Conducting Empirical Research on Informed Consent:

Challenges and Questions

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he informed consent projects (ICPs) we describe here were designed to produce (1) new and improved methods for the informed consent process, (2) methods for confronting the challenges of obtaining consent for special or vulnerable populations, and (3) data to help inform and guide public policy development (Table 1). From the outset, the project investigators identified a number of conceptual and practical concerns and challenges in conducting empirical research on informed consent. These concerns and challenges were shared by all the investigators, despite the significant variability in the research methods used and the populations studied. Experienced researchers will recognize that some of these concerns and challenges are common to many kinds of research involving human subjects. Some, however, are unique to research on informed consent. We describe these matters for the purpose of fostering ongoing dialogue about the challenges researchers face in studying the informed consent process.

Common Research Challenges

Study Design Issues. As is the case with other kinds of research, investigators who study the informed consent process face basic study design issues. Some of the ICPs examined the disclosure or informing part of the informed consent process; others focused on autonomy and decision making for research participation; and some examined the process in its entirety. The range of study designs included (1) studying factors influencing decision-making preferences of potential research subjects (sometimes using hypothetical research protocols), (2) testing innovative informed consent procedures, (3) observing the informed consent process of research being conducted by other investigators, and (4) experimenting with various informed consent methods for active clinical trials being conducted by other investigators

As with other research, tradeoffs are involved in selecting one design or another. Examining responses of potential research subjects to hypothetical protocols, for example, allows researchers the greatest control over study conditions. On the other hand, responses to hypothetical vignettes may not accurately reflect how potential subjects make decisions in real consent encounters. Surveys or interviews with participants in actual research moves a step closer to informed consent encounters as they occur, but are subject to recall, social desirability, and other forms of reporting bias.

Some of the ICPs either directly observed informed consent processes of other researchers, or audiotaped or videotaped these consent encounters. These approaches have the advantage of directly studying the events a potential research subject encounters when asked to give informed consent. On the other hand, such methods might have the unintended consequence of altering the behavior of the observed participants (i.e., "Hawthorne effects").1 Furthermore, to the extent that any of the research designs concentrated on informed consent as a single encounter, they risked missing the import of viewing informed consent as a process consisting of multiple conversations and interactions.

Approaches that rely on access to other investigators' subjects raise additional concerns because the informed consent researcher is asking an investigator and his or her staff to be subjects of an informed consent study. These concerns provoked extensive discussion among the ICP investigators and will be discussed separately below.

Another design issue not unique

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	Table 1. Nin-funded investigators and Projects				
Investigator	Co-Investigators	Institutional Affiliation	Title of Project		
Agre, Patricia	Dougherty, Holland, Kurtz, Offit, Rapkin, Wilson	Memorial Sloan-Kettering Cancer Center	A Comparison of Methods to Provide Informed Consent Information		
Broome, Marion	Liaschenko, R Nelson, Pletsch, Richards, Snethen, Stevens, Underwood	University of Alabama, Birmingham	III Children and Their Parents: Experience with Research		

Table 1 NIH-funded Investigators and Projects

Campbell, Frances	Boccia, Goldman	University of North Carolina	Improving the Consent Process for Low-Literacy Parents
Geller, Gail	Bernhardt, Tambor, Fraser, Wissow	Johns Hopkins University (Medicine)	Minors at Risk of Future Disease: Their Role in Research
Gribble, James	Bostrum, Fischhoff, Helzlsouer, Miller	Research Triangle Institute	Evaluating Informed Consent in BRCA 1/2 Screening
Kass, Nancy	J Sugarman, Fogarty, Taylor	Johns Hopkins University (Public Health), Duke University Medical Center	Improving Understanding in Early Phase Clinical Research
Kodish, Eric	L Siminoff, Drotar, Lange, Noll, Angiolillo, Ruccione, Pentz	Rainbow Center for Pediatric Ethics, Case Western Reserve University	Informed Consent in the Children's Cancer Group
Lidz, Charles	P Appelbaum, Grisso	University of Massachusetts,Worcester	Informed Consent and the Therapeutic Misconception

