

**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)

TERMINALLY ILL PATIENTS

Must the research involve terminally ill patients to achieve its objectives?

Does the ICF include:

- A clear explanation of the patient's eligibility for the study
- Specific treatment alternatives, including the option of no treatment
- Realistically, simply stated benefits and risks (and their probability)
- Clearly described ways in which participation may affect the patient's lifestyle (e.g., "You will be hospitalized each month for 5-7 days.") ?

If withdrawal from the research will result in a patient's discharge from a research unit or end the patient's access to health care that has been provided in conjunction with the research, is that fully explained?

Should a witness or patient advocate be present during the consent process?

Is there reason to require that the patient's physician not be the clinical investigator?

If the research is done under a Treatment IND or other expanded access mechanism, is the lack of conclusive effectiveness data made clear?

Are all costs to subjects of receiving a drug or device under an expanded availability mechanism clearly specified?

If a drug is administered at the community level, does the subject's physician have access to information about the drug's potential usefulness and potential risks?

The Opinion Pages | OP-ED CONTRIBUTOR

The University of Minnesota's Medical Research Mess

By CARL ELLIOTT MAY 26, 2015

MINNEAPOLIS — IF you want to see just how long an academic institution can tolerate a string of slow, festering research scandals, let me invite you to the University of Minnesota, where I teach medical ethics.

Over the past 25 years, our department of psychiatry has been party to the following disgraces: a felony conviction and a Food and Drug Administration research disqualification for a psychiatrist guilty of fraud in a drug study; the F.D.A. disqualification of another psychiatrist, for enrolling illiterate Hmong refugees in a drug study without their consent; the suspended license of yet another psychiatrist, who was charged with “reckless, if not willful, disregard” for dozens of patients; and, in 2004, the discovery, in a halfway house bathroom, of the near-decapitated corpse of Dan Markingson, a seriously mentally ill young man under an involuntary commitment order who committed suicide after enrolling, over the objections of his mother, in an industry-funded antipsychotic study run by members of the department.

And those, unfortunately, are just the highlights.

The problem extends well beyond the department of psychiatry and into the university administration. Rather than dealing forthrightly with these ethical breaches, university officials have seemed more interested in covering up wrongdoing with a variety of underhanded tactics. Reporting in *The Star Tribune* discovered, for example, that in the felony case, university officials hid an internal investigation of the fraud from federal investigators for nearly four years.

I hope that the situation at the University of Minnesota is exceptional. But I know that at least one underlying cause of our problems is not limited to us: namely,

the antiquated bureaucratic apparatus of institutional review boards, or I.R.B.s, which are supposed to protect subjects of medical experimentation. Indeed, whether other institutions have seen the kinds of abuses that have emerged at the University of Minnesota is difficult to know, precisely because the current research oversight system is inadequate to detect them.

The current I.R.B. system of research protection arose in the 1970s. At the time, many reformers believed the main threat to research subjects came from overambitious government and university researchers who might be tempted to overlook the welfare of research subjects.

As a result, the scheme put in place for protecting subjects was not a formal regulatory system but essentially an honor code. Under the I.R.B. system, medical research studies are evaluated — on paper — by a panel of academic volunteers. I.R.B.s do not usually monitor research as it is taking place. They rarely see a research subject or even a researcher face to face. Instead, they simply trust researchers to tell the truth, report mishaps honestly and conduct their studies in the way that they claim to be conducting them.

These days, of course, medical research is not just a scholarly affair. It is also a global, multibillion-dollar business enterprise, powered by the pharmaceutical and medical-device industries. The ethical problem today is not merely that these corporations have plenty of money to grease the wheels of university research. It's also that researchers themselves are often given powerful financial incentives to do unethical things: pressure vulnerable subjects to enroll in studies, fudge diagnoses to recruit otherwise ineligible subjects and keep subjects in studies even when they are doing poorly.

