Points to Consider when Reviewing Research with Vulnerable Populations Not Explicitly Protected in CFR
(from OHRP Institutional Review Board Guidebook: Chapter VI, Special Classes of Subjects)

TRAUMATIZED AND COMATOSE PATIENTS

Do the anticipated benefits to the subjects justify proceeding with the research even though it is not possible to obtain their prior informed consent?

Proceeding without prior informed consent is acceptable only for minimal risk research under DHHS regulations and in life-threatening situations under FDA regulations.

Is there a need for additional monitoring, either of the consent process or the conduct of the research itself?

If a preliminary consent procedure is employed, what amount of time should reasonably be allowed to elapse before requiring that a valid consent be obtained or the subject be removed from the study?

Is consent from the patient's next-of-kin required? Is it sufficient?
As Data Overflows Online, Researchers Grapple With Ethics

By VINDU GOEL  AUG. 12, 2014

Scholars are exhilarated by the prospect of tapping into the vast troves of personal data collected by Facebook, Google, Amazon and a host of start-ups, which they say could transform social science research.

Once forced to conduct painstaking personal interviews with subjects, scientists can now sit at a screen and instantly play with the digital experiences of millions of Internet users. It’s the frontier of social science — experiments on people who may never even know they are subjects of study, let alone explicitly consent.

“This is a new era,” said Jeffrey T. Hancock, a Cornell University professor of communication and information science. “I liken it a little bit to when chemistry got the microscope.”

But the new era has brought some controversy with it. Professor Hancock was a co-author of the Facebook study in which the social network quietly manipulated the news feeds of nearly 700,000 people to learn how the changes affected their emotions. When the research was published in June, the outrage was immediate.

Now Professor Hancock and other university and corporate researchers are grappling with how to create ethical guidelines for this kind of research. In his first interview since the Facebook study was made public, Professor Hancock said he would help develop such guidelines by leading a series of discussions among academics, corporate researchers and government agencies like the National Science Foundation.

“As part of moving forward on this, we’ve got to engage,” he said. “This is a giant societal conversation that needs to take place.”
Scholars from M.I.T. and Stanford University are planning panels and conferences on the topic, and several academic journals are working on special issues devoted to ethics.

Microsoft Research, a quasi-independent arm of the software company, is a prominent voice in the conversation. It hosted a panel last month on the Facebook research with Professor Hancock and is offering a software tool to scholars to help them quickly survey consumers about the ethics of a project in its early stages.

The Federal Trade Commission, which regulates companies on issues like privacy and fair treatment of Internet users, is also planning to get involved. Although the agency declined to comment specifically on the Facebook study, the broader issues touch on principles important to the agency’s chairwoman, Edith Ramirez.

“Consumers should be in the driver’s seat when it comes to their data,” Ms. Ramirez said in an interview. “They don’t want to be left in the dark and they don’t want to be surprised at how it’s used.”

Facebook, which has apologized for its experiment, declined further comment, except to say, “We’re talking with academics and industry about how to improve our research process.”

Much of the research done by the Internet companies is in-house and aimed at product adjustments, like whether people prefer news articles or cat videos in their Facebook feeds or how to make Google’s search results more accurate.

But bigger social questions are studied as well, often in partnership with academic institutions, and scientists are eager to conduct even more ambitious research.

The Facebook emotion experiment was in that vein. The brainchild of a company data scientist, Adam D. I. Kramer, but designed and analyzed with help from Professor Hancock and another academic researcher, Jamie E. Guillory, it was intended to shed light on how emotions spread through large populations. Facebook deliberately changed the number of positive and negative posts in the subjects’ news feeds over a week in January 2012, then looked at how the changes affected the emotional tone of the users’ subsequent Facebook posts.

In another well-known experiment, Facebook sent voting reminders to 61 million American users on Election Day in 2010. Some users also saw a list of their friends who said they had already voted, and the researchers found that the
specific social nudge prompted more of those people to go to the polls. The study prompted some to suggest that Facebook had the power to sway election results.

Such testing raises fundamental questions. What types of experiments are so intrusive that they need prior consent or prompt disclosure after the fact? How do companies make sure that customers have a clear understanding of how their personal information might be used? Who even decides what the rules should be?

Existing federal rules governing research on human subjects, intended for medical research, generally require consent from those studied unless the potential for harm is minimal. But many social science scholars say the federal rules never contemplated large-scale research on Internet users and provide inadequate guidance for it.

For Internet projects conducted by university researchers, institutional review boards can be helpful in vetting projects. However, corporate researchers like those at Facebook don’t face such formal reviews.