to the ICPs relates to the use of qualitative versus quantitative research methods. While most physician-investigators involved in clinical or health services research commonly use quantitative measures (e.g., blood pressure response to new agents), social scientists often use qualitative methods in the medical research context (e.g., analyzing subjects' responses to open-ended questions).² The pros and cons of qualitative and quantitative methods are well described elsewhere.3 Many of the ICP investigators believe that a combination of the two approaches is most appropriate in studying the informed consent process.4

Institutional Review Board **Approval.** Investigators of all kinds often view institutional review board (IRB) approval of their protocols as an obstacle to be overcome. One might presume that the ICP

investigators, some of whom are recognized experts on informed consent, ought to have knowledge and experience that would allow them to readily negotiate the IRB review process. To the contrary, many of the ICP investigators experienced more difficulty in obtaining IRB approval for the informed consent studies than they did for much higher risk research, such as cancer chemotherapy trials. We believe some of these IRB delays were attributable to the use of research methods that are routine in the social sciences but that are unfamiliar to biomedical-oriented IRBs.

Some ICP investigators involved in multi-center studies experienced significant variability in how IRBs at different institutions handled the same protocol, a common issue for all researchers conducting multi-center clinical trials.5 For example,

IRBs at three different institutions that reviewed one of the informed consent projects made suggestions for consent procedures that spanned the spectrum from simple oral consent to an extensive, multi-part written consent form.

For the project that involved randomly assigning subjects to one of four different consent methods (standard form, booklet form, video, and computer assisted instruction) the relevant IRB initially insisted that investigators approach prospective participants only after these individuals had signed a consent form for the primary clinical trial. Obtaining informed consent under this scenario would have confounded the informed consent study because study subjects would already have completed the standard informed consent process and enrolled in the primary study. After



Investigator	Co-Investigators	Institutional Affiliation	Title of Project
McCullough, Laurence	Paterniti	Baylor College of Medicine	Enhancing the Autonomy of Vulnerable Subjects of Research
McKay, Mary M.		University of Illinois, Chicago	Informed Consent in Urban AIDS and Mental Health Research
Merz, Jon F.	P Sankar	University of Pennsylvania	Informed Consent to DNA Banking for Research
Miller, Suzanne	Driscoll, Green	Fox Chase Cancer Center	Facilitating Well-Informed Decisions for BRCA Testing
Mintz, Jim	D Wirshing	UCLA	Consenting to Psychiatric and Medical Treatment Research
Meuller, Mary-Rose		University of California, San Diego	Dynamics of Informed Consent in AIDS Clinical Trials
Roberts, Laura W.	Brody, Roberts, Warner	University of New Mexico	Vulnerability and Informed Consent in Clinical Research
Sachs, Greg A.	GW Hougham, D Brauner, D Danner, W Friesen, P Whitehouse, M Patterson, D Ripich	University of Chicago, University of Kentucky, Case Western Reserve University	Dementia Research: Informed, Proxy, and Advance Consent
Siminoff, Laura	AH Weiss	Case Western Reserve University	Therapeutic Research Consent: Empirical/Ethical Analysis
Sorenson, James	T Jennings-Grant, C Lakon, T Spinney	University of North Carolina	An Experimental Study to Improve Risk/Benefit Appraisal

much discussion, the IRB approved the informed consent study as originally designed. These and other similar examples demonstrate how novel and unfamiliar empirical research on informed consent might appear to some IRBs, despite decades of ethical, legal, and regulatory analysis of informed consent.