In what other potentially dangerous industry do we rely on an honor code to keep people safe? Imagine if inspectors never actually set foot in meatpacking plants or coal mines, but gave approvals based entirely on paperwork filled out by the owners.

With so much money at stake in drug research, research subjects need a full-blown regulatory system. I.R.B.s should be replaced with oversight bodies that are fully independent — both financially and institutionally — of the research they are overseeing. These bodies must have the staffing and the authority to monitor research on the ground. And they must have the power to punish researchers who break the rules and institutions that cover up wrongdoing.

Here at the University of Minnesota, we have reached a critical point. Two months ago, after two blistering external investigations, university officials finally agreed to suspend recruitment for psychiatric drug studies. Yet they still refuse to admit any serious wrongdoing.

An honor code is a fragile thing. All the parts have to be in place: pride in the integrity of an institution, vigilant self-policing, a collective sense of shame when the code is violated and a willingness to punish those who break it. At the University of Minnesota, we have very few of those things. And so without sustained, relentless pressure from the outside, I am afraid we are doomed to more of the same.

Carl Elliott, a professor at the Center for Bioethics at the University of Minnesota, is the author of “White Coat, Black Hat: Adventures on the Dark Side of Medicine.”

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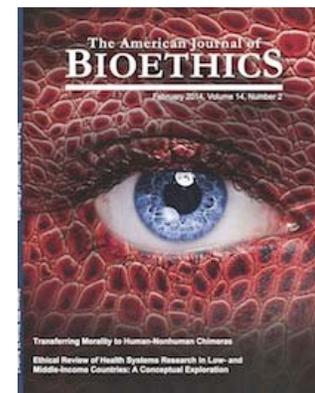
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RESEARCH 2.0: RISE OF THE CITIZEN-SCIENTIST AND THE DEATH OF PRIVACY
([HTTP://WWW.BIOETHICS.NET/2015/03/RESEARCH-2-0-RISE-OF-THE-CITIZEN-SCIENTIST-AND-THE-DEATH-OF-PRIVACY/](http://www.bioethics.net/2015/03/research-2-0-rise-of-the-citizen-scientist-and-the-death-of-privacy/))

by Craig Klugman, Ph.D.

On Monday I attended a symposium on inter-professional education. During a session on new technologies in medicine (telemedicine, wearables, and mobile devices) I brought up the question of preserving privacy. The foundation sponsoring the event replied to me, "There is no such thing as privacy. It's dead." For someone who works in bioethics, serves on an IRB, and was formerly a journalist, this notion is scary. Perhaps, I have simply been in denial. After all, I use a mobile phone that tracks my position, synchs with the cloud, and provides much convenience. In exchange, my information is collected, analyzed, sorted, and used for marketing and more.

Another sign of the end of privacy is the Open Humans Network, a project of the Harvard Personal Genome Project. The project has researchers at Harvard, NYU, and UC San Diego backed by grants from the Knight Foundation and Robert Wood Johnson. The project seeks to connect people willing to share their personal information with researchers on an open platform.

"The value of sharing data is abundantly clear, and technical barriers are now surmountable thanks to the Internet and advances in information technology. The remaining barriers are legal and ethical, not technical." (https://www.openhumans.org/static/public-data/docs/Research_Protocol_20141212_2aaedae6aee9.pdf) The study protocol goes on to explain that promises of privacy "restrain" researchers in "data silos." Such "silos" mean there are limitations on sharing data between studies and researchers on different projects, between subjects, and with the public.

