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Upcoming Issues of Virtual Mentor

December: Standards of Care: An Ethical Examination
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From the Editor

**Medicine in an Age of Science**

The theme editor introduces a special issue examining the balance between medical research, patient safety, and medical ethics.

At few other times in a long and illustrious history stretching back to Hippocrates has it been so exciting to be a physician. At the beginning of a new millennium heralded by the sequencing of the human genome, the promise of medical breakthroughs built upon a foundation of translational research shines brightly indeed. Yet the unprecedented pace of discovery in the biological sciences and the tremendous potential for advancement in the treatment of such scourges as cancer, neurodegenerative disease, and HIV do not come without a cost. For while the developments of the laboratory have given clinicians the expanded arsenal with which to attack the very DNA of a tumor or the enzymes of a retrovirus, they have also constructed a chasm between experimental science and effective clinical care that can only be bridged by a chain of human research subjects.

How do we respect the most universally recognized creed of the physician—first do no harm—when our ability to advance as a profession depends on at least some of our patients undergoing treatments that are not yet known to be efficacious and may in fact turn out to be quite harmful? How do we best regulate the design, operation, and reporting of clinical trials so that the ethical and professional demands of both science and medicine are satisfied? How do we define what constitutes "medical research" and how is the next generation of physicians, today's medical students and residents, educated to understand this process? How do we face the repercussions of a situation in which both patient and physician are willing to extend the accepted boundaries of medical care in pursuit of a second chance at life for the former? How do we sustain the integrity of the research relationship when vast sums of money are at stake? In short, how do we protect the patient when the patient is also a human research subject?

The November issue of *Virtual Mentor* centers around this theme of protecting the patient and presents a series of articles which expand upon some of the questions at the heart of this discussion. In the first case commentaries, David Alberts and Lucy Godley tackle the challenge of clinical trials as an option for patients with a terminal illness, those individuals simultaneously having the most to lose and the most to gain by participating in an experimental protocol. In the next pair of commentaries, Charles Weijer and Karen Kreiner weigh in on a different dilemma: how to consider experimental therapies for a patient with a disease for which successful treatments are already available. In the final clinical case, Vijaya Arekapudi comments on the rarely discussed middle ground—the actual process of conducting the clinical trial rather than its design or analysis—when things don't go as planned.

Following the clinical cases, the next set of articles begin to construct the social, legal, and policy framework of human subjects research. In their journal discussions, Alison Bickford and Abe Schwab shed light on 2 cornerstone topics: academic-industry partnerships and clinical equipoise, respectively. These analyses complement the related issues addressed in the 2 Policy Forum articles and the Medicine and Society piece. The risks and benefits in creating a clinical trials registry are expanded by Christian Krautkramer and Shane Green, while Daniel Carpenter takes up a related theme in his analysis of the FDA as the primary regulatory body for human subjects experimentation in the United States. Michael Berens and Gary Marchant consider the corollary social, legal, and scientific questions raised by advances in scientific technology; a legal analysis is further extended in Laura Lin and Bryan Liang's discussion of the Wright v. Fred Hutchinson case.

Finally, in keeping with its interdisciplinary tradition, this issue of *Virtual Mentor* also includes several pieces that speak to the humanities. Stephen Leapman and Sharon Moe reflect on past developments and the need for future
advances in the way in which medical students and then residents are trained to sustain and support medical research. Dr. Victoria Maizes and Dr. Randy Horwitz expand our consideration of medical research to encompass complementary and alternative medicine. Helle Mathiasen harnesses the power of literature, in this case a fictionalized account of a 19th–century Japanese surgeon who experiments on members of his own family, to express the complex connectedness of humanity. Yet perhaps most compelling is the story that is also autobiography. In a fitting conclusion for this particular issue of *Virtual Mentor*, Tricia Higgins reminds us of medicine's true central figure: the patient.

Together, these articles challenge us to consider anew the tenets of bioethics as applied to medical research while simultaneously moving inward to identify the unique role of the physician as a liaison between a patient and her disease. The ability of the physician to serve in this capacity depends on our ability to first identify, then seek to understand, and finally begin to address the questions arising from the paradigm of modern medicine. If the history of medicine makes one fact painfully obvious it is that no achievement, no matter how remarkable, occurs in a vacuum. The shadows cast by the physicians of the Third Reich or by those conducting a small study in the backwoods of Tuskegee County, Alabama, provide a stark reminder of the consequences of allowing the quest for knowledge to trump personal integrity. Advances in medical science are hurtling us at record speed towards the future of medicine; the time to address the challenges of bioethics and professional responsibility raised by human subjects research is today, not tomorrow.

Mandy Redig

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Clinical Cases

Clinical Trials and End-of-Life Decision Making

Physicians can help oncology patients decide whether to focus on aggressive chemotherapy or less aggressive comfort measures for end-of-life care.

Commentary by Dave Alberts, MD, and Lucy Godley, MD, PhD

Alice Wilson's daughter finally convinced her mother to make an appointment with the family physician 2 weeks after Alice's 65th birthday. Alice organized a garden party to celebrate, and it was a great success with all 5 children, 14 grandchildren, and most of her neighbors in attendance. Alice attributed her 20-pound weight loss and fatigue to the preparations for the party. She didn't tell anyone about the pain in her stomach that had been keeping her awake off-and-on for 6 months. It was only after the party—when she could no longer explain her fatigue—that Alice reluctantly agreed to see her physician.

