

Virtual Mentor
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FROM THE EDITOR

The Escalating Importance of Clinical Research

In 2004, the National Institutes of Health (NIH) launched its NIH Roadmap for Medical Research, an ambitious plan to delineate the agency's priorities and to serve as a guide for scientific research in the coming years [1]. Central to this plan is the promotion of clinical and translational research. Since then, the NIH has shifted more extramural funding to these areas and added funding for didactic-degree programs in clinical research at academic institutions around the country to train the next generation of clinical researchers. As part of recent economic stimulus efforts, the American Recovery and Reinvestment Act of 2009 will infuse the NIH with hundreds of millions of dollars, much of it slated for clinical-research endeavors [2].

Opportunities in clinical research abound for medical students and residents. And as the focus of the leading scientific agency in the country shifts more toward research involving human subjects, there is little doubt that increasing conflicts between the agenda of scientific advancement and biomedical ethics will surface. This issue of *Virtual Mentor* explores a number of these aspects of clinical research.

The three clinical cases in this issue describe scenarios that are particularly salient for medical trainees engaged in clinical research. In the first case, Julie Freischlag explains how to avoid faculty favoritism in recognizing the efforts of a resident who enrolls patients in a clinical trial being conducted by his department chair. The second case commentary, written by Mark T. Hughes, charts the course a research trainee should take when asked to add honorary authors to a scientific publication. Timothy M. Pawlik tackles the thorny issue of how to handle suspected research misconduct in the final clinical case.

This month's journal discussion and clinical pearl relate to the ethics of statistics. In the former, Garrett M. Sparks reviews a 2008 article from the *New England Journal of Medicine* that describes the negative publication bias in studies of antidepressants and its effect on the public's perception of their efficacy [3]. The clinical pearl by Chandra Y. Osborn focuses on the importance of statistical literacy and explains how to interpret several frequently misunderstood statistical concepts.

As alluded to earlier, the NIH is funding many programs to develop future clinical researchers. In the medical education section, Emily Abdoler writes about some of the opportunities available to medical students and residents and the efforts to ensure that ethics is an integral part of that training. In the medicine and society section, Rebecca Dresser takes up the question of how the NIH determines its research priorities and the ethical considerations that must be part of those decisions.

The medical history and medical narrative sections this month highlight the human side of clinical experimentation. In the narrative section, Amanda Redig interviews participants in human-research studies and explores their motivations for subjecting themselves to pain and possible side effects of treatment, often with no known benefit. In a similar vein, Akhil Mehra writes about the incentives for participation in Walter Reed's historic yellow-fever experiments in the beginning of the 20th century.

Inherent to the conduct of clinical research in this day and age is the role of the institutional review board (IRB)—the oversight body responsible for the protection of human subjects involved in clinical experimentation. In a two-part policy forum, Margaret R. Moon and Felix Khin-Maung-Gyi explore the role of IRBs and debate the pros and cons of for-profit “central” IRBs and not-for-profit, academic institution-based “local” IRBs. Finally, Micah R. Onixt and Robyn L. Sterling review the liability and scrutiny that IRBs face when adverse events do occur in the course of clinical research.

I would like to thank all the distinguished authors for their contributions to this month's issue of *Virtual Mentor*. In addition, many thanks are owed to the staff at the American Medical Association—Audiey Kao, Faith Lagay, Phil Perry, and Jennifer Schooley—for their creative input, editorial efforts, and administrative support. It is our sincere hope that you enjoy reading about the aspects of clinical-research ethics covered in this issue and that you find it challenging and educational.

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CLINICAL CASE

Are Honorary Authorships Ethical?

Commentary by Mark T. Hughes, MD, MA

After finishing the first 3 years of medical school, Sarah decided to take a year off to spend time in a basic science laboratory. The aspect of the lab that she liked most was the tremendous latitude and independence to devise, develop, and test her own project idea while still receiving the necessary support and guidance from her postdoctoral fellow and her primary investigator, Bill.

As the year-long experience began to draw to a close, Sarah began to spend more nights and weekends in the lab to finish the project before returning to her clinical duties. When she sent the first draft of the manuscript to Bill for review, she was pleased that he believed it to be nearly publication-ready, suggesting only a few minor changes. She was surprised, however, by one of his first comments: “Include Drs. Smith and Jones as coauthors—this is a topic of interest to them.” Drs. Smith and Jones were nationally known, well-regarded senior investigators in the department, but Sarah had never even met either of them.

Commentary

Why would Bill want Sarah to include Drs. Smith and Jones as coauthors? Clearly, their inclusion in the byline is honorary and not reflective of work on the research project or manuscript. Three reasons could be hypothesized [1, 2]. First, Bill might hope that having the names of these researchers attached to the paper will garner better reviews of it. We know that they are interested in the field and are nationally known, so perhaps Bill anticipates the paper’s peer reviewers will recognize their names on the byline and think favorably of the paper, irrespective of its content. Second, Bill may be wishing for some sort of *quid pro quo*—either returning a favor from Drs. Smith and Jones or hoping they will include him on their papers or pay him back in some way. Third, Bill may be obligated to include them because they are senior investigators. It may be a departmental expectation that Drs. Smith and Jones be listed as authors because of their positions of authority (e.g., division or department chair). Or there could be covert pressure or coercion on Bill by Drs. Smith or Jones to be included on the paper.

Why should Sarah care? If she were purely self-interested, she would think that including the doctors as coauthors would add prestige to the paper and increase its chance of being published. She wants the paper to be published so she can gain recognition for her work and add the publication to her CV. If she asks other medical students or perhaps the postdoctoral fellow in her lab, they may tell her that this is a common practice and that she should not rock the boat.

According to medical literature, the assertion of Sarah's colleagues appears, in fact, to be true. As far back as 1982, it was recognized that the scientific literature contained many names on the byline of people who had fulfilled no real criteria for authorship [3]. Since then, several studies have examined the contributions of authors to multi-authored articles. A 1994 study of 10 leading biomedical journals again showed that a significant number of coauthors had made little to no substantive contributions to the reported research [4]. A study of *BMJ* articles over a 20-year period found not only an increase in the overall number of authors per article but also a higher percentage of professors and department chairs being listed as authors [5]. It can be speculated that their inclusion was more honorary than anything else. Eleven to 25 percent of articles in American journals, with large and small circulation, have included honorary authors [6]. Similar concerns have been found in Cochrane reviews; 39 percent of reviews published in 1999 had evidence of honorary authors [7].

A study of articles published in the *American Journal of Roentgenology* in the 1990s yielded interesting results [8]. First, as the number of coauthors increased, so did the percentage of undeserved authors, to as high as 30 percent. Second, nearly 40 percent of undeserved authorship was attributed to the first author's feeling obliged to or fearful of the honorary coauthor. This was more likely to occur when the first author was a non-tenured staff member in a position of vulnerability relative to a senior author. Lastly, the most common reason cited was concern about academic promotion.

Should Sarah just accept the notion of honorary authorship as part of the price of "doing business" in academia? In an academic world ruled by the publish-or-perish paradigm, why not just spread the wealth and assign authorship to one's colleagues, so they can get ahead too? The answer, of course, is that this practice would be unfair to those who actually have put in the work. If a name on a byline is the currency by which we value that individual's contributions to scientific advancement, it would be wrong to give credit where credit is not due. Sarah's answer lies in confronting the age-old conundrum in ethics called the "is, ought" problem. This commonly voiced ethical concern argues that merely identifying what *is* being done does not tell us what *ought* to be done. Just because Sarah learns that students in her situation *do* accept honorary authors on their publications does not entail that Sarah *ought* to do the same.

Several options are available to help Sarah determine what she ought to do. Journals have well-established guidelines about what counts toward authorship. Her institution may have student and faculty policies about proper scientific authorship. Perhaps most importantly, Sarah has a cogent ethical argument based in the core definition of science. She has taken a year off to learn how to be a researcher, and one of the key lessons in the research community is that a scientist must be true to science. The aim of scientific research is to seek the truth—to explain a phenomenon by following a rigorous methodology. When she publishes results of her research,

she is affirming that they are accurate and have been generated as a consequence of the scientific method. Putting on a research paper the name of someone who has not been part of that process is neither accurate nor truthful.

Guidelines for Assigning Authorship

Sarah should set up a meeting with Bill to discuss her concerns about including Drs. Smith and Jones on the manuscript. She should appeal to the authorship guidelines, which have existed for over 30 years. The International Committee of Medical Journal Editors (ICMJE), originally known as the Vancouver Group, has established uniform requirements for authorship and other aspects of writing a manuscript for a biomedical journal. According to the ICMJE, two principles guide authorship decisions—contributorship and guarantorship [9].

The latter principle, guarantorship, mandates that each author agrees to take public responsibility for the content of the article. In Sarah's case, Drs. Smith and Jones may agree to take public responsibility, but if they have not been part of the study, it may be difficult for them to speak to all aspects of the research project. The public responsibility cuts both ways, of course—if the paper is well-received, the authors can accept the accolades, but if problems are found in the manuscript or research project, they must be ready to accept criticism. Moreover, there have been instances of senior authors who did not even know they were listed in a byline, so Sarah may want to ask Bill if he has spoken to either doctor about the research. Have they even read the manuscript?

Irrespective of whether Drs. Smith and Jones are ready to serve as guarantors of the manuscript, Bill still has to address the principle of contributorship. Authors' contributions to research articles have received a great deal of attention over the past decade. A study of authorship in *The Lancet* developed a taxonomy of the contributions by each author on the byline; the investigators found that 44 percent of contributors in the articles did not meet the ICJME guidelines [10]. Earlier, the same authors (Rennie et al.) proposed moving toward disclosure of each author's specific contribution as a means of ensuring accountability [11]. While some commentators have suggested abandoning the concept of authorship altogether, academia still sees a role for assigning authorship, provided there is transparency in "who did what" [12]. Some journals have moved in the direction of disclosure of contributions to allow better acceptance of credit and responsibility by authors. This is not a failsafe mechanism, especially if it relies on self-reporting, but it is supported by the *AMA Manual of Style* [13-16].

According to the ICJME uniform requirements, "authorship credit should be based on: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of the data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published" [9]. Sarah should point out to Bill that Drs. Smith and Jones have not been involved in the study over the past year and therefore do not fulfill the first criterion. Perhaps some of this turmoil could have been avoided had a prior

agreement been negotiated to clarify roles and plans for the paper, but this is Bill's role [17]. As a student, Sarah is in a relatively vulnerable position, so Bill has a responsibility as her mentor to establish clear authorship guidelines for the research team.

Confronting Bill about this will not be easy. Sarah will need to use negotiating and conflict-resolution skills [18, 19]. Since she clearly has the guidelines on her side, she should not yield to pressure, only to principled arguments. As with any difficult conversation, it would be wise for her to understand Bill's perspective [20]. Maybe he's under pressure from Drs. Smith or Jones. Maybe there's more to the story than he initially told Sarah. Learning this additional information does not mean that Sarah has to alter her position, but it can at least provide a path to a solution that is amicable and mutually advantageous.