Sinan Aral, a professor at the Massachusetts Institute of Technology’s Sloan School of Management who has conducted large-scale social experiments with several tech companies, said any new rules must be carefully formulated.

“We need to understand how to think about these rules without chilling the research that has the promise of moving us miles and miles ahead of where we are today in understanding human populations,” he said. Professor Aral is planning a panel discussion on ethics at a M.I.T. conference on digital experimentation in October. (The professor also does some data analysis for The New York Times Company.)

Some scientists had been thinking about these issues for several years, but the discussions have boiled over since the Facebook experiment.

“It’s the case study we’re all talking about,” said Lucy Bernholz, a visiting scholar at Stanford’s Center on Philanthropy and Civil Society, who is organizing a conference in September on the ethics of digital data, including what limits should be placed on its use.

Mary L. Gray, a senior researcher at Microsoft Research and associate professor at Indiana University’s Media School, who has worked extensively on ethics in social science, said that too often, researchers conducting digital experiments work in isolation with little outside guidance.
She and others at Microsoft Research spent the last two years setting up an ethics advisory committee and training program to provide guidance to researchers in the company's labs who are working with human subjects. She is now working with Professor Hancock to bring such thinking to the broader research world.

"If everyone knew the right thing to do, we would never have anyone hurt," she said. "We really don't have a place where we can have these conversations."

Dr. Gray advocates a simple litmus test for researchers: If you're afraid to ask your subjects for their permission to conduct the research, there's probably a deeper ethical issue that must be considered.

For Professor Hancock, solutions could include an opt-in process for projects that involve big changes in an Internet user's experience, and a debriefing system to inform users about smaller tests after the fact.

Companies won't willingly participate in anything that limits their ability to innovate quickly, he said, so any process has to be "effective, lightweight, quick and accountable."

While some would say the risks of the Facebook study were obvious, Professor Hancock said the researchers didn't realize that manipulating the news feed, even modestly, would make some people feel violated.

He learned otherwise from hundreds of anguished and angry emails he received after the work was published. "They said, 'You can't mess with my emotions. It's like messing with me. It's mind control.' "

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Consent and the Autonomy of Human Subjects

by Elisa A. Hurley, PhD, Executive Director

We all know that designing a mechanism for obtaining valid informed consent is a perennial challenge, but it seems to be receiving special and renewed interest lately.

The United States Food and Drug Administration (FDA) recently released a draft guidance, *Informed Consent Information Sheet: Guidance for IRBs, Clinical Investigators, and Sponsors*, for public comment. The draft is intended to replace the FDA’s previous, and much briefer, guidance on informed consent, which dates from 1998. Throughout the new draft guidance, the FDA emphasizes that informed consent involves more than a form, and encourages investigators, IRBs, and sponsors to think of informed consent as a dynamic process that can be adapted to reflect the unique needs of potential subjects, as well as local context.

The introduction to the FDA draft states it plainly:

“To many, the term informed consent is mistakenly viewed as synonymous with obtaining a subject’s signature on the consent form. FDA believes that obtaining a subject’s oral or written informed consent is only part of the consent process. Informed consent involves providing a potential subject with adequate information to allow for an informed decision about participation in the clinical investigation, facilitating the potential subject’s comprehension of the information, providing adequate opportunity for the potential subject to ask questions and to consider whether to participate, obtaining the potential subject’s voluntary agreement to participate, and continuing to provide information as the clinical investigation progresses or as the subject or situation requires. To be effective, the process must provide sufficient opportunity for the subject to consider whether to participate.”

PRIM&R has long championed this approach to thinking about informed consent, and we commend the FDA for recognizing that this guidance document can be used to foster improved understanding of the purpose and goals of informed consent. PRIM&R will submit comments to the FDA on the draft guidance, and I encourage you to share your thoughts and comments on the guidance, along with those on other topics, at the end of this post.

Additionally, the Secretary’s Advisory Committee on Human Research Protections (SACHRP), the body charged with making recommendations to the Secretary of Health and Human Services regarding human subjects protections issues, devoted a full quarter of its July 2014 meeting agenda to a discussion of the informed consent process, in a session aptly titled, *Informing Informed Consent: Defining and Validating Comprehension*.

There is a common thread between these two examples—a renewed emphasis on the role and importance of subject understanding in the consent process.

The FDA draft guidance focuses on the importance of consent documents being written in language understandable to subjects, and includes expanded sections on informed consent with respect to non-English speakers. The SACHRP session concentrated on barriers to

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subject comprehension, including the fact that therapeutic misconception persists despite increasingly well-informed efforts to educate potential subjects about the purposes of research.