Instead of a garden party, Alice spent her 66th birthday in the hospital recovering from her second surgery, this time to remove 3 suspicious lymph nodes and intra-abdominal metastases seeded from the advanced adenocarcinoma removed from her colon the previous summer. Since the first surgery, one of her children or her husband Will have been driving Alice for her weekly rounds of chemotherapy with Dr. Tseng, her oncologist. Almost a year later, he knows the names of all 5 children and most of the grandchildren, including the 2-week-old granddaughter named Alice.

Alice resumed her chemotherapy 3 weeks after the second surgery. At every visit she asks Dr. Tseng the same question: "What are my numbers, Doctor?" she wants to know. Immediately following the surgery Alice's CEA levels dropped, and for a few weeks she would joke with the nurses who started her IV. "Careful with that," she would say, smiling, as one of them slipped a needle into the vein behind her elbow. Several months later the jokes stopped as her CEA values began to creep up again, gradually at first and then faster and faster.

At a special appointment between rounds of chemotherapy, Dr. Tseng tells Alice that the surgery and chemotherapy are slowing down the cancer growth, but they haven't been able to stop it. Alice doesn't say anything. She is tired all the time, she doesn't want to eat, the pain in her stomach still keeps her awake at night, and she has lost an additional 25 pounds. She has not yet been able to take baby Alice for a walk because she is too tired to push the stroller more than a few blocks. Dr. Tseng hesitates. Should he tell Alice about Zorvax, a new angiogenesis inhibitor in Phase II clinical trials? Clinically, Alice would be an ideal patient to enroll in the trial, and the latest publications about Zorvax indicate that many patients respond favorably. "There is something else we can try," he tells her, as he explains about the experimental medication. "This drug works in a different way than your current chemotherapy," he says. "It might be able to help slow down the cancer and give you more energy." Alice pauses for a moment. "I don't know," she says at last. "I don't know how much more chemotherapy I want to do. Will I still be so tired all of the time? I just don't know. What do you think I should do?"

Commentary 1

by David S. Alberts, MD

AW's clinical situation, unfortunately, is still commonplace in the management of stage IV colorectal cancer. There
are approximately 146,900 new cases of colorectal cancer each year in the United States and approximately two-thirds of these patients present with regional or distant disease [1]. Obviously, for both AW and the US population, this situation represents a sad public health failure, in that colorectal cancer is a preventable disease.

AW has undergone primary surgery, followed by adjuvant chemotherapy and secondary surgery, as a result of recurrent disease, which appears to be progressing intra-abdominally on the basis of a rapidly rising serum CEA. She has lost at least 20 to 25 percent of her body weight, has become weak, experiences moderately severe abdominal pain, and clearly has had a major reduction in her clinically determined performance status. Her medical oncologist has developed a close relationship with AW and her family and is being asked critically important questions related to end-of-life care.

There are several important issues to discuss concerning the current and future management of the more than 56,000 patients who will die from colorectal cancer each year. First, let us examine the role for secondary or tertiary chemotherapy of progressive, recurrent, metastatic colorectal cancer. Recently, 2 molecularly targeted agents, bevacizumab (VEGF inhibitor) and cetuximab (EGFR inhibitor) and 1 new cytotoxic agent, oxaliplatin, have been approved by the FDA to treat newly diagnosed or recurrent metastatic disease [2-4]. Responses to these agents either as first- or second-line single agents or in combination with 5-fluorouracil plus leucovorin or irinotecan are in the range of 10 to 50 percent with survival prolongation of perhaps 2 to 4 months. However, the population of patients treated in the phase III clinical trials establishing the activity of these 3 new drugs likely all had a better performance status than does AW. This is important, because response rates and survival durations are highly correlated with performance status. AW's weight loss and severe weakness generally translate to a poor performance status category (ie, performance status grade 2/3 on the Southwest Oncology Group scale) [5]. In fact, such an excessive weight loss (ie, 45 lbs) is associated with negative nitrogen balance and significantly compromised immune function, all of which predict lack of response to either cytotoxic or molecularly targeted agents. Most early phase clinical trials of new cytotoxic or biologic drugs require a patient performance status of at least 2 (ie, moderately symptomatic, but not requiring physical assistance) and, commonly, 0-1 (ie, either a totally asymptomatic patient or one whose symptomatology does not impair function). Thus, it is unlikely that AW would qualify for a clinical trial of the new agent, Zorvax, as discussed in the case report.

Does this mean that there is no treatment or hope for AW? The answer is a resounding "no." There is treatment for this very deserving woman who wants to spend quality time with her family at this point in her disease process. Any board-certified medical oncologist should have received training in end-of-life management that included knowledge of therapeutic modalities for pain management, prevention of nausea and emesis, anorexia control, and management of severe constipation. Modern therapeutics requires intensive intervention in the end-of-life situation, and no form of cytotoxic agent or biological therapy can be successful without adequate supportive care. Finally, considerable effort is being directed toward understanding the cachexia syndrome, clearly affecting the quality of AW's life [5]. With the identification of cachetic factors, it will be possible to develop a rational approach to therapeutics for this devastating condition.

Should Dr. Tseng put AW on a clinical trial, if she qualifies for enrollment? Obviously, the most important person to answer that question is AW. Given direct and honest answers to her questions, it is highly likely that AW would choose best supportive care for her end-of-life management. All too often, the medical oncologist replaces excellent supportive care with a cytotoxic or biologic agent that may have virtually no chance for producing tumor response or improved quality of life. The choice to pursue further drug therapy also replaces vitally important, direct and honest patient-physician communication. Unfortunately, this critically important aspect of clinical oncology is still inadequate in our post-doctoral fellowship training programs.