Authorship determination in biomedical research is a combination of etiquette and ethics. Polite, respectful dialogue among colleagues can resolve many conflicts. When there are truly disputes about assigning proper credit, the concerns affect ethics. Justice, fairness, and truthfulness dictate that Sarah speak to Bill and question the inclusion of Drs. Smith and Jones as coauthors on the paper. The byline should include Sarah as first author, the postdoctoral fellow as second author, and Bill as last author.

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The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental.

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CLINICAL CASE

Avoiding the Appearance of Faculty Favoritism

Commentary by Julie Freischlag, MD

Jon was a second-year internal medicine resident at a large, academic medical center. Through a series of coincidences, he encountered two patients in clinic whom he believed would benefit from enrollment in a clinical trial getting underway at the center. The trial, about which Jon was particularly knowledgeable, was being conducted by the chairperson of the Department of Medicine, Dr. Anderson. Jon contacted the study coordinator about the patients, and then explained the risks and benefits of participating in the trial to patients.

The following week, at the conclusion of grand rounds, many faculty members, residents, and students were mingling outside the auditorium and grabbing a last cup of coffee before heading back to work. Jon was catching up with a few of his fellow residents when Dr. Anderson stopped to thank him for enrolling the patients in the trial.

“We’ve had a heck of a time getting patients recruited for this study, so I appreciate all the time you spent getting them enrolled,” Dr. Anderson said.

After asking how Jon’s current rotation was going, Dr. Anderson said, “By the way, I have tickets to the game Saturday, and I’ll be out of town, so you’re welcome to them if you can use them. Just let me know.”

Commentary

Placing patients in a clinical trial is one of the cornerstones of academic medicine and I believe these participants are real heroes—especially those who consent to a prospective randomized trial prior to knowing which arm of the study they will be assigned to. It is customary for the investigators running the trials to have funding, primarily so that the clinical trial’s nurse can be paid for following the patients and filling out the requisite case-report forms. Often research is funded on a per-subject basis, so it is important to recruit as many patients as possible who qualify. In the past, our institution has given tokens of appreciation to faculty or residents (as in this case) who helped enroll subjects. Past rewards have included books, certificates to book stores, travel to the clinical trial meeting, and even a percentage of the payment per case. These tokens, however, were described in writing prior to the trial and available to everyone.

Many new regulations aim to manage potential conflicts of interest between industry and physicians. It would make sense to practice these common-sense principles with those who work with us.

In this scenario, thanking Jon for placing the patient in the clinical trial is appropriate—and can be done in front of others. What is not acceptable is offering the gift of the tickets in the same conversation. Quite possibly the conversation took place by accident, and Dr. Anderson did not intend to offer the tickets to Jon before he ran into him. The offer, nonetheless, shows favoritism and should not have been made. Even presenting the tickets to one resident in front of others without any mention of the patients' being placed in the trial is not appropriate when the person offering the gift is the chairperson or someone who is of superior status to the resident. Jon should make an appointment with Dr. Anderson, turn down the tickets, and tell him how uncomfortable he felt when the offer was made. Doing so would help Dr. Anderson understand how his gesture could have been perceived as a reward.

As a department chair, I invite our chief residents to dinners for visiting professors, but I invite them all. I give them each a holiday gift, and, when they are on my service, I encourage them to attend events with or without me—again due to their present role—not because of who they are personally or as a payback for something they did for me.

The field of surgery has become a club or family or, as Jerry Shuck, a former chair of surgery at Case Western Reserve called us, a clan [1]. We may sometimes step over the line of appropriate behavior because we spend long periods of time with our residents in the operating room, often during life-and-death struggles. True, we probably should adopt a more business-like relationship with them that still enables us to know and mentor them, and give every resident the same chance for a close but appropriate relationship with those who represent departmental leadership.

Since our current residents are from many different backgrounds, it is most important to keep our interactions fair and above board. As leaders, we also need to learn that a “thank you” is more than enough. Most employees, students, residents, and faculty feel that thanking them for a job well done is plenty. It means their efforts were noticed and attention was paid to the small contributions we are all making. Instead of tickets, take good care our patients—and take good care of our residents, staff, and colleagues.

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Julie Freischlag, MD, is the William Stewart Halsted Professor and chair of the Department of Surgery and surgeon-in-chief at the Johns Hopkins Hospital in Baltimore. Before 2003, she was chief of the Vascular Surgery Division and director

of the Gonda (Goldschmied) Vascular Center at UCLA, where she also completed her surgical residency and post-residency vascular fellowship. Dr. Freischlag is the editor of the *Archives of Surgery*, has published more than 150 manuscripts and numerous abstracts and book chapters, and serves on several editorial boards.

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CLINICAL CASE

Suspected Ethical Misconduct in Research

Commentary by Timothy M. Pawlik, MD, MPH

Michael, an MD/PhD student, was working for Dr. Adams, an ambitious, tenure-track associate professor who specialized in several rare genetic diseases. Michael was working on a project of his own, but he heard updates about all of the projects in the research group during a weekly lab meeting.

Michael was rather surprised when, at one of the lab meetings, Dr. Adams announced that the results of a recently concluded clinical trial were positive and had been submitted to a prestigious journal for possible publication. No one else acted surprised or asked Dr. Adams any questions about this report.

After the lab meeting, Michael and his postdoctoral fellow, Lisa, grabbed a cup of coffee before starting their work. Michael said, "It's kind of surprising that Dr. Adams' study results were positive. For the last year, everyone has been grumbling about how badly the study was going."

Lisa, who was also uninvolved in the study, said "Well, that's why we have peer review. If there are any inconsistencies, they'll get picked up. So, any big plans this weekend?"

Despite Michael's marginal involvement with the study, inexperience in the conduct of clinical trials, and lack of training in statistical methodologies, he could not shake the feeling that something was amiss.

In a moment of privacy with Teddy, one of the more junior members of the lab and a listed co-author on the paper, Michael casually mentioned, "Congrats on finishing the paper. That's pretty exciting. I thought you guys were having trouble recruiting people that fit the inclusion criteria, but it seems like everything has come together."

Teddy responded, "Thanks, but I can't take too much credit. In the last few months, Dr. Adams really became more hands-on with this trial. He pretty much took over every aspect of it, which was nice because I have been able to wrap up some loose ends with a few other projects. To tell you the truth, I was pretty surprised when he said it was over and ready to submit for publication."

Commentary

When conducting scientific research, residents and students need to be mindful of unethical activity in which they may be directly or indirectly involved. Although it is

not the job of residents and students to act as investigators and monitor the ethical behavior of every fellow researcher, they do need to be aware of possible scientific misconduct in the research setting. In fact, a scrutinizing eye toward one's colleague's conduct is both scientifically and ethically desirable. Not only is this part of one's moral duty, but remaining vigilant in the research environment also helps to maintain high standards of scientific integrity. As in this case, however, residents and students will often not directly witness scientific misconduct or fraud, such as a researcher changing data points or manipulating experimental conditions and study eligibility criteria to suit his or her needs. Rather, scientific misconduct is more frequently suspected based on circumstantial evidence. For example, in the current case, Michael did not directly witness Dr. Adams violating the inclusion criteria of the study to facilitate increased trial accrual. Rather, he had a feeling that something was amiss based on Dr. Adams' positive study results. Although Michael has no direct evidence to prove that Dr. Adams has acted wrongly, he has a strong suspicion, and therefore an ethical duty to act. But what should Michael do?

Gathering Information

Accusing a researcher of ethical misconduct is a serious matter. The shadow of an accusation can hang over someone's career even if later investigations exonerate the individual. A number of criteria need to be satisfied before "blowing the whistle." First, Michael has a responsibility to ensure his information is accurate and based on a thorough understanding of Dr. Adams' work. For example, suppose Dr. Adams—realizing that study-inclusion criteria were too strict and severely limited accrual—had applied for and received institutional review board (IRB) approval for revised study-inclusion criteria. Perhaps this is how Dr. Adams had become more hands-on with this trial, and these new IRB-approved inclusion criteria were the reason for the newfound success of the trial. Since Michael is inexperienced in the conduct of clinical trials and lacks training in statistical methodologies, he may not be able to assess accurately whether Dr. Adams is engaging in unethical behavior.

Did Dr. Adams purposely miscalculate the sample size in the study to meet anticipated low accrual or accept a lower statistical power for the study because he anticipated low accrual? Sometimes only an individual with specialized knowledge is in the position to identify behavior as unethical. On the other hand, Dr. Adams may indeed have accrued patients outside the inclusion criteria or manipulated data. Since Michael has his own project and only hears about other projects in the research group during weekly lab meetings, he may not be fully up-to-date on the trial. Michael may be able to get more information by talking with other colleagues in the lab. Discussions with colleagues should be undertaken in a nonaccusatory manner and reflect a genuine desire to understand how the study was completed successfully. If the matter cannot be clarified by this means, Michael should consider talking directly to Dr. Adams.

Facing the Problem One-on-One

In general, a prospective accuser should first attempt to confront the researcher he thinks is performing the ethically questionable activity. If Michael chooses to do this,

however, the conversation must be handled with care and in a nonconfrontational manner. Ideally, after identifying an ethically questionable situation, the concerned resident or student should approach the researcher in question to allow him or her the opportunity to clarify, or even rectify, what may be an honest, unintended misunderstanding or error. Michael might say, for example, “Dr. Adams, I was happy to hear that your research project had a positive outcome after the early setbacks last year. What was the main reason for the turnaround?” Unfortunately, even this can be an unrealistic expectation. Fear of retaliation or being blackballed by the entire research team or community often makes an open conversation about these issues unworkable, especially in situations where there is a power disequilibrium involving residents or students. If a researcher feels threatened by a resident or student who is questioning his or her work, that faculty member may be inclined to retaliate, affecting the individual’s career path adversely. On the other hand, if the resident or student proceeds directly to an institutional review process without first approaching the researcher in question, the opportunity to remedy the situation before it becomes public is lost. This course of events would be especially damaging to the resident or student if the complaint were found to be erroneous and based on a misunderstanding of the situation.

When a resident or student suspects ethical misconduct, he or she should initially report the suspected ethical misconduct to an appropriate, trusted individual—ideally not another resident or student, but someone of an academic stature who could effectively investigate the matter as an advocate without fear of repercussions. After gathering more information and confirming that there is an ethical concern, Michael can execute his moral duty by “kicking it up the ladder.” With the assistance of a mentor, Michael can help assure that his concerns are communicated to the appropriate authorities for further investigation and adjudication.

Managing the Situation

Michael has a responsibility to report suspected—and substantiated—ethical misconduct to the appropriate authorities. He should not, however, gossip about suspected ethical misconduct with friends, colleagues, or unsanctioned individuals outside the department or hospital. As noted, discussions of suspected ethical misconduct are best initiated with one’s departmental mentor who can then assist in further investigating the situation before reporting the incident. By reporting to appropriate authorities such as departmental mentors or division chiefs, Michael will be respecting the due process that Dr. Adams deserves.

If indeed the suspicion of ethical-research misconduct rises to the level of a formal complaint to the departmental authoritative body, a full formal investigation usually ensues. Depending on the situation, this may range from review of data files and trial folders, interviews with research nurses and participants, or even the involvement of legal authorities. Most institutions have a system to deal with suspected scientific misconduct that includes assessing the validity of the accusation, properly investigating the grievance, and establishing punishment or rectifying the situation.