If that was not concerning enough, consider that participants are called "members" not subjects. This makes people feel more like part of a club rather than an object of study. People can share demographic information, genomic data, and location data. This is enough information for someone to re-identify participants. (<http://www.bioethics.net/2013/01/whose-dna/>)

Members select what information to share and what to keep private. These choices can be made for their public profiles as well as for each research study. They can choose which research studies they want their data to be used in (there are three at the moment). Members' identities are publicly available and mini-profiles allow them to share what studies they are involved with. As the consent form says:

"When you share data publicly on the Open Humans website, it will be publicly visible and associated with your member profile. We anticipate researchers are likely to use this data, but there is no restriction: anyone may download it and it may be used for any purpose." ([https://www.openhumans.org/static/public-data/docs/Consent_Document_20141212_\(stamped\).f8b466a946f7.pdf](https://www.openhumans.org/static/public-data/docs/Consent_Document_20141212_(stamped).f8b466a946f7.pdf))

In exchange, members have access to aggregated raw data from the studies. This is Research 2.0 full interaction where a subject not only contributes data but can also be part of analysis and discovery. Subjects can share their data with each other, the general public, companies (such as direct-to-consumer testing groups), and even for fitness data tracking.

The cost of Research 2.0 is that "We do not guarantee privacy." ([https://www.openhumans.org/static/public-data/docs/Consent_Document_20141212_\(stamped\).f8b466a946f7.pdf](https://www.openhumans.org/static/public-data/docs/Consent_Document_20141212_(stamped).f8b466a946f7.pdf)) Participants may be identifiable depending on what the member chooses to share. The risks to participation include "identity theft, embarrassment, discrimination, and data may later become sensitive." However, members do have the option to withdraw at anytime and their data will be removed from the database

Open Humans is not the first attempt to democratize personal information for research. The [1000Genomes](http://www.1000genomes.org) (<http://www.1000genomes.org>) project is a notable example. Earlier this month Apple announced its "ResearchKit" (<http://www.apple.com/researchkit/?cid=wwa-us-kwg-iphone-com>) for collecting medical data from mobile devices. This information collected will be used for researchers to write medical apps and make new discoveries. Similar to Open Human, ResearchKit users can choose what information will be shared with what apps and studies. One of the advantages claimed for these systems is that they make informed consent easier.

A feature of signing up for Open Humans is their consent process, which gives 7 quiz questions to make sure that you have read and understood the consent document. If you do not get them correct, then you cannot complete your sign up.

The notion of crowd-based research is not new. You can already donate your idle computer time to 40 research projects: [climate modeling](http://www.climateprediction.net/) (<http://www.climateprediction.net/>), space modeling, protein modeling, mapping the brain, calculating large prime numbers, even sorting through radio waves for signs of intelligent life elsewhere.

Research 2.0 may not take place in expensive labs and clinics. It may take place on mobile phones and wearables collecting health data, and in the computers in our homes and offices analyzing the data. Perhaps the notion of a citizen-scientist will demonstrate biases and blind spots perpetuated by how we teach scientists to go about their work.

This kind of open platform networking may be the future of medical research. But it seems to me that this is a technology created to make researchers' lives easier rather than to boost protections for potential participants. I may be old fashioned, but I am not ready to give up my privacy and confidentiality just yet. As a society we need a conversation on the role of privacy and confidentiality in distributed human subjects research. It could be a decade before the rules and regulations catch up with this technology. In the meantime, the researchers should voluntarily develop guidelines that put subject (member) protection first, even if it presents a bit more of a barrier. Realistically though, with declining dollars for research though, this model is a creative approach that will prove itself if it leads to scientific and medical innovation.

Changing the Discourse on Health Systems Research: Response to Open Peer Commentaries on "Ethical Review of Health Systems Research in Low- and Middle-Income Countries: A Conceptual Exploration"

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Not All RCTs Are Created Equal: Lessons From Early AIDS Trials

Liza Dawson, National Institutes of Health

Caplan and colleagues (Caplan, Plunkett, and Levin 2015) raise important concerns about balancing ethical and scientific criteria in clinical trial design. They have discussed several distinct characteristics of trials that may or may not be present in any given RCT, such as use of placebos, double-blinding, and concerns about small sample size. However, in the case of Ebola treatment trials, the main area of disagreement amongst commentators has been about whether these trials should include a concurrent randomized control group consisting of best available supportive care (BASC). There are ethical arguments pro and con regarding a BASC control group. Determining the best clinical trial design depends critically on the state of the evidence for the investigational product being tested, among other factors.