References


Commentary 2

by Lucy Godley, MD, PhD

This case illustrates a common situation in the treatment of cancer patients—deciding when to continue therapy aimed at disease control and when to initiate measures designed to maximize patient comfort. In this example, the patient is a 66-year-old woman who has been treated aggressively with multiple surgeries and numerous chemotherapy regimens for advanced-stage colon cancer. This is a realistic scenario, since there are many active chemotherapy agents available for colon cancer and several different ways to combine them. The patient, now tired, worn out, and in pain, asks her doctor whether she should continue therapy directed at controlling her disease.

Chemotherapy treatment today is much better tolerated than in years past, thanks to numerous agents that support cancer patients [1]. Several growth factors are available that stimulate white blood cell production by the bone marrow (G-CSF and GM-CSF), thus allowing chemotherapy regimens to be given with high intensity and on accelerated schedules with improved efficacy [2]. Chemotherapy-induced anemia can be treated with erythropoietin and its derivatives, which stimulate red blood cell production, alleviate the tiredness associated with prolonged chemotherapy, and augment chemotherapy and radiation effectiveness [3]. Several new and highly effective agents are available to treat chemotherapy-induced nausea and vomiting, making chemotherapy much more tolerable [4]. Cannabinoids can stimulate the appetite as well as control nausea and vomiting. Many narcotic and non-narcotic analgesic agents are available to treat cancer-associated pain. For example, radiation can often be used to palliate the pain associated with bony metastases. In the case at hand, one wonders whether Mrs. Wilson's symptoms of tiredness, anorexia, and pain have been adequately addressed. She has been seeing her oncologist weekly for some time, so there should have been ample opportunity to discuss these issues. Oncologists should aggressively manage the symptoms associated with cancer therapy in the interests of improving quality of life for patients.

When oncologists are faced with questions like Mrs. Wilson's—should she try an experimental therapy or just accept palliative care—they must use careful judgment in answering. Since physicians in private practice receive direct financial payment based on the administration of chemotherapy, oncologists must conscientiously separate clinical assessment of the patient from the financial needs of their practices, and they must be clear with themselves and their patients that patient welfare—not personal interest—is their primary concern. Physicians in academic centers may feel less of a direct financial reward from treating patients. Nonetheless, all physicians must ask themselves when treating relapsed patients, "When should we change the focus of care from one of controlling the disease to one of comforting the symptoms?"

Patients whose disease progresses after they have received standard treatment regimens often become candidates for...
investigational agents. Drugs in Phase I testing are being studied for toxicity in humans, while drugs in Phase II testing are being studied for efficacy. The decision to enter into a clinical trial must be preceded by full disclosure to the patient as to the purposes of the study. Patients should be given written consent forms to read and discuss before entering into the study. They should have realistic expectations as to what outcomes they seek to gain from the trial. Achieving this can be difficult with patients who are in denial about their disease and its prognosis, but physicians must be forthright and persistent about realistic expectations.

Hospice and programs with similar goals accept patients with an approximate life expectancy of 6 months to 1 year [5]. Unfortunately, oncologists are notorious for referring patients to such programs when they have only a few days or hours to live. Such late referrals do not allow patients or family members to experience the benefit of the superb care provided by these programs. Comfort-care approaches should not be seen as "giving up" on a patient but as active management of patients. Physicians and nurses should help patients accept that they are at the end of their lives and that the focus of care will now shift to controlling their symptoms instead of the primary disease process.

Each patient is unique and has his or her own style of decision making. Physicians should try to incorporate patient and family goals into each decision. In this case, when Mrs. Wilson asks, "What do you think I should do?" Dr. Tseng can be most helpful by redirecting the question to her and saying, "Well, that depends on what your goals are at this point." The doctor, patient, and family members can then discuss expectations of further chemotherapy versus comfort-level approaches. If Mrs. Wilson wants to do everything medically possible to treat her disease, then she might decide to continue on with a Phase I or II study. If, however, she feels that she is getting incrementally less and less benefit with each treatment and would prefer staying home and maximizing her comfort at this time, she might choose to stop chemotherapy and enter a hospice program.

The most appropriate and informed decision will result from open, candid discussion among the patient, her family, and her doctor, after realistic expectations have been outlined. Once engaged in such a conversation, Mrs. Wilson may again ask Dr. Tseng what he thinks she should do. At that point, Dr. Tseng may feel comfortable expressing his opinion directly. If Mrs. Wilson were my patient, I would speak with her and her family and encourage her to consider entering a hospice-type program.

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   PubMed  Google Scholar
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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. The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.
Heads or Tails: Randomized Placebo-Controlled Trials

Physicians are obligated to inform patients involved in a clinical trial that there is a chance of receiving a placebo, which can result in a deterioration of a medical condition.

Commentary by Charles Weijer, MD, PhD, and Karen Kreiner, MS

Upon inspecting his schedule for the day, psychiatrist David Kimball was surprised to learn that his first patient of the morning was Geoffrey Allen. Geoff had been in for an appointment less than 2 weeks ago to discuss his response to a monoamine oxidase inhibitor (MAOI) as treatment for chronic depression. At the time, it seemed as though the medication was working, a relief for both Geoff and Dr. Kimball after several years of searching for the right way to manage Geoff's illness.