Conclusion

Michael's moral duty lies not in acting as investigator, judge, or jury of suspected ethical-research misconduct. Rather, his moral duty is to be aware of possible scientific misconduct. When misconduct is suspected, Michael has an ethical duty to ensure that he has his facts straight. He should not engage in unconstructive gossip about any of his suspicions, but should talk with Dr. Adams about the research project and its surprise outcome. More realistically, Michael should enlist the support of a trusted mentor who can help explore his sense that something is amiss. If, in conversations and exploration of the facts with this mentor, the concerns remain, the mentor can assist Michael in formally reporting the suspected ethical misconduct to the appropriate departmental or institutional authorities.

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The people and events in this case are fictional. Resemblance to real events or to names of people, living or dead, is entirely coincidental.

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MEDICAL EDUCATION

NIH Ethics Education Programs and Initiatives: Training the Next Generation of Clinical and Translational Researchers

Emily Abdoler

The National Institute of Health's (NIH) longstanding commitment to ensuring that its research is undertaken ethically serves both as a safeguard against abuse and an investment in the public's trust in research [1, 2]. This commitment is manifest in a variety of programs and initiatives—a number of which focus on training future clinical and translational researchers. In some cases, these programs are required or highly encouraged; in others, they are available for students with a special interest.

The NIH invests heavily in the education of future researchers, particularly with regard to their ability to design and carry out robust and valuable research projects. Some intramural training programs and initiatives geared to medical students and residents may be found on the web site for the NIH Office of Intramural Training & Education and the NIH Clinical Center Office of Clinical Research Training & Medical Education (OCRTME). Medical students and residents can also benefit from various extramural initiatives, which are NIH-funded but organized by other institutions; examples include individual and institutional NIH training grants, as well as the National Center for Research Resources Clinical and Translational Science Awards.

While instruction on such topics as statistical design and hypothesis generation may seem only tangentially related to training ethical clinical and translational researchers, it is actually an essential component. The first two of seven requirements for ethical clinical research are social value and scientific validity [3]. Clinical research that exposes subjects to risks is ethical only when it is designed to generate valuable knowledge through the use of valid methods. The NIH provides training in other aspects of ethical clinical research through specific initiatives, described below (see [Table 1](#)).

Intramural Courses and Programs

Intramurally, the NIH offers a variety of opportunities for medical students and residents to learn about the ethical conduct of research.

Introduction to the Principles and Practice of Clinical Research. This free course, offered at the NIH by the OCRTME, covers topics related to ethical human-subjects research within the context of general clinical-research training [4]. It is open to any interested party and may be viewed from approved videoconference sites or online. At least 22 of last year's 952 participants were medical students or residents,

although the number participating is probably much higher since enrollees are not required to designate their status.

Clinical Research Training On-Line. The OCRTME also offers Clinical Research Training On-Line, which includes instruction in the ethical conduct of human-subjects research [5]. The course is free to all interested parties and required for all NIH intramural principal investigators.

Ethical and Regulatory Aspects of Clinical Research. This free course, offered each fall by the Clinical Center's Bioethics Department, was developed to help investigators fulfill the NIH's requirement for education in the protection of human-research participants [6]. The course is open to all and frequently includes remote groups (including some in Peru, Sri Lanka, Maryland, and Washington) who attend via satellite. It is also available online and through podcasts. Since 2005, approximately 250 to 350 individuals have enrolled annually. This enrollment includes medical students, residents, and fellows, but the exact numbers are unknown.

Clinical Research Training Program (CRTP). Specifically for medical and dental students who have completed at least one year of clinical rotations, the NIH CRTP provides a year of intensive training and experience in clinical and translational research, including ethical conduct, through the program's required clinical research group seminar [7]. CRTP enrollment is limited to 30 students each year.

Summer Internship Program (SIP) in Biomedical Research. SIP, coordinated by the Office of Intramural Training & Education, offers clinical and basic research experiences for high school, college, graduate, and professional students [8]. Students can undertake research projects in the Clinical Center's Bioethics Department or attend the optional summer lecture series, which includes the session, "What Makes Clinical Research Ethical?"

Additional intramural NIH initiatives for medical students and residents interested in clinical research include:

- Inter-Institute Bioethics Interest Group—monthly discussion forum of specific ethical issues open to all; cosponsors "Bioethics Resource on the Web" with the Office of Science Policy.
- Ethics Grand Rounds—regular discussions of ethical issues in clinical research for all interested participants.
- Clinical Investigator Student Trainee Forum—annual forum for medical and dental students in certain "year out" research enrichment programs that sometimes includes a session on clinical-research ethics [9].
- NIH GME programs—some require training in the ethics of clinical research [10].
- NIH-Duke Training Program in Clinical Research—open to physicians who have already completed residency training, dentists, and advanced-degree

nurses, has coursework in research ethics, and requires training in responsible conduct of research [11].

Extramural Training Grants and Awards

Extramurally, the NIH's efforts to train the next generation of ethical clinical researchers are generally tied to training grants and other awards meant to support education in biomedical research.

Training Grants. All individual and institutional NIH training grants and K awards (career development), some of which can be applicable to medical students and residents, require participants to receive training in the responsible conduct of research (RCR). The NIH encourages institutions to involve *all* graduate students and postdoctoral fellows in their RCR initiatives [12].

While the NIH RCR requirement is deliberately flexible, allowing institutions to determine much of the form and content of the training, issues related to the use of human and animal subjects must be included [12, 13]. RCR training is designed for all types of investigators, including clinical and translational researchers.

Clinical & Translational Science Awards (CTSA). CTSA fund the development of centers for clinical and translational research at academic institutions across the country and, more broadly, bring the centers together in the form of a national consortium for shared resources and endeavors [14]. The CTSA centers are designed to be the sites where the next generation of clinical and translation researchers will be trained. Most CTSA sites have graduate and postgraduate programs in clinical and translational research, sharing curriculum through an online repository. As with similar NIH training initiatives, CTSA-sponsored clinical-research training programs should include research ethics; each CTSA center has a faculty member trained in research ethics to coordinate this training and lead research studies in bioethics or research ethics.

K30 Clinical Research Curriculum Award (CRCA.) CRCAs focus exclusively on formal, multidisciplinary clinical-research training programs and curricula and seek a diverse pool of trainees, including those with backgrounds in medicine; they are especially designed for early career professionals and academics [15, 16]. The core curriculum funded by a CRCA must include coursework in bioethics.

Development of a Short-Term Course in Research Ethics (T15). Earlier this decade, the NIH awarded 29 T15 grants for institutions to design and undertake short-term courses in research ethics [17, 18]. While these courses were intended for researchers rather than students or trainees, and although only one course retains an active award, many may still be offered at their original institutions. In such instances, medical students and residents can take advantage of the curricula developed by the T15 grants.

Fogarty International Center—International Research Ethics Education and Curriculum Development Award (R25). As the NIH's largest bioethics training program, this development award supports courses and training related to the education and professional development of ethical clinical researchers and bioethicists from developing countries [19, 20].

Required Education in the Protection of Human-Research Participants

A final component of the NIH's effort to train ethical clinical researchers includes its requirement, beginning in 2000, that all key personnel for NIH-funded research studies involving human subjects complete training on the protection of human-research participants [21, 22]. Insofar as medical students and residents are involved in research with human participants, they are subject to the requirement. While institutions may design their own educational program (much like the RCR mandate), both the free online tutorial provided by the NIH Office of Extramural Research and the OCRTME's Clinical Research Training On-Line course may be used to meet this requirement [23].

Conclusion

A recent survey found that the average number of hours of required coursework for medical students in bioethics may be as low as 35.6 across all four years of medical school and distributed disproportionately to the preclinical years (where it may be less relevant) [24]. It is likely that only a small percentage of this training extends to clinical and translational research ethics.

While the NIH provides opportunities for instruction in this area, medical students are in a unique position to contribute positively to their own training in the ethical conduct of clinical and translational research. Through the organization of interest groups, forums, and other student-led programs and activities, they can enhance their own educational experience and that of their peers. They can also lobby their institutions to provide more in-depth training through the bioethics curriculum. Interested students and trainees can take the initiative to pursue training themselves, taking advantage of the myriad free courses and programs offered by the NIH. Finally, students and trainees at institutions with CTSA's or CRCAs may have an opportunity to involve themselves actively in research projects focused on the ethics of clinical and translational research, increasing their own familiarity with the subject while furthering the work of the field in general.

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[Research Ethics and Medical Education](#), November 2004

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JOURNAL DISCUSSION

Prying Open the File Drawer

Garrett M. Sparks, MD, MS

Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med.* 2008;358(3):252-260.

In 1979, Robert Rosenthal coined the term “file drawer problem” to describe the tendency of researchers to publish positive results much more readily than negative results, skewing our ability to discern exactly what an accumulating body of knowledge actually means [1]. He posited the worse-case scenario for experimental trials: journals filled with 5 percent of the studies that show type 1 errors (i.e., find positive results when no positive effect exists), and file drawers filled with 95 percent of the studies that show nonsignificant results. In 1979, sans Watergate-style break-ins, there were few means to estimate how many papers were stuffed into the file drawers. In 2008, former Food and Drug Administration reviewer Erick Turner et al. pried open the file drawer by examining the FDA registry and results database on all phase II and III clinical trials for 12 antidepressant agents approved by the FDA between 1987 and 2004 [2].

To assure transparency in the data submitted for review, drug companies must register with the FDA all trials they intend to use in support of an application for marketing approval or a change in labeling. The registration process requires that drug companies specify the exact methods by which they will collect and analyze data. Raw data must be submitted to prevent biased reporting of favorable trial results. While FDA reviewers have full access to the entire body of data used to make decisions regarding the safety and efficacy of a drug, the clinicians who will be ultimately prescribing these drugs and counseling patients do not.

Turner et al. could not find evidence of publication for 23 out of 74 studies included in their analysis. Thirty-seven out of 38 studies that the FDA deemed “positive” were published. Of the 36 remaining studies classified as “negative” (24) or “questionable” (12), 3 were published as not positive, 11 were published in a way that, in the opinion of Turner et al., conveyed a positive outcome, and 22 were not published at all. By the authors’ estimate, studies judged positively by the FDA were 12 times more likely to be published than studies judged nonpositively. This publication bias leads to an overestimation of total effect size by 32 percent relative to the FDA reviews, ranging from 11 to 69 percent for particular agents. All of the antidepressants still outperform placebo, but not by as much as the published literature would suggest.

The key to understanding the significance of this study lies in the first sentence of the conclusion of the abstract, “We cannot determine whether the bias observed resulted from a failure to submit manuscripts on the part of authors and sponsors, from decisions by journal editors and reviewers not to publish, or both” [3]. The efficacy of the antidepressants studied in these reports is a secondary concern. Turner et al. do not have the means to prove beyond a reasonable doubt that selective dissemination of information regarding the safety and efficacy of these drugs was part of a conscious attempt by researchers to mislead journal readers, but their indictment effectively raises clear suspicion that clinicians should be extremely wary of publication bias when reading clinical-trial results.

