





Informed Consent and Respecting Autonomy

What's a Signature Got to Do with It?

BY DAVID WENDLER AND JONATHAN E. RACKOFF

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Clinical investigators and institutional review boards (IRBs) cannot ignore elements of the federal human subjects regulations they deem ethically inappropriate in particular cases. Doing so would undermine the integrity of the federal regulations, and threaten public trust in human subjects research generally. At the same moment, strictly enforcing each and every regulatory requirement can inadvertently harm subjects and inhibit the progress of important clinical research. Given that substantial revisions to the federal Common Rule are likely in the near future,¹⁻³ a solution to this dilemma that both protects subjects and facilitates biomedical discovery is urgently needed.

The federal requirement that research subjects sign informed consent documents (45 CFR 46.117a) illustrates that even ostensibly minor requirements can have unintended negative consequences. Arguments that the purpose of the signature requirement is to protect institutions and investigators⁴ raise a question for IRBs about what role, if any, the signature requirement should play in the protection of human subjects. To address this question, we consider a number of cases in which the requirement for a signature conflicts with subjects' preferences and values, poses risks to their well-being, and slows the pace of research. Based on these cases, we offer an analysis of the protections that must be in place

to ensure that subjects' consent is obtained appropriately, and the measures IRBs can approve to implement these protections.

The signature requirement has unintended negative consequences in four kinds of cases. First, it sometimes inadvertently conflicts with subjects' values. For instance, the Old Order Amish community has a long history of regarding verbal agreements as binding, leading to a cultural norm proscribing signatures on contracts. Given this tradition, many Amish view requests for a signature as insults to their personal and cultural integrity.⁵ As a result, the requirement that they sign a consent form forces them to choose between access to research versus acting in accord with their values. If enough Amish choose to act in accord with their values, some of the opportunities that this population presents for conducting important genetic research—the 75,000-130,000 Amish are descended from just 47 families—may be lost.

One might assume that the solution to this difficulty is straightforward: IRBs and investigators should simply ignore the signature requirement when its use would be inappropriate. Unfortunately, the fact that a signature is required in most cases, not simply recommended, and that the Office for Protection from Research Risks (now the Office of Human Research Protection) has taken this requirement seriously, preclude this solution. To take one example, a National Institute of Deafness and Communicative Disorders (NIDCD) working group

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report cites an international study of congenitally deaf, illiterate individuals who use a unique sign language. After the investigators developed a culturally appropriate oral consent process, OPRR blocked the proposal because it did not satisfy the signature requirement.⁶

Although one might object to this response, investigators and IRBs cannot be allowed to choose which elements of the regulations they follow and the regulations do not allow for waiver of specific requirements in individual cases. Given these difficulties, the NIDCD working group recommends revision of the federal regulations to allow "videotapes, interactive computer programs, and other oral and electronic means to obtain informed consent" for individuals who do not read or write and deaf people who do not vocalize, but could give consent using sign language.

Because research funded by the NIH must follow the U.S. regulations, conflicts between the signature requirement and subjects' values are likely to increase as U.S. investigators become more involved in areas of the world that rely on verbal agreements. Most international guidelines recognize this concern and allow IRBs to better respect subjects and their cultures by allowing alternatives to signature in particular cases. For instance, the Declaration of Helsinki states that researchers should obtain subjects' informed consent "preferably in writing,"⁷ while the Council for International Organizations of Medical Sciences (CIOMS) states that "as a general rule" investigators should obtain a signed form.⁸ Similarly, the Canadian Tri-Council states: "In some cultures, written consent is the norm whereas in others, verbal consent may not only be the norm, but it also may be regarded as the only acceptable mode of formal consent."⁹ To avoid even the appearance of cultural imperialism, the U.S. federal regulations should be amended along the same lines.