Geoff had been referred to Dr. Kimball's practice by Student Health during his freshman year. After discussing Geoff's symptoms of insomnia, lethargy, and weight loss as well as learning of a family history of depressive disorders, Dr. Kimball prescribed the first of what would be a long list of medications. Through the course of his magna cum laude degree in political science and now into his doctoral dissertation, Geoff had tried several tricyclic antidepressants, selective serotonin reuptake inhibitors, and second generation antidepressants. While he would have periods of stability ranging from a few weeks to a few months as in the case of fluoxetine, eventually either the medication stopped working or the side effects became too bothersome.

At his last appointment, Dr. Kimball had been pleased with Geoff's clinical response to the MAOI, even though a brief physical exam revealed the presence of mild orthostatic hypotension. When queried, Geoff himself said he felt better than he had in months with the exception of the fact that he and his girlfriend were less than thrilled about the side effects. In response, Dr. Kimball adjusted the prescription and reminded Geoff not to hesitate to schedule another appointment if things changed.

"Well, you're always reminding me to come see you if something comes up," Geoff said, when Dr. Kimball asked about the purpose of Geoff's visit, "and there's something I need to talk about. I'm starting to feel tired again, like I have no energy, and my motivation to do things is slipping." Geoff went on to describe an elevation in his depressive symptoms as well as a growing dissatisfaction with the MAOI side effects. Then, he mentioned a recent conversation with one of his cousins—also with a history of depression—and her enthusiastic description of her participation in a clinical trial for Licol, a new lithium-based antidepressant. Dr. Kimball was familiar with Licol and thus far it showed great promise for the treatment of atypical depression, especially in younger adults. However, ongoing clinical trials for the medication utilized double-blind placebo controls. In addition, data was not yet available concerning the follow-up treatment of patients who withdrew from the trials. "So I'm thinking I might like to try something like that," Geoff continued. "Something new maybe, since I've tried so many older drugs. And I might be able to help make a difference. I mean, what, have I got to lose? I'd really like to participate in the trial—how do I sign up?"

Commentary 1

by Charles Weijer, MD
The question facing Dr. David Kimball is this: Ought he to recommend that his patient, Geoffrey Allan, enter a randomized trial in which he has a 50 percent chance of getting a new and potentially beneficial drug, Licol, and a 50 percent chance of getting placebo? Is doing so consistent with his duties to the patient? The general permissibility of physicians enrolling patients in clinical trials received a great deal of scrutiny in the literature in the 1980s and 1990s. Some argued that the physician has a duty to provide the patient with the best possible care. Accordingly, offering enrolment in a clinical trial in which treatment would be determined by the flip of a coin seems problematic. The concern is well expressed as follows:

Consider first the initial formulation of a trial…A new agent that promises more effectiveness is the subject of study. The control group must be given either an unsatisfactory treatment or a placebo. Even though the therapeutic value of the new agent is unproved, if physicians think it has promise, are they acting in the best interests of their patients in allowing them to be randomly assigned to the control group? [1].

But do physicians owe patients the best possible care? And, is offering enrolment in a randomized controlled trial inconsistent with important legal and moral duties physicians have towards their patients?

Philosopher Benjamin Freedman offers an authoritative answer to both questions with his concept of clinical equipoise [2]. Clinical equipoise starts from the recognition that physicians owe patients competent care, that is, treatment endorsed by at least a respectable minority of expert clinicians. For any one condition, there may be a range of treatments that may be competently prescribed. Thus, a patient seeking treatment for a condition might see physician X and receive a recommendation for treatment A, or she might have seen his colleague across the hall, physician Y, and received a recommendation for treatment B. Under these circumstances, it would be unproblematic for either physician X or Y to offer the patient enrolment in a clinical trial that would randomize her to treatment A or B. Treatments A and B are consistent with competent medical care, and whatever the idiosyncratic choices of physicians X and Y, they must respect the preferences of equally competent colleagues.

Formally, clinical equipoise states that at the start of a randomized clinical trial there must exist a state of honest, professional disagreement as to the preferred treatment in the community of expert clinicians. To put it bluntly, doctors must disagree as to the preferred treatment. In the case of treatments A and B above, the disagreement is actual. Clinical equipoise also covers cases of potential disagreement. In these cases, a particular treatment, perhaps Licol, the new and experimental treatment, is supported by sufficient evidence, perhaps from Phase I and Phase II clinical trials, such that, were it widely known, physicians would disagree about the preferred treatment. Thus, clinical equipoise allows trials to proceed in instances of actual and potential disagreement as to the preferred medical treatment.

The use of the placebo control poses special challenges for clinical trials [3]. Generally speaking, when there exists a standard treatment for a medical condition, a novel treatment ought to be compared to it rather than to a placebo. The use of a placebo control is legitimate in a number of circumstances: (1) where there is no known treatment for a medical condition; (2) where the subject population of the trial has failed to respond to first and second line standard treatments for the condition and there exists no effective third line treatment; (3) where a new treatment is being tested as an add-on to a regimen of standard treatments, and all subjects will receive the regimen of standard treatments; (4) when research is conducted in a undeveloped country in which no treatment is broadly available due to cost or short supply; and (5) for minor conditions for which receiving no treatment is consistent with competent medical care (eg, seasonal allergies).

As the story is told to us, Geoffrey Allan has suffered chronic depression for years and has tried most available drugs at one point or another. After initial relief with the latest drug, an MAO-I, he feels the effect is declining and the side effects are increasing. It seems therefore that he may well fit into the second exemption for the use of placebo controls. He has tried first and second line drugs and they have failed him, and now there exists no standard third line drug for him. At this stage, entering a placebo controlled clinical trial testing the effectiveness of Licol seems appropriate.