Researchers who expend resources on clinical trials to prove drug efficacy no doubt have a personal investment in positive results; rarely are research careers made by demonstrating what *does not* work, and there is a reason why trials that do not show positive results are deemed failures. If researchers expect positive results, they may be more likely to view their negative results as inherently flawed or lacking much value. Study methods are frequently limited by practical and logistical considerations that may be overlooked in a positive trial but judged the cause of type 2 error in a negative trial. Researchers simply have less incentive to expend effort toward preparing a manuscript of a negative trial. Ninan, Poole, and Stiles defend their unpublished negative trial of low-dose venlafaxine by stating that it established a dose-response relationship, which, they imply, while useful from a regulatory standpoint, did not warrant publication except as supplementary data in another manuscript [4, 5]. Finally, drug companies have responsibilities to shareholders to generate profits by developing and marketing safe, effective drugs. Incentive exists for researchers to publish their data in a way that supports the enterprise of the drug company that funds their work, even if that involves suppressing the data itself.

Similarly, journal editors and reviewers have dual responsibilities to evaluate publications for scientific value and integrity and produce a journal product that justifies its subscription fees. Clinicians treating patients are interested in learning about new treatments that work for the conditions they treat. Drug-company representatives distribute studies that demonstrate what a new drug can do—not what it cannot do. Patients come to physicians looking for answers about how they can be helped, not how they cannot be helped. While negative trials are certainly not absent from published literature, studies with positive results inevitably generate more interest than studies that lack positive results.

Not one of these explanations, however, changes the fact that clinicians who aspire to use treatments that offer the greatest probabilities of fulfilling their patients’ needs find themselves handicapped by publication bias. Popular media readily interpret and package medical literature in ways that often stand to damage the patient-physician relationship. *The New York Times* review of Turner et al. shows particular restraint in exploring the article’s significance, focusing on the issues surrounding publication bias, but a report by *CNNMoney* the day before led with the headline

“Antidepressants May Not Work: Antidepressant Drugs May Have Little Effect on Patients, Many Unpublished Studies Show” [6, 7].

When physicians appropriately prescribe antidepressants, patients often struggle with the fact that antidepressants work slowly and do not work for everyone. If an antibiotic clears up an infection in a few days, it is not unreasonable for patients to ask why their Prozac doesn't clear up their depression just as quickly. When CNN tells them that their doctors were either lying to them or unwittingly giving them false information, they understandably question where they can place their trust.

Psychiatry is no stranger to controversy in popular media and serious academic circles. Psychiatric patients suffer stigma nearly unparalleled in other medical specialties, despite improved understanding of the biological contributions to mental illness by the scientific community and culture at large. Much of the popular psychoeducation has unfortunately come in the form of drug-company advertisements. Popular culture myths suggest that psychiatry has worked in conjunction with drug companies to pathologize natural human behavior and emotions in order to make money. Similar criticisms have been heaped upon other medical specialties; consider popular treatment of the increased use of statins, despite extensive evidence supporting their use in the management and prevention of coronary artery disease. Psychiatry, like all fields of medicine, has been working to develop practice models that use principles of evidence-based medicine to optimize patient care. The development of evidence-based practice, however, requires that transparent evidence is easily accessible to clinicians and researchers.

Publication bias is by no means limited to psychiatry. In September 2004, the *New England Journal of Medicine*, *The Lancet*, *JAMA*, *Annals of Internal Medicine*, and several other publications announced they would no longer publish the results of pharmaceutical company-sponsored studies that were not registered in a public database prior to the start of the study. Clinicaltrials.gov, the NIH-sponsored registry of federally and privately supported clinical trials conducted worldwide, currently has 68,630 trials with locations in 161 countries [8]. While such registration may not fully force all studies out of the file drawer, it better ensures that those seeking to perform meta-analyses will have the fullest data record possible.

Evidence-based medicine seeks to do much more than simply predict desirable outcomes in populations; it requires that physicians use their knowledge base and clinical experience to collaborate with patients to achieve better health. Published literature informs physicians' understanding of how to make decisions regarding how they counsel their patients. Less obviously, the unpublished literature must be accounted for as well, as we seek to use the best statistical and experimental methods to treat patients in ways that are worthy of their trust and collaboration.

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[Shared Decision Making Requires Statistical Literacy](#), April 2009

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CLINICAL PEARL

Shared Decision Making Requires Statistical Literacy

Chandra Y. Osborn, PhD, MPH

The movement toward evidence-based medicine has emphasized the integration of clinical expertise, patient values, and the best evidence (clinical research based on sound methodology) in the decision-making process for patient care [1, 2]. Identifying the best evidence requires physicians to have new skills, including the ability to search the literature efficiently, apply formal rules to evaluate research, and understand health statistics.

Gigerenzer et al. have coined the term “statistical illiteracy” to describe the widespread difficulty in understanding, interpreting, and communicating health statistics [1]. Shared decision making is a cornerstone of evidence-based medicine that requires a level of statistical literacy on the part of physicians, who have an increased responsibility to communicate numerical information effectively to patients. An example will make this clear. Let’s take prostate cancer as a case in point.

Prostate cancer is the most common cancer in American men, with an estimated 186,320 new cases and 28,660 deaths in 2008 [3]. About 1 man in 6 will be diagnosed with prostate cancer during his lifetime, but only 1 in 35 will die from the disease [3]. Screening for prostate cancer remains controversial, due to insufficient evidence to recommend or oppose screening [4, 5]. Although many medical and professional organizations agree that patients should be involved in the decision to undergo screening, studies show that, prior to screening, physicians often give patients little or no information about the test and its implications [2, 3, 5-12]. The reason for this is that few physicians are prepared to explain the test’s positive predictive value to patients.

A panel of national experts and patients has developed a list of 10 facts men should know before giving consent to PSA screening [13]. One of these facts is that false-positive PSA results can occur (when the PSA level is elevated, but there is no cancer). Sheridan et al. found that 24 percent of patients were unaware of the potential for inaccurate test results [14]. Prior to engaging patients in a shared decision-making discussion, urologists should know a man’s chance of actually having prostate cancer if he test positive in his PSA.

Although one might assume that every physician knows the answer, Hoffrage et al. suggest that many experts, including physicians, have difficulty making sense of health statistics [15]. Faculty, staff, and students at Harvard Medical School were asked to estimate the probability of a disease given the following information: if a

test to detect a disease whose prevalence is 1/1,000 has a false-positive rate of 5 percent, what is the chance that a person found to have a positive result actually has the disease, assuming that you know nothing about the person's symptoms or signs [15, 16]? The estimates varied wildly, ranging from the most frequent estimate, 95 percent (given by 27 out of 60 participants), to the correct answer, 2 percent (given by 11 out of 60 participants) [15, 16]. A separate study showed that physicians confuse the sensitivity of a test (the proportion of positive test results among individuals with the disease) with its positive predictive value (the proportion of individuals with the disease among those who receive a positive test result) [15].

Gigerenzer et al. illustrate the widespread problem of statistical illiteracy using various examples, one of which has been modified here [1]. Assume you want to perform a PSA screening test on a patient who lives in a specific region of the country. You know the following information about men in this region:

- The probability that a man has prostate cancer is 1 percent (prevalence).
- If a man has prostate cancer, the probability that he tests positive is 90 percent (sensitivity).
- If a man does not have prostate cancer, the probability that he nevertheless tests positive is 9 percent (false-positive rate).

During the pre-screening discussion with this patient, he asks you what the chances are of having prostate cancer if the test comes back positive. What is the best answer?

- A. The probability that he has prostate cancer is about 81 percent.
- B. Out of 10 men with a positive PSA test, about 9 have prostate cancer.
- C. Out of 10 men with a positive PSA test, about 1 has prostate cancer.
- D. The probability that he has prostate cancer is about 1 percent.

The best answer is “C”—one out of every 10 men who test positive in screening actually has prostate cancer. The other nine are false alarms [1]. The answer can be derived from the health statistics provided.

Health statistics are commonly framed in a way that tends to cloud peoples' minds [1]. The information is presented in terms of conditional probabilities—which include the sensitivity and the false-positive rate (or 1 specificity) [1]. Presenting the information in terms of natural frequencies can foster greater insight [1, 15, 17, 18]. Here, following Gigerenzer et al., is the same information from the above problem translated into natural frequencies [1]. Assume you want to perform a PSA screening test on a patient who lives in a particular area of the country. You know the following information about men in this region:

- Ten out of every 1,000 men have prostate cancer.
- Of these 10 men with prostate cancer, 9 test positive.
- Of the 990 men without prostate cancer, about 89 nevertheless test positive.

How can this simple change in representation turn innumeracy into insight? Natural frequencies facilitate computation and represent the way humans encode information

[1, 16]. Unlike relative frequencies and conditional probabilities, they are simple counts that are not normalized with respect to base rates [17, 19].

A fundamental problem in health care is that many physicians do not know the probabilities that a person has a disease given a positive screening test—that is, the positive predictive value [1]. Nor are they able to estimate it from the relevant health statistics when they are framed in terms of conditional probabilities, even when this test is in their area of specialty [18]. Careful training on how to translate probabilities into natural frequencies is needed [15]. The following four steps have been proposed [15]:

1. Select a population and use the base rate to determine how many individuals in the population have the disease.
2. Take that result and use the test's sensitivity to determine how many individuals have the disease and test positive.
3. Take the remaining number of healthy individuals and use the test's false-positive rate to determine how many individuals do not have the disease but still test positive.
4. Compare the number obtained in step 2 with the sum of those obtained in steps 2 and 3 to determine how many individuals with a positive test actually have the disease.

Conclusion

Framing information in a way that is most readily understood by the human mind is the first step toward educating doctors, and ultimately patients, in risk literacy [1]. Prior to PSA screening, patients should know the risks and benefits associated with the test, and the implications of a positive result. Physicians, in turn, have an ethical responsibility to be functionally literate in health statistics when delivering that information to patients. Given that false-positive test results have been linked to increased cancer-related worry and problems with sexual function, effective discussion about inaccurate test results is needed prior to screening [20].

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HEALTH LAW

Institutional Review Board Liability for Adverse Outcomes

Micah R. Onixt, JD, MBA, and Robyn L. Sterling, JD, MPH

In 1998, the U.S. Department of Health and Human Services, Office of Inspector General placed institutional review boards (IRBs) under the spotlight. In its examination of clinical trials, the inspector general reported that IRBs, charged with approving all federally funded research, demonstrated a clear lack of cogent oversight, which raised safety concerns for the subjects [1]. In early 2009, the Office for Human Research Protections released a list of various IRB deficiencies—further highlighting their continuing and pervasive problems [2]. Often times, IRBs must cope with pressures from hospitals or universities to grow revenues from research and development, which, in turn, causes the IRB to accept greater liability for adverse clinical-trial outcomes in return for increased monetary compensation. Simply put, today's IRBs face a multitude of issues from different directions. To better understand these issues, it is important to take a look at the history and significance of IRBs.

Background

Throughout history, people have heinously violated human rights and human dignity in the name of biomedical research. The Nazi doctors' experiments during World War II and the infamous Tuskegee Syphilis Study conducted by the U.S. Public Health Service represent the most well-known abuses in modern history. The Nazi experiments ultimately resulted in the torture and death of thousands of unwilling human subjects. These atrocities led to the development of the Nuremberg Code in 1947, which declared the overriding and guiding principle required for any clinical research—informed consent.