Responding to Rapid Change in Clinical Care. Some of the ICP investigators confronted challenges to their study plans due to unexpected and significant changes in the clinical arena. Investigators with experience conducting clinical trials may have had studies altered or stopped due to new findings presented at national scientific meetings or published in medical and scientific journals. A striking example of this kind of change amongst the ICPs was a study that planned to examine informed consent in early phase research studies enrolling patients with cancer or HIV. With the tremendous success of highly active anti-retroviral therapy for HIV infection, the number of people eligible for phase I and other early stage HIV drug research plummeted. As a consequence, informed consent researchers had to make major changes in their plans to study HIV patients.

Another area in which the changing clinical scene affected at least the rate of subject accrual involved two ICPs that examined the consent process of phase III studies of drugs for Alzheimer disease. Enrollment rates for these studies slowed with the availability of three approved medications for the disease. Many patients and family members appeared less eager to enroll in studies, especially placebo-controlled trials, once even modestly effective drugs became available.

Special Challenges for Empirical Research on Informed Consent

Researchers as Gatekeepers to Subjects. Researchers conducting studies on informed consent face a number of challenges surrounding the thorny issues of recruiting, enrolling, and studying other researchers, as well as the researchers' subjects. Difficulty recruiting subjects is a common problem in all kinds of human subjects research.⁶ Investigators often need the cooperation or "buy-in" of clinicians caring for patients who are potential subjects of trials. For those of us studying informed consent, there were added layers of complexity. We had to gain cooperation of clinical researchers, clinical providers, and patient-subjects-all

who were in some ways "subjects" of the ICP investigators. On the simplest level, this meant that clinical researchers functioned as gatekeepers to our access to the informed consent process. From the standpoint of those interested in studying informed consent, the more people who can say "no" along the way, the greater the difficulty in conducting adequate numbers of studies and recruiting adequate numbers of subjects.

The ICP investigators were also faced with the problem of selection biases, some operating potentially on more than one level. None of the ICP investigators attempted to study a randomly drawn sample of research projects. The methods used to select the clinical investigators to approach for our studies introduced a number of potential biases. Investigators who were willing to allow us to examine, or even modify, their informed consent procedures may have been a self-selected group, perhaps those most confident that they were already doing a good job with informed consent. It is also possible that selection bias entered if a clinical researcher selected or limited the trials made available for scrutiny. For example, one ICP investigator met with resistance to inclusion of protocols paid for by pharmaceutical companies due to concerns about "ownership" of participants and data involved in these trials.

Similarly, clinical researchers might have limited our access to subjects or pre-selected subjects from their trials for participation in ICP studies. Some researchers might have altered their selection practices to recruit more clearly competent subjects because they anticipated that subjects would be closely observed and perhaps subjected to formal testing of comprehension. Researchers might also have limited our access to subjects due to concerns about potential additional burdens or distress for their research subjects in an effort to avoid risking higher refusal or attrition rates in their own studies. Conversely, one ICP investigator had to decide how to respond to a research colleague who was seemingly overly cooperative in referring subjects for the informed consent study. The ICP investigator was concerned that the individuals the colleague referred would never have considered declining to participate. Some ICP investigators thought it best to have their own staff responsible for recruitment to avoid these potential problems.

We also recognized that clinical research staff and subjects might alter their behavior during the consent process simply because they knew they were being observed. For example, the clinical research staff might improve their standard consent process to the extent that potential differences between standard and innovative consent methods would be obscured. This could result in false negative study conclusions-deciding an intervention does not improve the consent process and thus abandoning it because of a ceiling effect induced by the studies themselves. An effect such as this is troubling because the improvements in the standard consent process on the part of the clinical research staff might not continue once observation by ICP investigators ended.7

One ICP investigator pointed out that tensions between clinical researchers and investigators studying informed consent could be traced to understandable concerns about self-interest and personal agendas. Clinical researchers presumably have an interest in demonstrating that "problems" with the consent process are either non-existent, less serious than thought, or remediable; ethics researchers arguably have an agenda to find issues worthy of thought, debate, and remediation. The challenge to the ICP investigators was to remain objective in the face of widespread

acceptance of the tenet that "the process is broken" and that various populations are "at risk" or "vulnerable," including those deemed to have decisional impairments.

