paradigms for research in PCTs, we believe that minimal risk should be interpreted in such a way that standard treatments are viewed as beneficial and not as risks, and thus the bounds for what is defined as minimal risk are set more broadly. The current proposed guidance regarding standard of care research from the OHRP converts everyday circumstances into a risk, which we do not believe is in the best interest of patients.[40,41] In addition, practicability should be defined more broadly than in the recent SACHRP guidance, because there is nothing intrinsically wrong with a more concise consent document that focuses on helping potential research subjects make a sound decision regarding whether to participate. In short, the guidance and rules should be provided to enable more consistent interpretation by IRBs, and to increase their willingness to use consent processes that are designed to maximize clarity. The goal should be research subject understanding, not the successful application of rigid formula designed decades ago for a different type of research.

As an illustration of the flexibility intended by the authors of the regulations, the Common Rule (45 CFR 46.117(c)(2)) allows that the IRB may waive documentation of written consent "if it finds that the research presents no more than minimal risk of harm to subjects *and involves no procedures for which written consent is normally required outside the research context*" (emphasis added).[42] If regulations concerning waiver/alteration of consent (45 CFR 46.116(d)) were modified to include a similar stipulation concerning studies in which all interventions are standard clinical care, investigators and IRBs alike would have a clearer understanding about the ability to waive or alter consents in PCTs.

Conclusions

Conservative interpretations of the Common Rule with respect to minimal risk, practicability, and the use of waiver/alteration of consent present barriers to pragmatic clinical research. However, actual regulatory language permits individual IRBs to make nuanced determinations about the degree of incremental risk imposed by research. Regulations could be revised to make this permission even more explicit and offer additional guidance. Overly conservative interpretations of federal regulations governing altered consent pose an important but remediable barrier to conducting needed PCTs. The risks to all future patients of not knowing the most appropriate treatments constitutes are just as real as the relatively mild risks present in most pragmatic clinical trials involving standard care. Since these new approaches do make it harder to exercise personal autonomy, it is important to provide multiple forums for the patient community to learn about these new standards for research and work with them to find the most acceptable and appropriate options.

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Table 1

Eight elements of informed consent required under 45 CFR 46.116.[2]

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
(2) A description of any reasonably foreseeable risks or discomforts to the subject;
(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Table 2

Options for consent/waiver of consent.

Option	Characteristics	Examples
Complete waiver	• No attempt is made to notify or request permission from research subjects prior to participation.	Strategies and Opportunities to Stop Colorectal Cancer (STOP CRC)[28] Lumbar Image Reporting with Epidemiology (LIRE)[29] Active Bathing to Eliminate Infection (ABATE)[30]
Broadcast information	• Waiver of consent is allowed, but there is widespread public notification of the research process at the institution or in the community. • The notice may consist of a general statement that the institution engages in clinical research and that individual patients may be enrolled in research as part of their care, or it may be more specific (for example, a given category of patients may be notified they could be participating in research).	–
Integrated consent	• The question of research participation is discussed as part of the consent process for clinical care, and permission obtained for both in a manner consistent with the consent for clinical care. • The process may involve opting in or out, and giving oral or written consent as described in the following options. All 8 required elements from 45 CFR 46.116(a) would not need to be included in the consent process.	—
Simple opt-out	• Potential participants are told they will be included in the research process unless they decide not to participate. • Usually potential participants are able to opt out orally and are not required to document this decision in writing.	Time to Reduce Mortality in End-Stage Renal Disease (TiME).[27] In the TiME trial, potential participants receive written information about the trial and have access to research personnel to have questions answered and/or to opt-out.
Simple opt-In – oral	• Potential participants are asked if they would like to participate in the research and may provide oral consent. • Investigative staff would generally document that consent in the medical and/or research record (similar to Integrated Consent model).	Collaborative Care for Chronic Pain in Primary Care/Pain Program for Active Coping and Training (PPACT)[31]
Simple opt-In - written	• Potential participants are asked if they would like to participate in the research and provide written consent via a simplified consent form.	—
“Short form”	• A short form is a standardized, regulation-defined approach to informed consent that is based on 45 CFR 46.117 (b)(2) and may be used in situations in which a translator is required.[32] • Although the document that the research subject signs is shorter, the defined consent process is often longer than the use of a standard form.	—
Electronic consent	• Options include electronic tablets and Internet applications using a web browser and a laptop or desktop computer. • The electronic consent may or may not emulate a standard 8-required-element informed consent document.	—
Standard informed consent	• The consent process is conducted in person and a written informed consent form is signed by the participant.	—

Option	Characteristics	Examples
	• The informed consent form contains all 8 required elements from 45 CFR 46.116(a).	