These points are well taken: empirical research dating back to the 1980s consistently shows that research subjects have limited understanding of study information (Falagas et al., 2009; King and Heubi, 2014), and that consent forms are often to blame. Long, dense, and technically written consent documents do a better job of legally protecting research institutions than enabling potential subjects to make informed decisions about research participation. And while legal protection is important for both the subject and the institution housing the research, the focus on avoiding future litigation puts the interests of the institution above the interests of individuals who are being asked to take on sometimes significant risks for the sake of, at least primarily, generating scientific knowledge. Without subject comprehension, consent can’t meet its intended goal: to afford potential research subjects the opportunity to autonomously agree to participate in a research study, with full and well-considered knowledge of all that participation entails.

None of this is news, of course. And valiant efforts are being made to offer empirically grounded recommendations about how to improve both consent forms and processes, precisely to increase subject comprehension (Nishimura et al., 2013; Koyfman et al., 2009; Stunkel et al., 2010; Kass et al., 2011). But attending the SACHRP meeting and then shortly afterward working on PRIM&R’s comments on the FDA guidance, got me thinking about the tenacity of the problems around subject comprehension in informed consent. This led me to reflect on another practice around consent I’ve noticed and always objected to: the use of “consenting” as a transitive verb – as in, “we consented the subject into the study….” This may seem like a minor detail; in fact you hear it all the time. But I think this way of speaking reflects the same general attitude toward consent that results in overly lengthy, poorly constructed consent forms: that it’s something done to subjects so that research can get started.

Thinking this way does real violence to the very idea of what consent is supposed to do: respect, acknowledge, and invoke the agency of potential research subjects as they think about and knowledgeably decide whether they want to participate in research. Again, the phrasing may seem like a small detail, but words matter. They convey an attitude. In this case, it’s an attitude reflective of a more general corruption of the spirit of informed consent, namely, that in practice, on the ground, there is not enough regard for its role as our primary mechanism for respecting the autonomous, informed choices of individuals to participate in this important endeavor we call research.

What do you think? Is this an issue of mere semantics, or a point requiring a culture change? What are your reactions to the FDA’s draft guidance? And what are some best practices you’ve seen or used to foster subject comprehension during the informed consent process?
Sham Controls in Medical Device Trials

Rita F. Redberg, M.D.

When a drug is found, after being approved by the Food and Drug Administration (FDA), to have unacceptably dangerous side effects or insufficient therapeutic benefits to outweigh its risks, patients can discontinue its use. But what if the approved therapy that is later discovered to be ineffective or unsafe is an invasive procedure or an implanted medical device? Patients who have already undergone the procedure were put at unwarranted risk, and those with an ineffective or dangerous implanted device must decide whether to leave it in their body or incur the risk associated with another procedure in order to remove it. In this sense, medical procedures and devices pose potentially greater harm to patients than drugs do.

Approval standards for high-risk medical devices, however, are generally less rigorous than those for pharmaceuticals. Only 1% of all medical devices reach the market through the premarket-approval route — the only pathway that requires the submission of clinical data. Research has shown that premarket approvals are often based on data from one small trial that used surrogate end points and included only short-term follow-up.1 Blinded, randomized, controlled trials (RCTs), in which the proposed therapy is compared with a placebo or a “sham” (nontherapeutic) intervention, are common for drugs but rare for medical devices. The lack of such trials for devices is, in part, to the understandable reluctance to conduct a trial in which some patients are subjected to a sham procedure or implant. However, it has long been established that benefits do not have to accrue to all patients in a clinical trial.

In light of mounting evidence that medical procedures can produce a strong placebo effect that can be mistaken for actual effectiveness, I believe it is time for more frequent use of interventional trials in which patients are unaware of their randomized assignment.

For example, on the basis of unblinded trials, a catheter-based radiofrequency ablation of the renal arteries, known as renal-artery denervation, was thought to lower blood pressure. The recent SYMPLICITY trial, however, found renal-artery denervation had no beneficial effect on blood pressure beyond that achieved with a sham procedure.2 Although the reasons for this lack of benefit will be debated for some time, this important result would not have been discovered without use of a nontherapeutic intervention.

