

ALTERED INFORMED CONSENT IN PRAGMATIC CLINICAL TRIALS

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Overall

- Definition of the problem to address
- Relevant Regulations
- Ethical observations
- Models of altered consent
- Recommendations

Published Version of the Talk

Article

**CLINICAL
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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 institutional review boards 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.

Keywords

Informed consent, clinical trial, cluster-randomized trial, pragmatic clinical research, practical clinical trial, Common Rule, institutional review board, bioethics

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Definition of the Problem

Goals of informed consent

- Informed consent comes in response to Kant's imperative that a "human being should not be used as a mere means to an end"
- We ask people to volunteer to participate in research – thus, while they may be a means to an end, they understand the purpose of their participation

Belmont

- The other, more familiar formulation for our basis for informed consent comes from Belmont's expectation that research should honor "respect for persons"
- In particular, that expectation includes honoring the autonomy of individuals, the right of self-determination

Autonomy

- Autonomy is not an absolute
 - We honor laws – stop signs offer a choice, but society expects people to stop
 - In some circumstances, choices may be limited
 - Autonomy is present, but may be rarely exercised
 - For example, when a healthy person presents to an emergency room in sepsis, they could decide to refuse antibiotics, but almost no one does

Goal of informed consent

- The goal of the informed consent process is to enable a “good” decision on the part of a potential participant
- The individual should be given the information they need to make that decision freely, information which is fair and balanced and not a sales pitch

Problems with standard consent

- Many consent document are like EULAs
- A long written consent for a minor study may make the research appear more onerous and risky than justified
- The key should be to give the right amount of information to make a good decision using an optimal format for the type of study being proposed

Problems with standard consent

- Many IRBs treat informed consent as one size fits all
- There are some decisions where a short oral presentation of the options might be most appropriate but that sort of option isn't available because it's research
- We believe IRBs should be allowed, and should take, more creative approaches to helping potential participants make better decisions regarding volunteering



Relevant Regulations

The rules of informed consent

- 45 CFR 46 specifies the 8 required elements of research informed consent
 - ▣ Additional elements may be required
 - ▣ The NPRM adds even more elements
- The net result is typically long, cumbersome, and more focused on the regulations than on the objective of using the informed consent process as a means to help potential research participants make a good decision whether to volunteer

The Required Elements

Table I. Eight elements of informed consent required under 45 CFR 46.116.²

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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
 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
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The escape clause

- The common rule defines situations where informed consent may be waived
- Unfortunately the same criteria used to allow a waiver of consent apply to altered informed consent
 - ▣ **Altered consent** would allow the omission of elements of a standard informed consent document

Stipulations for waiver

□ Requires all five:

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

Waiver Element #1

- The research involves no more than minimal risk to the participants
 - Minimal risk has been inconsistently interpreted
 - “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” (45 CFR 46.102)
 - Whose daily life? A patient? A healthy person sitting in a chair? A bicycle rider? Riding where?

Minimal Risk

- Fundamentalist interpretation: a stationary healthy person – assures consistency
- Permissive interpretation: a person comparable to someone eligible for the study
- For example, a person with a urinary tract infection can expect certain risks and discomforts
 - A comparison of two standard treatments by some definitions would be minimal risk because the risks are not greater than those that would be encountered in daily life by someone living with a UTI

Waiver Element #2

- The waiver or alteration will not adversely affect the rights and welfare of the participants
- It might be argued the right most likely to be threatened by waiver is autonomy, which would incline the argument toward altered informed consent instead of waiver, but that will be debated further later

Waiver Element #3

- The research could not practicably be carried out without the waiver or alteration
- What does “practicability” mean?
- IRBs vary, from “impossible” to “really really difficult but possible” to “it would be too expensive to accomplish”
- SACHRP argued that the expense argument wasn’t tenable – I don’t agree, if the research value is sufficient (I lean consequentialist)

Waiver Element #4

- Whenever appropriate, the participants will be provided with additional pertinent information after participation
- More an issue for management of waiver than a requirement to allow it

Waiver Element #5

- ❑ Not in 45 CFR 46, but waiver of consent isn't generally allowed in FDA regulated research
- ❑ Exceptions include emergency research of a test product or planned emergency research
- ❑ An exception is allowed for research with no more than minimal risk of harm where consent would not otherwise be normally obtained (21 CFR 56.109(c)(1))



Ethics Observations

Informed consent

- In addition to enabling a good decision, a good consent process builds trust
 - ▣ Volunteers who understand why they're in research are more likely to be adherent and to complete the study
 - ▣ People don't like being surprised by "gotchas"
 - ▣ Including everything in the informed consent is not an effective way to build trust – again, see the EULA model

Ideal

- Ideally, IRBs should be able to construct the informed consent process that will optimize the decision making process
- One size does not fit all, and regulatory rigidity serves no one well
- Inconsistency in large, multi-center trials is also problematic
- How to balance flexibility and consistency well is a puzzle

Models of Altered Consent

Alternative models

- ❑ Waiver of Consent
- ❑ Broadcast notification
- ❑ Integrated Consent
- ❑ Simple Opt-out
- ❑ Simple Opt-in – oral
- ❑ Simple Opt-in – written
- ❑ Electronic Consent

Alternative models

- **Waiver of consent**

- A standard for many forms of clinical research other than trials
- Be careful about trust, autonomy, and “gotchas”

- **Broadcast notification**

- Logical for Cluster Randomized Trials
- Gives people the option to find non-participating centers as an exercise of autonomy

Alternative models

- **Integrated consent**

- Blending the clinical and the research consent
- Consider for standard of care trials

- **Simple Opt-out**

- Inform people they are included unless they choose to Opt-out
- Opt-out can be verbal but tracked

Alternative models

□ Simple Opt-in

- Can be either written or oral (the latter is similar to the integrated consent model)
- Could use shorter form than usual for the written opt-in

□ Electronic Consent

- Could be usefully performed using a tablet or PC
- Could range from simple questions to the equivalent of a full standard informed consent



Recommendations

Recommendations

- Conservative interpretations of 45 CFR 46 may make informed consent less valid
 - One size of informed consent does not fit all
- Flexibility using current regulations might enable IRBs to design consent processes that more closely match the studies for which they're intended
- For many PCTs, altered consent might better match the potential participants needs and level of risk