Dr. Kimball will, of course, want to make careful inquiries regarding the trial before suggesting it for Geoffrey Allan. What is the evidence to date supporting the safety and efficacy of Licol? Has the study been approached by a duly constituted (and not for profit) Institutional Research Board (IRB)? What safety features are built into the trial should
Mr. Allan begin to deteriorate on study? Will he be withdrawn promptly and treated? Finally, what if Mr. Allan does very well on Licol? Will he be assured of access to the drug until the drug becomes licensed? This last fact is of great importance to patients who have searched for years for a treatment that will alleviate their symptoms.

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   [View Article](https://www.nejm.org/doi/full/10.1056/NEJM198707233170305)  


Charles Weijer, MD, PhD, is an associate professor of bioethics and surgery at Dalhousie University in Nova Scotia, with expertise in the ethics of human experimentation. Professor Weijer was a member of the World Medical Association's Working Group revising the Declaration of Helsinki (1998-1999), a member of the WHO/CIOMS Steering Committee that produced the most recent CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), and is a fellow of the Royal College of Physicians and Surgeons of Canada.

**Commentary 2**

by Karen Kreiner, MD

This case presents a common clinical dilemma physicians face when treating patients who have depression that is difficult to manage or refractory to available treatments. This high-functioning patient has tried numerous antidepressants in a clinically sound way, yet, while he has a temporary response to treatment, he has been unable to achieve either effective long-term maintenance or a tolerable degree of treatment side effects. In clinical psychiatry, both of these problems are common. In an effort to control his symptoms and address his challenging medical history, the patient now wants to try an investigational drug which has shown some promise in a controlled clinical setting.

The most desirable way for the psychiatrist to handle this situation is to enter into a dialogue with the patient to carefully go over each of the potential treatment options and ensure that the patient understands the risks and benefits of each one. First, if Geoff is willing to consider it, the psychiatrist could entertain the possibility of increasing the current dose of monoamine oxidase inhibitor (MAOI). MAOIs work by inhibiting the monoamine oxidase enzymes that metabolize serotonin, a neurotransmitter linked to mood disorders. By slowing the breakdown of serotonin, MAOIs can be effective pharmaceutical agents for the treatment of depression. Increasing the MAOI dose could lead to more severe side effects—but MAIOs also have a strong history of clinical utility—and for Geoff to make a truly informed decision, greater dialogue would need to take place between him and Dr. Kimball.

If Geoff is unwilling to consider increasing his current MAOI dose, another MAOI should be offered since he responded so well initially to the first one. Several different MAOIs have been approved for use in the treatment of depression, and it is important to consider all of the possibilities. Furthermore, the psychiatrist should also make sure that Geoff has tried all appropriate antidepressants as well as considered the use of mood stabilizers like lithium or lamotrigine. Lamotrigine was originally used as an anticonvulsant medication but was recently approved by the FDA for use in the treatment of depression; it is particularly effective in patients like Geoff who have failed to respond to more traditional antidepressants or mood stabilizers. Finally, additional atypical antipsychotics like olanzapine may be useful.

If Geoff still wants to enroll in the research trial after adequately considering all of his nonexperimental options, he
should be informed that he has a 50 percent chance of getting the placebo pill, in which case his condition could truly deteriorate. However, if he does get the investigational drug and responds, he will most likely be unable to continue the drug when the study ends. In the event of a successful clinical outcome, some drug companies will continue to supply the drug on a compassionate basis, but this is highly variable and cannot be guaranteed. More likely, Geoff will experience an ensuing drop in function due to the lack of medication, and that can be traumatic for many patients. According to the AMA Code of Medical Ethics, the physician should assist in trying to secure an ongoing supply of the drug until it is approved and reaches the open market, if there is a clear medical benefit [1]. Geoff should be aware of the hardship he may have to endure: to feel well during the trial therapy and then become depressed again because he loses access to an effective yet still-investigational medication.

Patients who have the capability to make decisions about their care always have the right to choose; we, as doctors, support the autonomy of the patient. If Geoff does decide to enter the study, it is the psychiatrist's responsibility to ensure that he is fully informed prior to making that decision. Unfortunately, for many treatment-resistant patients, research studies are their only hope of getting some relief from their disease. In terms of human suffering, depression exacts a high toll.

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Karen Kreiner, MD, is an instructor in clinical psychiatry and the psychiatry clerkship director at Northwestern University's Feinberg School of Medicine.

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Clinical Cases

Who Is That? Expanding the Clinical Encounter

Patients need to completely understand the role of any non-medical personnel present during a procedure and have the right to refuse their attendance.

Commentary by Vijaya Arekapudi, MD

Emily Watson, MD, was in a hurry. Ripping off her soiled gown and balling up her used gloves, she swung by the trash on her way out of room 3C. The patient within was waiting for her epidural, but Mrs. Sanchez in 21B was ready to deliver her twins. It was 2:00 pm after a night of being the OB resident on-call, and Emily was within a few hours of heading home to get some much-needed sleep. "She signed the consent form when she got here," one of the labor and delivery nurses told Emily as they half-walked, half-ran down the hall. "For that fetal oxygen study, and the company reps are here since it's the middle of the afternoon." Emily sighed. A local biotechnology and medical equipment company was working with the Women's Hospital to test a new device for monitoring fetal oxygen levels during labor and delivery. Whenever possible, the company liked to have representatives in the delivery room to monitor the use of the equipment. Prospective participants signed a detailed consent form prior to enrolling in the study, but Emily liked to verify with the staff member obtaining consent that the patient understood the clause granting permission for non-hospital staff to observe the birth. "Who obtained consent?" she asked, knowing without hearing the answer that it was someone from the earlier shift who had since gone home.