The Tuskegee Syphilis Study, which began in 1932, involved approximately 400 African American men infected with syphilis. The U.S. Public Health Service tracked these men for roughly 40 years without providing them with any information or treatment for the disease. As a result, hundreds of them and their families lost their lives to the scourge of a treatable disease. Congress responded with the National Research Act in 1974, which created the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research [3]. In 1979, this commission published the Belmont Report to identify the minimum ethical principles required for human-subject research [4].

The federal government did not stop with the Belmont Report. In 1991, the U.S. Department of Health and Human Services published the Common Rule, which mandated that IRBs approve any federally funded biomedical research in which the

federal government plays a significant regulatory role [5]. IRBs had been around since 1966 when they were created by the U.S. Public Health Service. But the Common Rule standardized their membership, operations, and record-keeping requirements [6]. Specifically, it said that IRBs must consist of at least five members who have diverse backgrounds and levels of experience, including both scientific and nonscientific qualifications. This diversity promotes well-rounded perspectives for review of study protocols and affected populations [7]. Most importantly, the Common Rule required that an IRB must include sufficiently knowledgeable and experienced members to protect the subjects from exploitation during the research process [7].

Overview of the IRB Role

IRBs must verify that new and ongoing research protocols comport with federal criteria ensuring human-subject protection [8]. Typically, an IRB serves a university or hospital, and membership is purely voluntary. Those that join an IRB assume great legal and ethical obligations to ensure the health, safety, and welfare of the human-research subjects. Specifically, an IRB must devise a risk-benefit ratio to determine whether the benefit of the research outweighs the risk to the subject [9]. The government charges IRBs to assess the following: (1) whether a protocol adequately minimizes the risks to study participants and provides for the equitable selection of subjects, (2) the adequacy of the informed-consent documents and procedures, (3) sufficiency of data safety, privacy, confidentiality, and monitoring, and (4) whether the study sufficiently protects vulnerable populations [9]. An IRB reviews and then approves, rejects, or modifies study protocols throughout the biomedical-research process as frequently as necessary to guarantee the safety of the subjects [8]. Failing to adequately insulate subjects from clinical-trial risk may impose liability on culpable IRBs.

Liability Concerns

As the number of clinical trials continues to increase, IRB protocol reviews increase to meet the growing demand. The greater number of protocols under review means greater risk for IRBs that an adverse outcome might occur. IRB members must balance that risk with increased pressure from an IRB member-employer to certify studies and boost cash flow. Hastily approved studies expose investigators, IRBs, and research institutions to significant liability should adverse outcomes occur.

This conundrum is best exemplified by the Jesse Gelsinger case. Jesse, an 18-year-old male with a rare genetic liver disease, enrolled in a phase I clinical trial of gene-therapy treatment conducted at the University of Pennsylvania. A serious, unfavorable reaction to the treatment occurred, and Gelsinger experienced multiple organ failure and died days later. Shortly after his death, new facts surfaced that highlighted significant irregularities in the IRB approval process for the clinical trial. The violations included: (1) a conflict of interest for the primary investigator in terms of pecuniary gain for trial success, (2) failure to report previous adverse events, (3) the enrollment of unqualified subjects, including Gelsinger, and (4) approval of inadequate informed-consent documents and procedures. Luckily for the university,

the plaintiffs did not name any of the IRB members as a party in the litigation, but such errors could have dire consequences for similarly acting IRBs. In particular, a culpable IRB may be subject to multiple types of liability including a breach of confidentiality and a breach of fiduciary duty.

Several high-profile cases brought against IRBs since the early 1970s have settled for undisclosed amounts or failed to reach a decision on the merits of the case [10-12]. An Oklahoma court dismissed *Robertson v. McGee* for lack of subject-matter jurisdiction, but not before the Office for Human Research Protections faulted the IRB for its failure to provide continuous review throughout the clinical-trial process [12]. Ultimately, past litigation signifies that delinquent IRBs can, and will continue to be, joined in litigation for the tort of negligence. This liability may carry severe economic consequences including punitive and consequential damages totaling millions of dollars. If IRBs are found legally negligent and IRB members are named as individuals in the suit, they may possibly have to pay out of their own pockets if ordered by the court or as part of a settlement. The IRB may be joined as part of a hospital or university, in which case, the larger entity would pay. More often than not, when an IRB is implicated, its members are folded as a single body—the IRB—into the suit against to the hospital or university.

Federal regulations delineate legal duties that IRBs must follow. Specifically, they have the responsibility to oversee clinical research, which creates a duty of care or standard of care to protect human subjects from a foreseeable harm that could occur during the course of the study. An IRB that fails to monitor research or halt a study that does not align with federal standards violates its duty of care. Other breaches include approving inadequate informed-consent documents and permitting conflicts of interest on the part of investigators or even IRB members themselves.

Even if these types of breaches occur, an IRB may escape liability if there is no tangible injury to a human subject. In other words, the IRB is not liable for negligence if an injury did not occur. As a reminder, negligence contains four elements: duty, breach of the standard of care, injury, and causation. Based on these elements, a plaintiff can successfully claim negligence against an IRB only by demonstrating that the IRB acted negligently with respect to each element. The degree of injury usually has an impact on the negligence claim, so the graver the injury due to the clinical trial, the easier for the harmed subject to prove negligence against the IRB.

IRBs play a pivotal role in the protection of human subjects participating in biomedical research. This role has its origins in both a checkered history of human research as well as federal regulations designed to prevent atrocious incidences from recurring. Unfortunately, as both the Office of Inspector General and the Office for Human Research Protections reported, despite this critical role and the severe consequences that may result from failed implementation, IRBs routinely fail to provide adequate oversight of biomedical research [2]. As the number of clinical

trials and IRB reviews increase, IRBs will continue to expose themselves to liability should human subjects experience adverse outcomes.

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POLICY FORUM

The History and Role of Institutional Review Boards

Margaret R. Moon, MD, MPH, and Felix Khin-Maung-Gyi, PharmD, MBA

Editor's Note:

Institutional review boards (IRBs) have evolved since the middle of the 1960s as independent reviewers of research protocols that, if approved, will be funded by the U.S. government or will test drugs or devices regulated by the Food and Drug Administration. As their name suggests, IRBs began and developed at academic research institutions. More recently, independent, so-called "central" IRBs have come on the scene. The following two articles recap the history of IRBs and examine the strengths and weaknesses of local, institution-affiliated IRBs and central, non-affiliated IRBs.

A Useful Tension

Margaret R. Moon, MD, MPH

"Act in such a way that you treat humanity, whether in your own person or in the person of any other, always at the same time as an end and never merely as a means to an end" [1].

Immanuel Kant's second maxim defines the tension that drives and bedevils IRBs. Human-subjects research uses humans as subjects, as a means to an end. The imperative that it is never *merely* as a means, but always *also* as an end in themselves, makes IRBs necessary.

The history of human-subjects research is replete with horrid examples of what happens when investigators fail to respect humans as ends in themselves. Even after the Nuremberg trials exposed the Nazi war crimes and the Nuremberg Code provided a clear statement of standards for research on human subjects, unethical research programs continued to be designed and conducted [2]. In the United States, the Willowbrook study of hepatitis transmission in a hospital for mentally impaired children, Tuskegee Syphilis Study, Fernald State School trials using radioactive minerals in impaired children, and Jewish Chronic Disease Hospital case in which chronically ill patients were injected with cancer cells to monitor rejection, are infamous examples of egregiously unethical research designed and conducted long after the Nuremberg Code was in place. In each of these studies, investigators were confident that the ends of research justified the means.

The National Research Act of 1974, passed in response to growing concern about the ethics violations in research, created the National Commission for the Protection of

Human Subjects of Biomedical and Behavioral Research. The Belmont Report of 1974 was the commission's summary of the ethical principles that form the basis of acceptable human-subjects research, and the three foundational Belmont principles were:

- *Respect for persons.* This principle includes both respect for the autonomy of human subjects and the importance of protecting vulnerable individuals.
- *Beneficence.* More than just promotion of well-being, the duty of beneficence requires that research maximize the benefit-to-harm ratio for individual subjects and for the research program as a whole.
- *Justice.* Justice in research focuses on the duty to assign the burden and benefits of research fairly.

Recent questions about the role of IRBs and their structure and affiliations are easier to understand in light of their historical and ethical foundations.

The essential conflict in research is the duty to avoid allowing the ends to justify the means. Individual investigators, although generally dedicated to promoting the well-being of their subjects, may not be well placed to identify and avoid the influence of inherent conflicts of interest. IRBs have to be independent from the investigator and the rewards of research. Arguments about the appropriate location of IRBs: so-called “central” IRBs versus “local” IRBs focus on the board's level of independence.

Central IRBs are usually for-profit ventures and receive payment from investigators for their services. Arguments against central IRBs maintain that these ventures are open to influence from the investigators who pay them and that their income derives from their ability to please the investigators, which may pressure the board to quick and easy approval.

Local IRBs are functions of the academic institutions that conduct research. Arguments against local IRBs point out that the academic institution itself has conflicts of interest about research. The institution benefits from the research dollars and the prestige associated with a far-reaching and well-funded research agenda. Local IRBs are under pressure to approve research to protect the financial resources and power of the institution.

Both sets of arguments are valid critiques of the risks in their respective structures. Neither structure is free from potential conflict, and neither is inevitably tainted. Other questions might be more reasonable. Are there benefits to locating an IRB within the academic institution conducting research that are not attainable in a central IRB structure, and if so, how can local IRB structure and function be optimized?

Advantages of Local IRBs

Local IRBs, through the academic institutions that house them, reflect those institutions' complex relationships with their communities. Academic institutions are not virtual, they are brick-and-mortar structures that exist within a geographic

community. The relationship between the institution and the community usually involves clinical care, education, and employment in addition to research. The interests and experiences of the community and academic institution are not easily separable. One of the most productive tensions within local IRBs reflects these shared interests. Subjects of research are often also patients in the hospital or clinic, family members of patients, students in the university, or other community members. Problems arising within the research setting affect the community, the standing of the institution within the community, and eventually the trust and respect between clinician and patient. These relationships are critical to the mission of the institution, as is the flow of research dollars and accompanying prestige. Local IRB members are directly affected by the relationship between “town and gown” and are well placed to want to protect it.

Within an institution, researchers are also recognized as clinicians, educators, and colleagues. The track record of a particular investigator with regard to other aspects of professional practice may be known to a local IRB in ways that are not available to central IRBs. Concerns that may impact the investigator’s ability to conduct research appropriately can be identified and monitored more effectively by local IRBs. Reliance on local IRBs makes it difficult for investigators to “shop” challenging protocols to IRBs they think will view the protocols favorably.

Human subjects are also patients, colleagues, students, and community members. Local IRBs may be best placed to consider human protections in the wider sense of the subjects’ experience and to incorporate the impact of research on communities and the relationships among subject, community, and institution as part of the review. Local IRBs emphasize the institution’s responsibility for the whole of the research enterprise and all of its ramifications.