One of the classic accounts of informed consent describes a second unintended consequence of the signature requirement:

In buying a house or a car, the signature on the dotted line completes the transaction. Buyer and seller are both committed. There is usually no turning back ... The same effect can be seen in medical treatment and research. Patients often see the signed form as binding them to go through with treatment to which they have consented.¹⁰

To the extent that this understanding cannot be altered by the research team's brief clarification prior to signing, mandating a signature conflicts with the requirement that individuals be assured that research participation is voluntary. A study of chronically ill elderly people (N=67; median age = 75.5) supports this possibility, finding that 25% of potential subjects who wanted to participate refused to sign the consent form. The authors point out that some elderly subjects regard signature as implying a binding commitment and conclude that its requirement may jeopardize "the feasibility of gaining a sample that is representative of the aging chronically ill population."¹¹ Unfortunately, there is no recent data to assess this possibility fully. Indeed, as long as the signature requirement remains, studies that include alternative methods for indicating consent will violate federal law. Thus in addition to better respecting subjects, amending the regulations to include alternative processes for indicating consent would allow investigators to conduct much needed research into how the signature requirement affects subjects' understanding of clinical research.

Next, the signature requirement sometimes poses risks to subjects' confidentiality. For instance, researchers working in Uganda find that many individuals are interested in participating in clinical research, but unwilling to sign a consent form. For some Ugandans, this reluctance may trace to ambivalence over enrolling in research. For others, however, it traces to Idi Amin's reign of terror: the fear remains that signing a consent form will lead to punishment by a xenophobic government.¹² Although the

regulations recognize that signing may pose risks, they allow IRBs to waive the signature requirement in two cases only:

- (1) The only record linking the subject and the research would be the consent document and the principal risk [of the research] would be potential harm resulting from breach of confidentiality, or
- (2) The research presents no more than minimal risk and involves no procedures for which written consent is normally required outside of the research context (45CFR 46.117).

Surveys and some observational studies meet these conditions; however, many cancer chemotherapy protocols, AIDS drug trials, malaria vaccine trials, stroke treatment trials, and heart disease protocols do not. The principal risks of many of these protocols trace to the side effects of the drugs and vaccines being tested, not breaches of confidentiality; and these risks are invariably greater than minimal. Since IRBs cannot waive the signature requirement for these studies, individuals whose values conflict with signing must act contrary to these values or be barred from a significant portion of clinical research. Similarly, those whose confidentiality is placed at risk by signing a consent document must accept those risks in order to enroll in these studies.

Finally, some individuals are perfectly willing to sign, but unable to do so. For instance, the Department of Clinical Bioethics at the NIH was asked to consult regarding an individual who had complete loss of motor control of his limbs of unknown etiology. While the individual was interested in participating in research, he was unable to sign a consent form. By not allowing IRBs to approve alternative methods for subjects to indicate their consent, the regulations inadvertently block such individuals from research and investigators from the scientific information that these subjects' participation might yield. This problem could affect all those with advanced multiple sclerosis and Lou Gehrig's disease and thereby inhibit important

research on these conditions. Similarly, many individuals present to emergency rooms without their next of kin,^{13, 14} and many next of kin do not have access to fax machines that would allow them to submit their signature by phone. Recognizing this difficulty, the federal regulations allow the requirement for informed consent to be waived provided several strict requirements are met, including that the research concerns a life-threatening condition.¹⁵ Limiting the possibility for waiving informed consent in emergency situations to life-threatening conditions leaves the possibility that the need for a signature may block important research on non-life-threatening conditions. For instance, to test new drugs that might reduce the sequelae of generalized seizure if given within an hour of onset, investigators need to enroll subjects who are at the time unable to give informed consent. When these subjects present to emergency departments without their legally authorized representatives the signature requirement blocks investigators from enrolling them in this important research for no apparent scientific or ethical reason.

Taken together, these examples reveal that the difficulties with the signature requirement are neither trivial nor restricted to a few individuals. In a broad range of cases, the requirement for a signature inadvertently conflicts with subjects' values, undermines the informed consent process, poses risks to subjects, and blocks important research. To avoid these costs, the regulations should be amended to allow IRBs the flexibility to approve alternative methods for indicating consent.

Embodying the Spirit of the Regulations

Any ethically valid process for enrolling competent subjects in research must satisfy three conditions: (1) sufficient evidence that subjects who enroll want to enroll; (2) subjects' control over whether they enroll; and (3) sufficient evidence, accessible to observers independent of the research team, that conditions one and

two have been satisfied when subjects are enrolled. To avoid the unintended negative consequences of the signature requirement, the federal regulations could state these protections explicitly and then allow IRBs the flexibility to approve alternative methods to meet them.