As she entered Mrs. Sanchez's room, Emily vaguely noticed the 2 gowned individuals who followed her and the nurse inside. Familiar with protocol, they unobtrusively stayed to the side of the room as Emily adjusted a fresh gown and gloves while the nurses helped position a flushed Mrs. Sanchez into the stirrups. "Are you ready to push?" Emily asked her, following a brief internal exam. "Your cervix is completely dilated and those babies are on their way!"

Mrs. Sanchez nodded weakly, her husband standing at her shoulder. This was her first pregnancy and she had been in labor for 18 hours. The nurses moved to help hold her knees and she reached up to grip her husband's hand. "What do you think?" she asked him, smiling weakly. "One of each," he replied.

"Okay Eva," Emily said. "Remember those classes, and let's meet your twins." As Eva took a deep breath and prepared to push, she suddenly noticed the unfamiliar man and woman who had quietly moved to the foot of her bed. On a tour of the hospital as part of her prenatal class, Eva and her husband had been told about the members of the medical team who would be present for the birth of her children. After a night of being in labor, she had been introduced to all of the nurses, medical students, and residents multiple times. "Wait a minute," she said, panicked. "Who are they? What are they doing here?" she asked Emily.

Commentary

Mrs. Sanchez's confusion as to the presence of 2 strangers in her room is the end-point of several mistakes that have been made while dealing with her labor and delivery. While a hectic maternity ward and a tired resident are not unusual, these factors do not obviate the errors that occurred here.

Before taking over responsibility for the patient care in labor and delivery from the previous resident, Dr. Watson
should have been given all of the maternity patients' information, including Mrs. Sanchez's. With this information about what is occurring in labor and delivery, Dr. Watson would then know who her patients are and what their conditions and labor statuses are, as well as any special considerations, such as the participation in the current study.

Since Dr. Watson is a resident, she needs to be supervised by an OB attending physician. Considering that Mrs. Sanchez is delivering twins, a high-risk delivery that might need to be done in a C-section room (depending on the presentation of the babies), Dr. Watson's lack of supervision by an experienced obstetrician is surprising. Unless Dr. Watson is a chief resident with a great deal of experience, she needs to be supervised. This lack of oversight is not directly related to Mrs. Sanchez's confusion, but the presence of a supervisor might well have ameliorated, if not completely eased, the situation.

These errors illustrate some fundamental systemic problems that go hand-in-hand with Mrs. Sanchez's confusion. The previous resident (assuming he or she was the one who obtained consent) should have clearly explained who would be attending Mrs. Sanchez's delivery and, if possible, should have introduced her to the company representatives prior to her delivery. Communication between residents would have at least allowed Dr. Watson to know who had, in fact, obtained consent.

Obtaining consent in this situation would require explaining to Mrs. Sanchez what the company representatives would be doing in her room as well as explaining what a fetal oxygen monitor is. Given the description of the study, it does not appear that there would be any great risk to Mrs. Sanchez or her babies, except the partial loss of privacy inherent in allowing non-medical personnel into the delivery room. Judging by her reaction, however, this level of invasion is unacceptable to the patient. While the informed consent document might be very detailed, these salient points should have been brought to Mrs. Sanchez's attention so that her decision was truly informed and educated.

Signing an informed consent document does not necessarily imply that a patient fully understands or is comfortable with what is going to occur. Given the importance of verbal explanation in obtaining consent, a physician should always be sure that the patient can understand him or her. This includes giving clinical explanations at a level the patient can understand, as well as using translators to make sure that a patient with limited English fluency fully understands what he or she is signing. Even if this was how the informed consent was obtained, it is quite possible that Mrs. Sanchez does not remember what she agreed to. If this is the case, a simple reminder might be all that is needed to make her comfortable.

Given Dr. Watson's situation, namely as a resident performing a high-risk procedure without adequate supervision, she has 2 options. If Dr. Watson feels that there is enough time to adequately explain to Mrs. Sanchez who these representatives are, then she may do so. Additionally, if after this explanation by Dr. Watson Mrs. Sanchez does not want the representatives present during delivery, even if she had previously signed a consent form and has now changed her mind, Dr. Watson should tell the representatives to leave the room. If Dr. Watson feels that there is limited time, the representatives should be asked to leave, while giving Mrs. Sanchez a brief explanation as to their presence so she is not left confused. The most important aspect of Dr. Watson's decision-making process is to give priority to Mrs. Sanchez and her babies before all others.

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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. The viewpoints expressed on this site are those of the authors and do not necessarily reflect the views and policies of the AMA.

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Journal Discussion

Determining Research through Underdetermined Treatment

Paul Miller and Charles Weijer defend the concept of equipoise in medical research in a recent journal article.

Abraham P. Schwab, PhD


When a medical expert cannot responsibly favor one treatment over another—when the available evidence does not indicate (or underdetermines) what is the best treatment—the treatments are in equipoise. Certainly, this happens in clinical practice every day; however, equipoise is applied by medical practitioners, institutional review board members, and bioethicists most frequently in the context of medical research.