Disadvantages of Local IRBs

Proponents of central IRBs argue that the nuanced view described above makes for slow and inconsistent reviews. Particularly with multicentered trials, local variations in review and requirements create havoc [3]. This is probably a valid observation, although not an unavoidable problem. However frustrating, the fact that the research itself takes place in a local setting, is conducted by local researchers, and enrolls local subjects ought to make an institution consider carefully before yielding its duty to protect subjects to an outside body.

Improving Local IRBs

If, as I argue, the local IRB structure offers something valuable, how can its function be optimized to best fulfill the duty of protecting human subjects? Three areas worthy of improvement are IRB membership, evidence base for IRB review, and IRB mission.

IRB membership. The Office for Human Research Protections’ guidelines on membership for IRBs are reasonably loose. IRBs must have at least five members including at least one member:

- Whose primary concern is scientific.
- Whose primary concern is nonscientific.
- Who is not affiliated with the academic institution.

The experience and expertise of members must be sound and relevant enough to promote respect for the board's advice in safeguarding the rights and welfare of human subjects. Membership should reflect the types of research the board reviews and should avoid any semblance of discrimination. Two specific areas of IRB membership deserve discussion: the role and use of community representatives, and the need for ethics expertise on IRBs.

Many academic (local) IRBs include a person who is asked to represent the interests of the community as a non-affiliated member. While this role can be extremely helpful, the usual process of identifying and engaging community members has not been conducive to meaningful involvement. Community members report that their main function seems to be to simplify the language of consent forms. Few have had significant training and many report feeling intimidated or disrespected by other IRB members [4]. Most importantly, the task of representing "the community" may be impossible given most communities' diverse interests and vulnerabilities [5]. Effective community representation may be necessary to help IRBs meet their mandate, but this requires a more directed and goal-oriented approach. Instead of relying on individual representatives, the IRB function might be better supported by well-organized and consistent use of community advisory boards for research that is (1) of particular interest to the local community, (2) of concern to a specific and identifiable subset of the community, or (3) community-based research that is nontherapeutic. Community advisory boards are able to represent a variety of stakeholders within the community, reducing reliance on an individual community member. They can be created for a specific protocol, including members with related experience or specific representation of vulnerable groups. Functioning in parallel to the IRB's, they can present reports and recommendations to the IRB without increasing the IRB workload.

Although the function of an IRB is fundamentally to answer questions about ethics, there is no requirement that IRBs include members with specific ethics expertise. This raises challenges for IRBs because, as the NIH explains:

45 CFR Part 46 is not a set of rules that can be applied rigidly to make determinations of whether a proposed research activity is ethically "right" or "wrong." Rather, these regulations provide a framework in which investigators and others can ensure that serious efforts have been made to protect the rights and welfare of research subjects [6].

With or without expertise, IRB members engage in discussion of complex questions about conflicting moral obligations such as the duty to: (1) protect human subjects while respecting their autonomy to engage as willing subjects, (2) consider the limits of parental authority to consent to research on their children, and (3) balance current

harms against future benefits when incompetent subjects are involved. Ethics expertise can be helpful to an IRB, particularly in identifying and analyzing conflicting moral obligations, considering research-ethics literature, encouraging a consistent approach to ethics issues, noting and clarifying the impact of the personal moral values of the IRB members, and explaining the ethics-related conclusions of IRB reviews. An IRB without ethics expertise among its members may benefit from consulting ethicists for particularly complex cases.

Evidence base for IRB review and clarifying the mission. IRB members volunteer their service. IRBs review complex research from a broad range of clinical and scientific disciplines, with single protocols sometimes running hundreds of pages in length. Careful review of protocols requires substantial clinical understanding and willingness to read deeply. Given these demands, some have unrealistic expectations of their members who face competing professional demands.

IRBs are experiencing a drift in mission that draws members away from the duty to ensure the fundamental protection of human subjects. “Mission drift” has two main causes, an interpretation of oversight requirements that employs the widest connotations of “research” and “risk,” and an increasing focus on process and documentation that takes time away from thoughtful review of important protocols. The definition of research in the federal guidelines is broad enough to include a vast array of efforts to produce generalizable knowledge, from oral histories to “first in human” drug trials. While there is potential for risk to human subjects in all such efforts, institutions that rely on the same IRB to identify and oversee all potential risks in types of research can easily overwhelm the board. Definitions of risk are both extensive and incomplete in the federal guidelines. Risks to human subjects are both biomedical and behavioral, and the latter can be psychological, social, and economic. Categorization of risk following the federal guidelines is open to wide and variable interpretation by individual IRBs. Better definitions of types of risk and data to encourage consistency in applications would help IRBs limit the types of research that require full IRB review and make reviews seem less capricious and unpredictable [7].

The seemingly inevitable expansion of process and documentation comes at the expense of meaningful dialogue; this phenomenon is common enough in institutions. In an overburdened IRB system, however, the result is “simultaneous overregulation and underprotection” [8]. Uncertainty about regulations and fear of disciplinary action encourages investigators to over report safety issues. HIPAA guidelines add layers of documentation with minimal functional benefit; compliance requirements of the IRB accreditation process compel unrealistic documentation; regulations require full IRB review of minor changes in massive protocols; and regulations on consent forms encourage a focus on structure over function. These are just a few of the influences that drive IRBs toward an unproductive balance of process over protection [9].

While the problems facing local IRBs are substantial, they are not inevitable. Local IRBs offer a unique benefit to researchers, institutions, and communities, most specifically to the relationships that bind these three entities. The defining role of IRBs, to protect human subjects of research, can and ought to be preserved and reinforced. Protecting local IRBs may require a review of IRB procedures with an eye toward a better business model with a more narrowly defined role and efficient process, reasonable salary support for IRB members, the development of better data upon which to justify risk decisions, and better use of community representation and ethics expertise. These changes should bring IRBs back toward their primary mandate and help preserve the unique value of local IRBs.

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Local and Central IRBs: A Single Mission

Felix Khin-Maung-Gyi, PharmD, MBA

The evolution of protection for human-research subjects in the United States is rooted in the tragic outcomes of unregulated, unethical research conducted worldwide [1-4]. Similarly, oversight of the development, marketing, and sale of safe foods and drugs has evolved into a more regulated environment following the revelation of several catastrophic and heartbreaking events associated with the consumption of mislabeled or adulterated products [5, 6].

In the United States, compliance with federal regulations is mandated if research involves federal funding or if a product (drugs, devices, biologics) or product component is regulated by the Food and Drug Administration. The federal regulations address the responsibility of a sponsor, principal investigator, and an independent reviewer—the institutional review board (IRB). Typically, the sponsor is a government agency or company that pays to conduct the research. The principal investigator carries out the research and collects the data. The role of the IRB is to review and approve proposals for research that involves human subjects to assure the protection of their rights and welfare before the research is undertaken. Following the initiation of the research, the IRB must continue to provide oversight at intervals appropriate to the degree of risk associated with the research, but not less than once per year.

Historical landmarks on the road leading to the current U.S. regulations include the Nuremberg Trials (and the Nuremberg Code), Willowbrook hepatitis study, Jewish Chronic Disease Hospital case, and Tuskegee Syphilis Study, among others. The most notable from a regulatory-reform perspective is the legacy of the U.S. Public Health Services' Tuskegee Syphilis Study, formally entitled Tuskegee Study of Untreated Syphilis in the Negro Male, conducted in rural Alabama. This deceptive and unethical study, which began in 1932 and terminated in 1972, was not an interventional study but observational in scope and intent. It denied treatment to infected individuals even after the commercial availability of penicillin—a known and accepted treatment for syphilis. Following the publicity of the study, the National Research Act became law in 1974, and prompted the creation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

The commission produced The Belmont Report, which identified ethical principles that served as the foundation for the regulations as we apply them today—the three being: respect for persons, beneficence, and justice [7]. Respect for persons allows individuals to be self-directed and make informed, voluntary decisions about whether they wish to participate in research. Fundamentally, this respect for individual decision making is operationalized by obtaining and documenting informed consent from the prospective subject. Beneficence assesses the risks of participating in research against the benefits a participant might realize, recognizing the obligation of the researcher to minimize risks while maximizing the benefits of participation. The

principle of justice, when applied to selecting subjects and populations for research, directs investigators to seek those who would benefit from the outcome of the research and to not impose undue risks on those who would not otherwise be helped from the research. A violation of the principle of justice occurred when prisoners were asked to participate in dermatologic research for cosmetic manufacturers chiefly because they were a captive group and willing to participate [8].

The Belmont Report also helped define the distinction between clinical research and clinical practice in the following manner:

For the most part, the term “practice” refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success. The purpose of medical or behavioral practice is to provide diagnosis, preventive treatment or therapy to particular individuals. By contrast, the term “research” designates an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships). Research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective [9].

The current regulatory definition of research is accepted to be activities that lead to contribution of generalizable knowledge and that require oversight by an independent body (IRB) for the protection of human-research subjects.

Regulatory authority of the IRB includes the authority to approve, disapprove, or require modifications to some aspect of the application or protocol before granting approval of the research it oversees. Applications that an IRB disapproves may not be approved by another individual. Research that an IRB approves, however, may be disapproved by a duly designated official of the institution. Criteria an IRB uses to make its determinations are described in the regulations and can be summarized as addressing aspects of the research that:

- Minimize risks to subjects.
- Include only those risks to subjects that are reasonable in relation to anticipated benefits, if any.
- Assure the equitable selection of subjects.
- Ensure respect for a subject’s rights by having each subject, or his or her legally authorized representative, give informed and voluntary consent that is appropriately documented.
- Ensure that the research plan makes adequate provisions for monitoring the research.
- Ensure that there are adequate provisions to protect the privacy of a subject and maintain the confidentiality of data.

- Ensure that additional safeguards have been included when some or all subjects are likely to be vulnerable and there is a potential for coercion or undue influence.

What the regulations don't mandate is where the IRB is located and *how* it carries out its duties. Traditionally, IRBs were located where the investigator conducted research, such as an academic medical center. But the research enterprise has evolved so that IRBs are now affiliated with community hospitals, associations providing funding for research, and regulatory agencies. Central or independent IRBs are not affiliated with any researcher or research institute.

All types must comply with the same regulations governing the protection of research subjects. Central and independent IRBs came into existence because researchers who had gravitated away from the academic medical centers and toward the community and private practice maintained their research interests. These investigators primarily conducted pharmaceutical, device, and biologics company-sponsored research but did not have access to an IRB. The independent IRBs fulfilled that requirement, enabling researchers outside the academic medical systems to conduct research in compliance with the regulations. Recent experiences and evaluations of the human-research protections systems have suggested that a centralized oversight system might be more appropriate, especially given the globalization of research [10-12].

The emergence of the various models of IRBs has raised concerns about a range of potential conflicts of interest, particularly for those IRBs that provide oversight for a fee. In the present environment, the role of accreditation by the Association for the Accreditation of Human Research Protections (AAHRP) has helped to formalize standards that research organizations can measure themselves against voluntarily. To attain AAHRP accreditation, IRBs and research organizations, independent or affiliated with teaching medical centers, must demonstrate and document compliance with applicable regulations and standards of practice. While the accreditation process is an optional supplement to industry and regulatory oversight, some industry thought-leaders have embraced it as the acceptable standard for conducting appropriate research [13].