Researchers as Subjects of Informed Consent Research. We also encountered a number of concerns related to the role of clinical researchers as subjects of the informed consent studies, rather than merely as gatekeepers to their patient-subjects. First, some of the ICP investigators reported that a number of clinical researchers were reluctant to be observed during informed consent processes, perhaps fearing being judged, critiqued, or having negative actions taken against them, their research, or their

institutions if serious shortcomings

were found. Second, though we promised confidentiality for subjects in the ICP studies, the clinical researchers were, in fact, at greater risk of having their confidentiality violated because they were more readily identifiable than typical research subjects. Many ICP investigators studied convenience samples of researchers at their own institutions. Depending on the size of the institution, the numbers of clinical researchers involved, and the nature of the clinical trials being studied, it is possible that the description of a clinical research protocol might make a researcher identifiable to knowledgeable readers, including funding agencies and research ethics monitors. Some ICP investigators informed the clinical researchers of this potential violation of confidentiality, even if they were not using a formal, written informed consent process for the researchers' participation. One ICP investigator urged that those studying informed consent routinely try to involve more than one institution in their work in order to provide greater anonymity to the clinical researchers under study.

Third, some clinical researchers



We also recognized that an improved informed consent process might increase enrollment or subject retention, especially if the improved process resulted in a better match between a subject's expectations and his or her experience within the study. Some clinical researchers were concerned specifically that our methods might be either too intrusive or too burdensome (e.g., video or audio taping). They feared that overwhelmed subjects might decline participation in both the informed consent study and the clinical research. For example, some complex oncology protocols presented multiple consent forms to prospective subjects prior to an ICP investigator introducing his or her own procedures or documents to empirically study the informed consent process. Disrupting patient flow in clinics or the process of counseling for genetic testing were two other concerns raised by some of the ICP investigators.

■ Informed Consent to Study

Informed Consent. Obtaining informed consent to study informed consent was an interesting phenomenon encountered by the ICP investigators. Some of the issues discussed regarding our own informed consent processes related to the type of consent required for this kind of research (written consent versus oral consent versus consent requirements being waived), and how IRBs were dealing with these issues around the country.

As mentioned above, for those of us either observing other researchers or intervening in someone else's research, there were many questions about obtaining the informed consent of clinical investigators and their research staff. What exactly are the potential risks and benefits to researchers who permit other researchers access to their work? Certainly, there are risks related to potential violations of confidentiality, especially in cases where problems with the consent process are uncovered. Moreover, if the informed consent study involved comparing different procedures for obtaining informed consent, could the clinical research staff reliably implement the alternative methods without contamination? Could clinical research staff be kept blinded to informed consent study procedures and interim analyses?

An early concern raised by some ICP investigators was the complexity of our informed consent procedures, especially for those of us whose subjects were also enrolling in clinical trials. Some of us were trying to explain to patients newly diagnosed with cancer or some other serious illness that we wanted their permission to randomly assign them to different consent processes that would be embedded in their being randomly assigned to one treatment regimen or another.

Situations like this complicate the already challenging task of explaining the primary clinical trial.8 One ICP investigator described asking patient-subjects eligible for cancer trials about their willingness to be in her informed consent study, which involved interviewing the patients about what they understood concerning cancer trials just described to them by oncology staff. For this researcher, it was somewhat disconcerting to have patient-subjects pick up the consent form for the informed consent study, sign it without reading it, smile, and say, "I don't need to read this, I trust you." Did they do the same when asked to participate in the cancer trial, and if they did, should this worry us? This encounter highlights the importance

of trust in the informed consent process, a factor potentially both more powerful and less well examined than aspects of disclosure and comprehension studied in so much of the empirical research on informed consent.⁹

When to Intervene? Some ICP investigators struggled with concerns about what they should do if they thought the clinical researchers they were observing were engaging in suboptimal, problematic, or potentially unethical practices during the informed consent process.¹ ° Some ICP investigators said they would feel morally obliged to intervene in such cases. Others expressed concerns about acting as the "ethics police" and potentially damaging their relationships with researchers who had allowed the observations to be made in the first place, perhaps even threatening their ability to conduct the informed consent studies altogether.