Equipoise was initially posited as a standard for determining worthwhile research by Charles Fried. His conception places the responsibility of reckoning equipoise solely in the hands of individual physicians, an opinion that was challenged by Benjamin Freedman [1]. Freedman's argument was not against the position of equipoise itself but rather based on the fact that Fried's conception of equipoise was so fragile that it could not be reliably achieved. An individual physician may think that one treatment is superior to another, but this opinion may or may not be accurate and has the potential to be unduly influenced by preliminary research results [2]. Consequently, Freedman argued for clinical equipoise, a modification of Fried's initial term, in which the community of physicians, as experts, determines when treatments are in equipoise. The determination of clinical equipoise depends on a larger number and wider array of experts, thus the conclusion should be more robust [2].

Besides differing opinions on how to define the term, the basic concept of equipoise has detractors, most notably Franklin Miller and Howard Brody [3,4]. In a challenge to the validity of equipoise, they argue that the responsibilities of physicians in research are diminished—as compared to their responsibilities in clinical care—due to the aims of medical research [4]. In clinical care, physicians attempt to care for a particular patient, but in research physicians attempt to illustrate the validity of a specific conclusion. Accordingly, Miller and Brody endorse a framework for patient-physician interactions which is constituted primarily by obtaining informed consent and avoiding exploitation [4].

In a recent publication, Paul Miller and Charles Weijer add a new dimension to this discussion in their attempt to "rehabilitate" equipoise by defending it from the critique of Miller and Brody while simultaneously re-casting it from Fried's initial description. They begin by minimizing Miller and Brody's critique, stating that "an ethics of clinical research that gives primary place to consent requirements nevertheless must acknowledge the role of fiduciary obligations and broader social standards in defining the boundaries of consent as moral and legal justification" [5].

Miller and Weijer go on to discuss in detail the contributions of Fried and Freedman and label their conceptions of equipoise FE (Fried's equipoise) and CE (clinical equipoise), respectively [5]. Indeed, this integration of apparently conflicting views of equipoise is perhaps the most significant contribution in their analysis. Rather than attempt to settle the question of individual expertise (FE) versus collective expertise (CE), Miller and Weijer couple them as complementary concepts. "FE provides a moral condition that satisfies the demands of the continuing fiduciary relationship between physician and patient. CE, on the other hand, addresses the overarching need of the state to
protect its citizens from harm, and provide clear guidance to IRBs as to when a RCT may ethically proceed" [5]. In short, uncertainty about the best treatment must pervade the clinical encounter and the medical literature.

There are two significant advantages to Miller and Weijer's "rehabilitated" equipoise. First, unlike CE, it caters to physician autonomy in a profession both dominated and characterized by decision-making. When an individual physician makes a judgment about treatment effectiveness for an individual patient, that judgment is generally respected. Second, unlike FE, rehabilitated equipoise allows for a collective determination of equipoise regardless of any particular physician's view. In at least some sense, we can responsibly claim treatments are in equipoise so long as the community of physicians is in equipoise. To describe this relationship hierarchically, CE (that is, the equipoise of the medical community) constrains legitimate individual equipoise (FE). Only when both the medical community and an individual physician are in equipoise can the physician legitimately be in equipoise about the best treatments.

However, there are two noteworthy pitfalls of this "rehabilitated" equipoise. First, it makes no direct mention of patient input. Should patients have any say in determining equipoise? Karlawish and Lantos, for example, argue that patients should play a greater role [6]. If the input of patients is not to be included in the determination of equipoise, it seems as though this should be accompanied by an explanation. It is, after all, the patients' as test subjects—and not the doctors'—bodies and lives which are most directly affected by medical research.

Furthermore, does the integration of FE and CE really avoid the fragile nature of FE? Freedman argued for CE because leaving the decision in the hands of individual physicians was both indeterminate and allowed for undue influence on the basis of poor judgment. Yet does the coupling of FE with CE adequately limit the effects of such decisions? If the medical community is in equipoise (CE) and the physician is expected to make a judgment that is relatively independent of the medical community's collective views (FE), the grounds for individual judgments will be the very grounds that made FE unreliable in the first place.

As with many questions of bioethics, there may be no perfect solution. The enduring uncertainty in medical decisionmaking combined with the persistent push for more clinical research ensure that the challenges of equipoise in determining ethically sound research will continue.

References


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Journal Discussion

Maintaining Integrity in Industry-Sponsored Research

Many ethical and legal issues arise when academic medical research is sponsored by pharmaceutical companies.

Alison Bickford


In recent years, a growing number of academic researchers have looked to private industry for funding. Ideally, both parties can benefit from this kind of exchange—the researcher receives resources and funds while the company can utilize highly skilled workers and functioning laboratories to conduct its research. Research can progress swiftly and efficiently by combining the intellectual resources of academia and the financial resources of industry.

This kind of relationship can be particularly important in translational research—the process of moving drugs and procedures from bench to bedside—where developments must be tested for safety and efficacy. Companies that are developing treatment protocols may not have access to human subjects for a clinical trial, but they can provide both financial resources and a supply of their drug to academic researchers who interact with patients at academic tertiary care facilities. From one perspective this situation offers tremendous promise: accelerated research means that successful treatments will benefit patients sooner. Unfortunately, there is also a drawback to this sort of partnership: the ethical problems that arise in privately funded research are only aggravated when patients and clinical trials are involved.