In summary, oversight of human-research protections, and specifically the IRB, has evolved to accommodate research that is being conducted in sectors outside the traditional academic setting. While one might assume that the users of independent IRBs may “shop” for the desired answer from existing organizations, the FDA concluded that there is no evidence to suggest that there is abuse of “answer shopping” [14].

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MEDICINE AND SOCIETY

Priority Setting in Biomedical Research

Rebecca Dresser, JD

The 21st century is replete with exciting discoveries in biomedical science. Even a superficial review of research conducted at or funded by the U.S. National Institutes of Health (NIH) supplies irrefutable evidence of the enormous range of opportunities that exists today. A survey of studies occurring in the private sector only adds to this evidence. And researchers in every field are enthusiastic about the knowledge and clinical benefits that their work could deliver.

The array of promising research areas presents itself in a context of limited resources, however. The NIH and private-sector funding sources must make difficult decisions about the fields and specific studies to support and must do so in a nation and world full of people vulnerable to an immense number of health problems.

Research-funding entities use broad criteria to allocate their limited resources. Under pressure to articulate the government's decision-making process, NIH officials issued a document explaining their allocation criteria in 1997. Five considerations play a role in the agency's spending choices: (1) public health needs; (2) scientific merit of specific study proposals; (3) potential for advances in a particular area; (4) distribution across diverse research areas (because it is impossible to predict exactly where advances will occur); and (5) national training and infrastructure needs.

The first NIH criterion, public health needs, is determined by the:

- Number of people with a specific disease.
- Number of deaths a specific disease causes.
- Degree of disability a specific disease produces.
- How much a specific disease shortens the average human lifespan.
- A specific disease's financial and social costs.
- Threats posed to others by contagious disease.

According to the NIH, these considerations are of equal importance in allocating research resources [1].

Resource allocation in the private sector may incorporate some of the same considerations as the NIH applies, but other factors play a role too. Pharmaceutical, biotechnology, and other companies are profit-making entities that consider the size of anticipated financial return as an essential guide to research investments. And nonprofit organizations often limit their support to research that could assist their specific disease constituencies.

Public and private choices about allocation of resources for research and public health needs raise social-justice issues. The ethical question is whether these funding sources make fair decisions about where to invest their resources. The NIH has the clearest obligation to distribute its resources fairly because it is taxpayer-supported. There is disagreement over whether private organizations have this obligation too; some believe that even businesses have a responsibility to consider the public good in their research investments [2].

The problem lies in deciding what qualifies as a fair allocation decision. The NIH lists factors that many people would use to determine fairness, but fails to rank them according to their importance. Moreover, its priority-setting criteria omit other ethical considerations that could bear on fairness, such as the relative significance of research needs of people in the United States compared to those in poor nations.

Not much attention is paid to fairness in research priority setting, but some writers have explored the topic and questioned the fairness of the NIH's current approach to resource allocation. For example, some criticize it for allowing current politics and political correctness to shape its allocation decisions [3]. A related charge is that interest-group lobbying plays too heavy a role. Others contend that the NIH should do more to show that its choices are aimed at conditions that impose the heaviest personal and social burdens. And at least one critic argues that the current criteria place too heavy an emphasis on extending the average lifespan and not enough on public health, disease prevention, and disability reduction [4].

It is not surprising that clear consensus is lacking on defensible research priorities. As the NIH criteria illustrate, there are many variables, and people differ in the value they assign to each. Is it more important to study childhood diseases than diseases affecting older individuals? Is extending life more important than ameliorating the burdensome symptoms of illness? Should life-threatening diseases that affect a small number of people take priority in the research agenda over less-serious diseases that affect many more individuals? Is it better to invest money in areas where breakthroughs appear imminent or in less-promising areas, where investments might jump-start research progress? People answer these questions differently based on their values and personal experiences with disease [5, 6].

Social justice becomes even more critical in the international context. Discussions of international research priorities often refer to the 10/90 split. Estimates are that just 10 percent of research focuses on the diseases that are responsible for 90 percent of the world's health problems. Most research occurs in wealthy countries and tends to study the diseases that affect people living in those countries [7]. Is it defensible for wealthy countries to devote so little to research on conditions like malaria, tuberculosis, diarrhea, and malnutrition, and so much to conditions that affect primarily people fortunate enough to live into their later decades [8]?

It may seem shocking to raise questions about the fairness of the current approach to biomedical research funding. But Daniel Callahan, a noted writer on bioethics and health policy, presents the following thought experiment:

Consider—as an imaginative exercise—what we would get if there was no progress at all from this point forward, and medicine remained restricted to what is now available. The rich countries would remain rich. Most of their citizens would make it to old age in reasonably good health. There would continue to be incremental gains in mortality and morbidity, the fruits of improved social, economic, and educational conditions, and improvements in the evaluation and use of present therapies. No prosperous country would sink from the lack of medical advances [4].

Callahan's points relate to a second matter of social justice, which concerns the trade-offs between funding research and established health care. The United States has a poor record of providing basic health care to its people. Estimates are that more than 40 million individuals lack health insurance coverage and even more have inadequate coverage [9]. As a result, a large part of the community has trouble obtaining established therapies that could extend and improve their lives. This situation raises questions about the justification for investing large amounts of money in research aimed at developing health care innovations, especially those that are likely to be expensive. As health plans expand to cover the fruits of emerging biomedical research, the added costs can lead to even more disparities in health care access.

Advocates contend that research is needed to assist people with illnesses or injuries that cannot now be adequately treated. For them, social justice supports research that assists this disadvantaged group. They see a “research imperative” to conduct studies that could save lives and avoid suffering by those who cannot be helped by established medicine [10].

The case for a moral duty to undertake research must consider a second position, however. Investing resources to expand access to standard health interventions would also save lives and avoid suffering among people now deprived of this help. Most established therapies have already been evaluated in research, their benefits are well known, and they are relatively inexpensive. In poor nations, many children and adults die from easily prevented or treatable diseases because their countries cannot afford to provide them with effective medicines [11]. For example, the HIV epidemic has imposed untold suffering and devastating social burdens on people unable to obtain treatment [12].

Should limited resources be invested in research to develop health care innovations or to allow more people to benefit from already existing therapies? This question is rarely addressed in debates about U.S. biomedical priorities [13]. The social-justice inquiry raises questions about which areas of biomedical research merit the highest priority and the relative priority of biomedical research when compared to health care delivery. Delivering meaningful help to people in need requires difficult choices about where to place our nation's limited resources.

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[The History and Role of Institutional Review Boards](#), April 2009

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HISTORY OF MEDICINE

Politics of Participation: Walter Reed's Yellow-Fever Experiments

Akhil Mehra, MD, MPhil

At the termination of the Spanish-American War in 1900, American military forces occupied the island of Cuba. Tropical diseases were a major concern of the government, and the American Surgeon General dispatched Major Walter Reed and a team of young doctors to investigate the diseases, particularly the pathogenic mechanism of yellow fever. Reed's team pursued a program of human experimentation by intentionally exposing human subjects, team members included, to potentially deadly virulent material. Despite several prominent fatalities during the experiment's run, Reed's experiments were a scientific success and instrumental in establishing that yellow fever was a mosquito-borne illness. Mosquito-control initiatives based on the findings were remarkably successful and began to reduce the incidence of the violent hemorrhagic fever significantly. For years following the experiments, the honor, bravery, and heroism of the volunteers were extensively celebrated in publicity campaigns, charity drives, a government-published "Yellow Fever Roll of Honor," popular books, a movie, and a Broadway play.

The abundant memorializing often assumed that heroism and bravery were the primary motivations of those who participated in the experiments. In looking at this piece of history, I seek to examine the question of motivation, using primary materials collected by the physician-historian Philip S. Hench in the 1940s, including first-person interviews with some of the surviving ex-volunteers. The analysis reveals that the actual self-stated motives for participation were more complex than simple honor or bravery; other factors such as ignorance of the risks, professional and occupational self-interest, and monetary inducements were pivotal. Moreover, as the experiments evolved in protocol and design, so too did subjects' assessments about the potential risks and rewards of participation. While honor and bravery should not be wholly written off as possible motivations, a re-analysis of the sources reveals that, at times, far more pedestrian concerns played into the decision to volunteer for the yellow-fever experiments.

The Experiments

Phase I. In the first days of the experiments, between August 6 and 16, 1900, Jesse Lazear, a young Johns Hopkins doctor and experimental board member, inoculated five soldiers with infected mosquitoes. The experimental protocol, including the process for selecting subjects, was haphazard at best. Reed, the lead investigator, had left Cuba and was not directly supervising the experiments. Nor did the board take seriously the mosquito theory, which had been widely dismissed in the medical press.

On August 16, 1900, Lazear inoculated himself. In an effort to confront anticipated ethical criticisms about using human subjects, the board members decided that they themselves would volunteer. The perceived level of danger that this presented, however, depended on how seriously the volunteers took the mosquito-vector theory. Throughout August 1900, the lack of confirmatory results made the mosquito-vector theory less and less plausible. After several failed inoculations with other volunteers, James Carroll (another physician board member) volunteered for self-experimentation on August 27. Several sources revealed that Carroll did not expect to get yellow fever from the inoculation because inoculations at this point were more likely to disprove rather than support the mosquito theory. It is probable the board wanted to move on to something more productive.

Everything changed when Carroll unexpectedly came down with a severe case of yellow fever a few days later. On the same day that his illness was confirmed, Lazear inoculated a Private Dean with an infected mosquito. By most accounts the inoculation was hasty and may well have been performed with a misleading disclosure of the risks to the young soldier. Dean came down with yellow fever around September 6, 1900. The spate of confirmatory results led the remaining board members to halt their own self-experimentation. Despite this, Lazear very likely inoculated himself again on September 13, with an infected mosquito. Tragically, he developed yellow fever and died 1 week later.

Why did Lazear knowingly infect himself this second time despite two confirmatory cases and the board's decision to curtail self-experimentation? One theory posits that his self-inoculation derived from guilt and sympathy for his colleague and fellow board member Carroll, who had not expected to contract the disease and had almost died from it. A better explanation is that Reed's absence, the pressure of scientific competition, and the lack of any guidelines or protocol during this disorganized experimental phase produced the circumstances that resulted in Lazear's death. This was the tragic end of the first phase [1].

Phase II. The second phase of the experiments began November 1, 1900. Following Lazear's death, Reed returned hastily to Cuba to design a new study protocol and supervise the experiments. The new protocol clarified guidelines for the selection and role of volunteers. While direct inoculations using infected mosquitoes continued, the second phase included several new treatment arms, such as an experimental building filled with the bodily fluids and infected clothing of those known to have yellow fever—so-called “fomites.” In this stage, volunteers were also directly injected with the blood of people known to have yellow fever.

The volunteers were now paid \$200 to participate and \$500 if they contracted yellow fever. This substantial payment, made in gold, would approximate \$8,000 and \$20,000, respectively, in today's dollars. Recent Spanish immigrants to Cuba were also sought as volunteers and were likewise well-compensated.

There is evidence that, after the public death of Lazear and confirmatory cases of Dean and Carroll, the mosquito theory became well accepted among volunteers during the second phase. For example, different arms of the experiment were regarded differently by some volunteers. And at times, volunteers refused to be moved from one protocol of the experiments to a potentially more dangerous or less desirable one [2].