In today's clinical trial environment, there is no such thing as a single gold standard RCT design. There are multiple designs, each with features that offer some trade-offs with regard to efficiency, accuracy, precision, potential patient benefit, and ease of implementation, to name just a few considerations.

In the current debate about Ebola treatment trials, the fundamental tension is between the obligation to treat patients with whatever intervention offers the best hope of success and the obligation to gather objective evidence in a scientifically rigorous manner. The stakes are high in a crisis in which time is short and consequences of treatment failure are deadly, especially in first human trials. In the first trials, there are high hopes for effective treatments but no direct evidence regarding effectiveness. What often happens in real-life trials is that hopes are dashed, or at least tempered, by evidence that the treatments are not the panacea we all wish for. Most new drugs fail to achieve the safety and effectiveness profile needed to be clinically useful. That does not diminish the importance of looking hard for those few interventions that will work, but does mean that advocating for patient welfare in the first Ebola

trials is considerably more complicated than advocating that every patient be treated with an experimental drug without a control group. When there is insufficient prior evidence of benefit, we cannot conclude that patients will be better off with new treatments than without.

Proponents of an alternative, non-RCT design (Adebamowo et al. 2014; Caplan et al. 2015) do not object, apparently, to the idea of randomization per se, but specifically to the idea of randomizing patients to a control that receives BASC and does not receive additional experimental therapeutic agents. Caplan and colleagues argue that standard arguments about need for rigorous control groups are irrelevant or inappropriate. They state that non-RCT designs will be better suited to determining what treatments work best when compared to alternatives, as opposed to determining whether a new treatment works at all. But in fact, without a comparison group, it is impossible to tell whether a new treatment works better or worse than alternatives. Furthermore, comparison of BASC alone to BASC plus experimental agent provides precisely the comparison that is most useful: Can a new agent improve on our best treatment practices, or not?

It is here I would allege that the principle of equipoise provides a useful framework, contrary to the views of Caplan and colleagues. Only in situations of genuine uncertainty can randomization to experimental treatment versus control be considered ethical. And new interventions for Ebola have uncertain effects. The challenge is managing changing levels of uncertainty. Certain trial designs are more suited to responding quickly to new evidence as the range of uncertainty is diminished. It is these responsive and adaptive trials that should be the ethical priority, not an abandonment of randomization or control groups. As the uncertainty decreases, evidence of benefit or lack of benefit emerges, and decision making regarding best ways to protect patient welfare may gradually change.

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Use of sophisticated adaptive designs, including Bayesian approaches, can help mediate the tensions between need for immediate access to therapies and need for rigorous evidence. Adaptive designs should be used and tailored for rapid response to emerging evidence. In fact, some trial planners are discussing designs that involve frequent “looks” at clinical outcomes, meaning preliminary statistical analyses conducted frequently as data are collected, and plans for stopping trials early if benefit emerges, to provide active treatment to control group patients as soon as there is evidence of clinical benefit. If treatment benefit emerges, this treatment would then be the new control group for newer agents introduced into trials, using an active control design.

It is also possible that new candidate Ebola treatments may be developed that already have strong evidence that they will be successful in human efficacy trials. When there is substantial prior evidence supporting effectiveness, an alternative design might be based in part on a suggestion by Goodman and Kass in a recent commentary (Kass and Goodman 2014). A small group of patients could be treated with the new agent in addition to BASC, without a control group, to see whether a definitive improvement in outcomes is observed. If no large, striking benefit is seen early on (but likewise no safety concerns), the trial could roll into an adaptive RCT design as described earlier. The purpose of the lead-in group would be to provide an opportunity to see whether the treatment is going to deliver definitive, highly effective results in a short time frame; if this definitive benefit does not emerge, more modest effects may still be present and can be studied with a controlled trial. This kind of lead-in to a trial makes the most sense if there is prior evidence to support a large positive treatment effect and there is useful, reliable, and consistent historical control data. These conditions are not met at present but could be in the future.