Several ICP investigators with extensive experience on their home IRBs suggested that although the content might be different, this issue does have a parallel in clinical trials. In clinical trials, thoughtful researchers disclose to subjects that a trial may be discontinued (or a particular subject's participation ended) for various predetermmined reasons, including uncovering new, clinically relevant information or because of results from other studies. For example, in a study to determine the prevalence of depression in nursing homes, investigators needed to decide how to handle the information when patients were found to be depressed on their screening exams and the depression had not been detected or treated by the patient's clinician.11

We wondered if informed consent researchers could develop in advance of going into the field a similar list of criteria and procedures for intervening. One ICP investigator suggested that ethics researchers ought to be held to a higher level of ethics accountability as leaders and potential role models within our respective institutions. Anticipated difficulties and responses could be disclosed to the IRB and communicated to researchers and other subjects during the informed consent process. Even with this disclosure, some ICP investigators expressed concerns about trying to balance duties to different parties in the research enterprise, especially with respect to clinical investigators who are subjects of informed consent research.

Anticipating the Public Policy

Implications. The final area for discussion is the importance of informed consent researchers giving careful and early consideration to the implications of their research findings, including how various stakeholders might use their findings. The scrutiny of research ethics is increasing steadily in the United States.12 Major medical centers have had their research operations suspended due to inadequate review of research or other ethical improprieties. To use language from a recent review, we are clearly moving toward an era of "strong protectionism" in human subjects research.¹³ However, the consequences of such a move will bring added costs, increased complexity, and possibly a halt to some kinds of research altogether.14 Everincreasing requirements on IRBs for ongoing review of research and other new regulations add to the work of those overseeing research. Findings of the ICPs that revealed deficiencies in an informed consent process could be used by interested parties to advocate for additional regulations, alterations in funding for some kinds of research, or other ends not intended by the ICP researchers.

One ICP investigator told of his difficulties getting results of an earlier study published. The paper reported some ethical concerns about research conducted in a specific setting. One reviewer at a prestigious journal referred to existing difficulties involved in conducting research in that setting, and contended that the difficulties would be exacerbated by publication of the ethics report. The other manuscript reviewer expressed concerns about the potential impact of the paper on funding for research in that particular setting. On the other hand, how would various stakeholders and interest groups (policy, science, or advocacy) respond to a study that found "no" or "little" evidence of problems with the informed consent process? It is clear that research on informed consent is rife with important policy and political ramifications.

Conclusion

W7e have discussed many of the challenges involved in conducting empirical research on informed consent. Some of these, such as the issues involved in relying on the cooperation of clinical researchers for access to the consent processes of their studies and having those researchers as subjects of the research on informed consent, do not have simple solutions. Like much of clinical research, there likely will be an ongoing tension in informed consent research between goals and a balancing of benefits and burdens of the various strategies used to address these issues.

Despite these challenges and concerns, the ICP studies have produced interesting and important findings. Some of these hold the promise of final products, such as an assessment instrument or an innovation to the informed consent process, that can be applied to other settings and potentially enhance the informed consent process.

One observation from the studies is that regardless of the subject population or type of research, the informed consent process appears to start far earlier than the encounter at which the consent form is signed. The process tends to be step-wise as information about the proposed research is framed, shared, and processed. By the time an official consent encounter takes place, subjects may already have made their decision about enrollment. Federal regulations that would bring greater scrutiny to the informed consent encounter itself may miss important social and even cultural dimensions about how subjects and researchers are brought together starting with initial, tentative, and often informal inquiries. Our research findings may generate new questions and challenges, even as we help answer existing questions about the informed consent process.

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