Phase III. By August 1901, the experiments entered a third phase and were transferred from the base to a hospital in Havana. The protocol was well structured now and involved more blood-injection experiments and investigation into a yellow-fever antiserum. The mosquito theory had been presented to the worldwide medical community by Reed, based on the success of the second phase. Four out of approximately 10 volunteers in this third phase were Americans (the others were Spanish). There were three fatalities among this cohort, including the experiment's only female volunteer, an American nurse named Clara Maas.

In an interview, one American volunteer, John Bullard, made forthright comments about his motivations for volunteering. Bullard, a civilian, was attempting to start a farm in Cuba. Since volunteers received free expert medical care and were immune to further attacks of yellow fever, he concluded the following:

Volunteering to Dr. Carroll for experimental yellow fever was, I can assure you, a cold-blooded business proposition. There were no heroics in it as far as I was concerned....I suspected that I would probably get it spontaneously anyhow, so I decided I'd rather have it under favorable circumstances [3].

Conclusion

Several important findings from the various phases of the yellow-fever experiments relate to volunteers' motivation to participate and their assessments of the risks. First, the experiments were conducted in different phases, and, as they evolved, so too did assessment of the potential risks. Second, there was a broad spectrum of motivations for participation. I do not wish to degrade the influence of honor and bravery which have been so wrapped up with the historical memory of these experiments. But, while honor and bravery could have been motivations, ignorance, self-interest, and simple pragmatism might also have been. In the first phase, once Reed left Cuba, the supervising board members did not take the mosquito theory very seriously and were left in Reed's absence to improvise the experimental protocol. The board members were eager for results, and pursued aggressive self-experimentation more as a means to put the mosquito theory to rest than to vindicate it.

While Lazear's bravery and martyrdom have been duly acknowledged, he most likely infected Dean, who had minimal understanding of the risks, acting against better judgment and an agreement among the board members not to do so. The rush, along with Reed's partial absence in the early phase of the experiments, no doubt led to the shoddy scientific conduct of the experiments and a division among the group

as to how seriously to view the mosquito theory. It is in this context that the initial period of human self-experimentation must be considered.

Reed was angry with his colleagues for the conduct of the first phase of the experiments. His major contribution was in the second phase, during which he designed the ingenious set of rigorously controlled experiments that satisfied international scientific criteria. But the diversity of volunteers was notable. Both Americans and Spaniards may well have been motivated by monetary inducement and fears that they were likely to get yellow fever regardless. Moreover, the presence of different experimental arms, such as the fomite volunteers, confounds the issue of motivation for bravery's sake.

Bullard's case reminds us that medical treatment was also an important motivator for participants. In a time when disease could easily strike down a young man's ambitions, it made sense to get yellow fever "out of the way," while receiving the very best medical care the U.S. Army could provide.

Heroism in the experiments, then, was not a monolithic motivation. Volunteers for the experiments represented a broad range of interests for participation, including self-interest. This is true even today, as inducements for the participation in clinical trials include monetary payments, free check-ups, psychosocial support, or receiving a potentially life-saving drug.

On the other side, just as researchers today risk their reputations on the outcomes of breakthrough studies, scientific and professional fame were very likely attractive motivators in the yellow-fever experiments. We cannot forget that yellow fever was one of the most feared diseases of its time and that its cure was a hotly pursued scientific prize.

Thus, in addition to revising the myths about honor and bravery as the sole inducements of volunteers for the yellow-fever experiments, I would like to offer the model of clinical investigation where the interests of volunteers exist in a dynamic linkage to the interests of investigators. Indeed, as Susan E. Lederer has shown, participation in an experiment can resemble the exercise of politics, where participants can resist and negotiate the terms set upon them [4]. Medical ethicists are becoming more cognizant of the political dimension—as exemplified by a vast literature and growing guidelines about the recruitment of patients into experiments, significance of payments and monetary inducements, and requirements for providing and accepting informed consent [5].

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MEDICAL NARRATIVE

Volunteers and the Great Unknown: Interview with Clinical-Trial Participants

Amanda Redig

Don't think, try.

—William Harvey, physician (1578-1657)

In one of the earliest recorded clinical trials, British physician Edward Jenner decided to test his theory that infection with the cowpox virus provided protection from the more deadly scourge of smallpox. Jenner's approach, however, is also a bioethicist's worst nightmare. In the waning days of the 18th century, there was no such thing as informed consent, institutional review boards, or human-subjects protection. So, without much fanfare, Jenner simply transferred pus from a cowpox pustule to an incision he created on the arm of his 8-year-old test subject, James Phipps, and subsequently exposed the boy to smallpox. Luckily for Phipps, Jenner's idea did not prove fatal: cowpox exposure did offer smallpox protection. When the Royal Society of London declined to publish his findings, Jenner simply turned to more pediatric subjects to prove his point. As legend has it, this included his own infant son [1].

In the end, Jenner's ideas—if not his methods—were not as far-fetched as first imagined. While his discoveries were responsible for the first smallpox vaccine and earned him a place in medical history as the father of immunology, much has changed in the way physicians interact with patient research subjects since Jenner's time. After the trials at Nuremberg and the Declaration of Helsinki, the rights and protection of the patient-subject are at the forefront of any modern research trial [2].

What motivates people to participate in research protocols today? Entire departments and layers upon layers of federally mandated paperwork exist to protect both the scientific integrity of research as well as the health and well-being of human test subjects. One fundamental detail, however, has not changed in the days since Jenner exposed neighborhood children to smallpox: clinical research must necessarily contain an element of the unknown. Yet people still participate.

I decided to interview some clinical-study participants to see what they had to say about their decision to participate in a study and whether or not they would do so again. The studies represented were a trial that compared a new cancer drug to existing therapy and two preclinical research studies in which normal (non-sick) volunteers underwent neurological imaging or donated bone marrow for laboratory studies. Given the diversity of study aims, the answers of study participants may surprise you. And in a way, their thoughts about participating in clinical-research

projects embody the same spirit of inquiry that first set Jenner on his way over 200 years ago.

In their own words. “Why would anyone want to do that?” This is one of the first questions that comes to mind when one considers the uncharted waters of a clinical protocol. Yet as those close to patient-subjects make clear, sometimes it is the promise of something new and different that makes a study appealing. “My mom participated in the study because we were out of options at that point,” a family member said, referring to a study that was designed to test the efficacy of a new medication to treat a particular kind of cancer.

The drug she had been taking...stopped working, and the side effects of interferon were nearly killing her. We heard about Gleevec and weren't sure she would qualify for the clinical trial...but we thought, if she qualified, then why not? We had nothing to lose. She wasn't paid, but the promise of a new drug gave us hope when we were already expecting the worst.

This particular patient-participant's disease was so advanced at the time of therapy initiation that she eventually succumbed to it. The drug she received, however, is now standard therapy for this type of leukemia (chronic *myelogenous* leukemia) and has had a profound influence on pharmaceutical drug design. “Ultimately my mom knew she was fighting a losing battle,” her daughter noted. But, “I think she would have done it again, especially to be on the trial for a drug that revolutionized the therapy of CML as we know it.”

The same thread of hope is also a part of the motivation for a normal volunteer who participated in a different study that involved donating bone marrow for laboratory research. “If I truly believe in the utility and promise of clinical studies,” he said, “then I feel obligated to participate in whatever way I can to further the research goals of others, even if it means enduring slight discomfort.” This thought is echoed by a participant in the same trial who, even though she initially thought the bone-marrow-donation process was too painful to consider doing again, decided the right trial might change her mind. “Well, actually maybe I would do it again if it was something to help children or a disease like cancer or MS,” she said. “Clinical research is a wonderful thing, and it should be funded more,” she said.

Financial reward. The promise of hope is indeed a powerful motivation. Yet the question of financial remuneration is also powerful and one of the most complex issues involved in clinical studies. To avoid coercion, money offered to participants cannot be deemed excessive. Yet, particularly for the non-sick volunteers needed to serve as healthy controls for many types of studies, shouldn't there be some payback for donation of time and the experience of undergoing unpleasant and often painful procedures? Who is to say how much is enough (or too much)? And does money of any kind make people more likely to participate? The answer appears to be more convoluted than one might imagine. As one participant stated,

I donated bone marrow for a friend's PhD research project. The money was nice (I was paid \$150), but I mostly donated because I liked the idea of being included in my friend's project. As a future physician, I wanted to know what it was like to donate bone marrow, so I would understand what patients experience during bone-marrow biopsies.

This thought was echoed by another participant in the same study who remarked,

While I was compensated for my time and discomfort, this was not the primary motivation for participation. Knowing that part of me might be used to help better understand disease and perhaps lead to an improved diagnostic method or therapy was rewarding enough.

A third participant who also donated bone marrow concurred. "Well, for the money, yes," she said, when asked why she participated. "But also for the science factor. Depending on what it was for, I wouldn't need to be paid to consider it."

Sometimes, this same sense of curiosity leads people to participate in multiple studies. Another participant in the bone-marrow study remarked, "While a laboratory technician...I participated in several studies that involved transcranial magnetic stimulation (TMS) and MRIs. I was not compensated for the studies, but I participated because I was fascinated by the science and really interested in seeing the scans of my own brain."

Would you do it again? Repeat participation in future studies is—of course—the best way to gauge a clinical subject's overall experience on a research protocol. For the volunteers interviewed here who were not sick, the overwhelming answer seems to be affirmation of the promise of clinical research. As one participant put it,

I would definitely do it [donate bone marrow] again. Since then, I have donated blood for basic science research....The first time I did it, the guy unfortunately missed three veins and couldn't get any blood. I would still go back. I love the idea that I can contribute to science.

Another volunteer on the bone-marrow protocol added, "I hope to continue in whatever way I can to help researchers pursue their studies."

Yet participation in a clinical study of any kind is not an entirely benign experience. It is sometimes difficult to tell whether the new drugs and devices being tested are working. "She did start to feel better," a family member noted about a cancer patient participating in a trial evaluating a new medication. "But the course of the illness...and her death were about the amount of time the doctor had predicted, regardless of the [drug]." Furthermore, the time commitment required for evaluation of new therapies can be exhausting for people who are already sick. As the daughter of one participant put it: "I think my mom was getting frustrated with the constant appointments." Even for normal volunteers who participate in studies that do not

involve long-term follow-up, there is still the upfront commitment of time, not to mention sometimes unpleasant procedures. “No, I wouldn’t do it again. It was too painful,” remarked a study participant in reference to a bone-marrow donation.

Much has changed since the early days of medical research, but what will never go away is the challenge of finding a way to pursue progress when that progress requires human experimentation. Participation in a clinical study of any kind is a significant commitment. Yet it seems that such studies will continue to move ahead thanks to the sense of purpose felt by patients and normal volunteers alike. This general optimism is perhaps best summarized by an individual who lost her mother to cancer: “...I knew the medicine probably wasn’t going to make a miracle happen, but at least the [experimental] drug gave us all something new to have hope and faith in. And even if [it] didn’t help my mom, we were at least playing a part in something that maybe would work for someone else’s mother. I am sure my mom would agree.”

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