Caplan and colleagues mention that many oncology trials do not include placebo controls. It is important to acknowledge the diversity of trial designs in oncology, and the enormous volume of clinical research experience in virtually all types of cancer. New treatments build on a long history of standard-of-care (SOC) approaches, and most trials involve add-on therapy: SOC in both arms and experimental intervention added to one arm. With Ebola, treatment outcomes and even approaches to rehydration or other aspects of supportive care vary significantly across treatment centers (McNeil 2015). There is not yet any clear evidence of predictors of survival based on patient characteristics or symptoms, and historical data on clinical outcomes are hugely variable. Use of a concurrent randomized control group provides the means for determining whether a given experimental treatment actually helps or harms patients.

The challenges to stakeholders in considering the design of Ebola treatment trials echo the debates and controversies of early AIDS trials. Activists in the early days of AIDS research were also concerned about patient welfare in the face of a deadly epidemic. While the course of disease with ultimate mortality of untreated HIV disease is

lengthier than the course of Ebola infection, prior to the development of highly active antiretroviral therapy, the mortality rate was more than 90% at 5 years postdiagnosis (Jacobson et al. 1993). Activists were rightly concerned that trials were taking too long and that researchers were too conservative in enrollment criteria for patients with comorbidities denying many patients their only chance to receive a possibly life-extending therapy (Epstein 1996). Some early trials were designed with rigid adherence to the original endpoint (mortality), obviating opportunities for patients to try alternative therapies if early results were not promising. Many of these clinical trial practices were, in fact, changed in response to demands of advocates (Merigan 1990).

Activists also challenged control groups in early trials. ACTG 019, which tested AZT versus placebo, was lambasted in news publications for the use of placebo. The trial showed that AZT provided clinical benefit (Volberding et al. 1990) delayed mortality and improved CD4 counts but that the virus ultimately evolved to become resistant to AZT, leading to treatment failure (Volberding et al. 1994). As we know now in hindsight, it takes a combination of three antiretroviral agents to provide long-lasting viral suppression and long-term benefit. Thus, the first key lesson for trial design is that the desperate need for effective treatment does not mean the first trials are more likely to deliver the “slam dunk” that is needed. The history of drug development shows the opposite: A sequence of trials is needed, each building on evidence from earlier research, to reach the ultimate goal of safe and highly effective life-saving treatment. The development of effective combinations of HIV therapy by the mid-1995, only 15 years after the emergence of the epidemic, was considered unparalleled, breakneck speed in terms of drug development (Gait and Karn 1995).

Another key lesson from the AIDS experience is the essential importance of education and dialogue among community representatives and trial designers. Community advocates can and should become knowledgeable about scientific aspects of trials in order to contribute meaningfully to discussions about trade-offs in clinical trial design. There is no perfect trial, but scientific principles can and should be balanced with consideration of patient welfare and maintaining trust among trialists and trial participants. No single trial provides all the needed answers, and a sequence of trials is necessary. Each trial must produce sound evidence on which to base the next step toward effective treatment; poorly designed trials thus have ripple effects for downstream research. Along this pathway toward development of truly effective regimens, stakeholder engagement and transparency are essential.

A final note from the history of AIDS therapeutics: Patient access to any therapies developed is critical, and effective translation from clinical trials to implementation should be part of the planning process throughout. It will take considerable effort on a global scale to address these problems with new treatments for Ebola or other emerging diseases.

The Ebola crisis provides a lens through which to focus on global health issues that have received insufficient attention. Hopefully, the lessons learned from other epidemics will help researchers and policymakers deliver needed relief in the form of new effective methods for prevention, treatment, and care, more quickly and effectively than in the past. ■

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