First, clinical investigators have an obligation to respect subjects' preferences and values. To guard against unwanted enrollment in research, any ethically valid process for indicating consent must provide sufficient evidence that subjects' preferences and values favor enrollment. Next, investigators have an obligation to respect subjects' autonomy. To meet this obligation, subjects must remain in control of their enrollment in research—they must actively enroll, as opposed to being enrolled. Finally, to ensure public accountability, the consent process must provide evidence that subjects are enrolled only when these two conditions have been met. To balance the need for public accountability with respect for subject confidentiality, the consent process should be accessible to at least one, but typically no more than a few observers who are independent of the research team.

In many cases, a signature meets these three conditions. As long as subjects are well informed and able to make an autonomous choice, it seems plausible to assume that they will sign the consent form only when they want to enroll. Furthermore, stipulating that subjects must perform the action of signing their names ensures that they remain in control of their enrollment in research. Finally, since the act of signing can be observed by others, requiring a signature allows for an independent witness to verify and document that conditions one and two have been satisfied. This suggests that allowing subjects to indicate their consent by signing a consent form makes sense. However, requiring that subjects sign a consent form, particularly given that a signature conflicts with many subjects' preferences, poses risks to some subjects, blocks important research, and does not make sense unless there are no alternative processes that satisfy these conditions as well.

Fortunately, "purely oral" consent provides such an alternative.

Purely oral consent is identical to the presently mandated consent process with the exception that subjects indicate their consent by means of an explicit verbal commitment, rather than a signature. To ensure that purely verbal consent does not trivialize the consent process, it should be standardized. First, as for any consent process, the investigator must fully explain the protocol, typically based on a written script or checklist approved by the IRB. The investigator should then answer any questions. To avoid blurring discussion of the protocol with the individual's enrollment decision, purely verbal consent should include a clearly demarcated decision phase. For instance, once all questions have been answered, the investigator should allow sufficient time for deliberation and consultation before stating: "Now I would like to ask you to make an enrollment decision. Would you like to enroll in the research study we have discussed?" Assuming the individual understands and is able to make a voluntary decision, an affirmative response constitutes consent to enroll, while a negative or ambiguous response implies a lack of consent.

Indicating one's decision verbally does not produce documentation for the institution or subject in the way that signing a consent form does. To verify and provide a record that the conditions of ethically valid consent have been met, the investigator should write a note detailing the consent process that gets signed by the independent witness. In other cases, the consent process could be videotaped or audiotaped. When documentation of consent would place the subject at increased risk, investigators should instead involve an independent consent consultant, such as a member of the institution's ethics committee or IRB, to verify that the process meets the three conditions on ethically valid consent. Finally, where appropriate, subjects should be provided with a summary of the study, typically a copy of the written script or checklist used by the investigator to explain the study.

Importantly, purely oral consent provides as much evidence concerning individuals' research preferences as a signature. As long as individuals understand that a verbal choice constitutes agreement to enroll, the assumption that they will say they want to enroll only when they really do want to is as strong as the assumption that individuals will sign only when they want to enroll. Likewise, individuals can control what they say as much as they control what they sign. Thus purely verbal consent ensures that individuals remain in control of their research enrollment. Finally, since a verbal statement is accessible to others, purely verbal consent allows for an independent witness to verify and document that the "evidence" and "control" conditions have been satisfied.

Conclusion

The signature requirement provides an important example of how the need to enforce all elements of the U.S. federal human subjects regulations can conflict with the regulations' own goal of respecting subjects and supporting important research. Although these problems appear insignificant, and have been widely ignored, the signature requirement has the potential to inadvertently conflict with subjects' values, pose risks, mislead subjects, and block research. To avoid these costs, the regulations should be amended to include the three requirements for methods of indicating consent and then allow IRBs the flexibility to approve meth-

ods other than signature that implement them. This approach would allow IRBs to avoid the unintended harms of the signature requirement and, more generally, offers a way to write regulations that minimizes their unintended negative consequences.

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