Debate over the ethics of performing a sham procedure or surgery dates back more than 15 years to double-blind trials of fetal-tissue transplantation for Parkinson’s disease, discussed by Freeman et al. (1999). The sham procedure involved making twist-drill holes in the patient’s forehead and was considered necessary and ethical for determining whether there was an effect of treatment beyond the placebo effect (there was not). The institutional review board believed that the risks of sham surgery had to be weighed against the greater risks of mistakenly believing an invasive procedure to be useful because of its placebo effect. Indeed, had there been no trial including sham surgery, many Americans with Parkinson’s disease might be receiving craniotomies for only a placebo benefit.

Another important lesson on the value of sham controls came from vertebroplasty, a procedure in which bone cement is injected into a fractured vertebra for treatment of a compression fracture. Vertebroplasty became popular in the early 2000s, on the basis of observational studies and a nonrandomized trial. Fueled by position statements from various U.S. radiologic and neurologic surgical societies arguing the benefits of these procedures, the number of vertebroplasties performed in Medicare patients nearly doubled between 2001 and 2005, increasing from 45.0 to 86.8 per 100,000 enrollees.3 In 2009, however, RCTs that included a group assigned to receive a nontherapeutic procedure found that pain relief in the sham-procedure group was no different from that in the group that received the actual procedure.4 These examples establish not just ethical precedent but also the importance of comparing device-based interventions and surgeries with an equivalent sham control.

It’s important to understand the power of the placebo effect. Researchers at the Institute of Medical Psychology in Munich recently quantified that power for various types of placebo treatments in studies of migraine prophylaxis. They found that 58% of patients had a positive response to sham surgery and 38% had a
positive response to sham acupuncture, while only 22% had a positive response to oral pharmacologic placebos.\(^5\) This research shows not only an astonishingly high response rate for sham procedures, but also a significantly higher response rate for placebo physical interventions than for placebo drugs. These results highlight the importance of devising a control that will sufficiently distinguish the specific effect attributable to the placebo.

Not all device trials necessarily require nontherapeutic controls. For example, after a therapeutic benefit beyond the placebo effect was established, subsequent iterations of a device would not need to be compared with a sham control. In addition, trials with only objective end points, such as mortality, do not need a nontherapeutic control. Interventional studies that would most appropriately be conducted as blinded RCTs include early studies of a new technology and studies whose primary outcome measure is susceptible to a placebo effect, such as pain.

For example, percutaneous coronary intervention (PCI), a widely used procedure for treating stable coronary artery disease, has never been investigated in a blinded trial. Some nonblinded RCTs have shown that PCI has a beneficial effect on anginal symptoms, but there appears to be no difference between PCI and medical therapy in rates of the objective end points of nonfatal myocardial infarction and death due to cardiac causes. It is possible, therefore, that the perceived symptomatic benefit is actually a placebo effect and not attributable to PCI. Although a blinded trial would be relatively straightfor-ward if two groups of patients were randomly assigned to a cardiac catheterization procedure, as was done for renal-artery denervation, such a study has yet to be performed, and the important question of PCI's actual clinical benefit therefore remains unanswered.

Subjecting patients to sham procedures is not without risk, and it gives rise to ethical concerns about “unnecessary” invasive procedures that will have no actual therapeutic effect. I believe, however, that the examples above show that sham interventions are ethical when the benefits of information from a sham-control trial exceed the risks of using an intervention not shown to be more therapeutic than a sham. Moreover, the risk associated with performing unnecessary procedures should be weighed against the risk of mistaking a placebo effect for therapeutic benefit and therefore subjecting thousands or millions of patients to a procedure that actually does them no good. In a controlled trial, patients are informed of and consent to the risks; when an ineffective procedure is accepted into practice, however, patients who subsequently undergo it most certainly have not knowingly consented to an ineffectual procedure. Without careful use of nontherapeutic controls, we may be subjecting millions of Americans to harm from risky, invasive procedures without benefit. Ethical concerns regarding a placebo group should, of course, be acknowledged and addressed by institutional review boards and through informed consent, as they are in drug trials and have been in the examples above.

In the SYMPLICITY trial, the risks were weighed and managed. There were risks associated with the sham control, which included a femoral-artery puncture and renal angiography. However, the finding that the procedure lacks any apparent benefit will spare many patients from undergoing a risky procedure that apparently has only placebo value. There are clear benefits of preventing ineffective procedures and devices from gaining widespread use, which means that true therapeutic benefit should be established before FDA approval.

The SYMPLICITY trial thus adds to mounting evidence that medical procedures can have a substantial placebo effect. This knowledge may require Congress to articulate a clear standard for establishing true therapeutic benefit for FDA approval, to ensure that all devices we provide to our patients are safe and effective.