One of the best-known cases that combines questions of biomedical ethics with translational research involves Dr. Nancy Olivieri and Apotex, Inc, a major Canadian manufacturer of generic drugs. While the Olivieri case is both lengthy and complex, it is the perfect case study for an applied understanding of the benefits and pitfalls of academic-industry partnerships. Consequently, much of this discussion will use the Olivieri saga to illustrate the general principles raised by Malcolm Parks and Mary Disis in their 2004 article in the Journal of Translational Medicine.

In 1991, leading hematologist Nancy Olivieri applied to the Medical Research Council of Canada for funding of a clinical trial to compare deferiprone (L1) with current iron-chelating treatments for thalassemia. Her application was rejected, and she was advised to seek funding from the pharmaceutical industry. She finally found funding in 1993 from Apotex. Dr. Olivieri signed a 3-year contract with the company, agreeing, among other things, not to disclose or publish any information or knowledge about L1 without the express consent of Apotex.

By early 1996, Dr. Olivieri became concerned that in certain patients the efficacy of L1 was decreasing over time. When she reported her findings to Apotex, the company argued that no drug could be universally effective and that there was no risk to her patients. But Olivieri thought that some patients taking L1 might respond better to the standard treatment while avoiding the risk of neutropenia, a side effect previously associated with L1.

Olivieri sent a report to the ethics board of her hospital. Apotex sent their own report, outlining their interpretation of her results. The ethics board concluded that Olivieri needed to change her consent forms and publish her conclusions. She drew up new consent forms, but when her grant came up for renewal in May of 1996, Apotex terminated the trials and reminded Olivieri that all information generated by her research under their grant was to remain confidential.
In June 1996, Olivieri agreed to continue administering Apotex-supplied L1 to informed patients who appeared to be benefiting from the drug and to monitor the risk. But by early 1997 Olivieri had data suggesting that L1 increased liver fibrosis. At the same time, Apotex began planning treatment using University of Toronto patients without liver biopsy, claiming the drug was safe and effective. Olivieri felt that concealment of her data would be unethical. Apotex saw her movement to publish as a violation of contract and issued legal warnings to Olivieri.

The University of Toronto acknowledged that Apotex was wrong to try to suppress Olivieri’s data, but never took any decisive action to stop the pharmaceutical company's plans. At the time, the university was anticipating a multimillion-dollar donation from Apotex for a new biomedical research center. When the controversy went public, the university issued a statement repeating Apotex's allegations about the quality of Olivieri's research.

For the next 2 years, Olivieri fought Apotex, her own hospital, and the university. On January 6, 1999, the Hospital for Sick Children (HSC) removed Olivieri from her position as director of the hemoglobinopathy program, after a further disagreement regarding plans to move the program for the treatment of sickle cell disease into regional pediatric centers. The university intervened, and Olivieri was reinstated on January 25, with a promise of legal support from the HSC. But in April 2000, the hospital issued a complaint against Olivieri regarding her treatment of patients during initial clinical trials in 1996. The complaint was referred to the College of Physicians and Surgeons of Ontario, and the charges were only dismissed after a period of 2 years.

The prolonged drama of the Olivieri case is an example of the potential for conflicts of interest and ethical dilemmas whenever industry funds clinical trials. Misinformation and miscommunication delayed resolution of the issue, and many reviews and reports were necessary to vindicate Olivieri (the main report, published by the Canadian Association of University Teachers, can be found at www.caut.ca/en/issues/academicfreedom, and an external review from the Hospital of Sick Children at www.sickkids.ca/l1trials).

While worthy of study in its own right, the Olivieri case also serves as an illustration of a basic question facing the medical research community: should universities allow their researchers to receive private funding? In their article, Malcolm Parks and Disis address several issues related to this fundamental question. Given the potential problems associated with industry funding—so clearly demonstrated in the Olivieri case—blanket prohibition may seem like the easiest solution. Parks and Disis point out, however, that this kind of blunt approach can leave other biasing interests in place and eliminate the resources and communication that can accelerate clinical advances [1]. Some authors argue that funding from industry has not improved clinical research, but the fact remains that nearly 75 percent of funding for clinical trials in America comes from corporate sponsors [2]. It is therefore important to examine the problems with industrial funding for translational research and find regulations that can minimize these ethical dilemmas.

The issue of academic freedom is central to the Olivieri case. Understandably, industrial sponsors would like to ensure that publications reflect their interests, but the investigator must be free to analyze and publish all findings, even if there is a legitimate difference of opinion about the interpretation of the data. Parks and Disis recommend allowing the sponsor to review material prior to publication without the power to limit distribution of information [1]. Other writers suggest appointing an independent review committee acceptable to both parties, or creating a national review center under the National Institutes of Health or equivalent bodies [3]. It is important that research sponsors never have the right to control publication and that both investigators and review boards ensure this as a standard of practice.

Other problems arise when an investigator stands to profit personally from the success or failure of a treatment. An investigator may profit directly from the sale of a drug, receive a higher payment from an industrial source if results are positive, or receive payments for each patient recruited into the trial [4]. Parks and Disis suggest that investigator bias can be minimized by assigning certain problematic activities (like recruitment of subjects, acquiring consent, and analysis of data) to disinterested team members; assigning independent committees to review the data; conducting multisite research to lessen the bias of any one investigator; and requiring all researchers to disclose their financial interests [1]. Other authors point out that institutional review board members and other institutional decision makers like presidents or trustees may also have extensive financial ties with industry and suggest that those without a declared legitimate justification for these financial ties should either give up these interests or remove themselves from the decision-making process [4]. This kind of institutional bias is illustrated by the financial connection between the University of Toronto and Apotex in the Olivieri case. In this situation, however, the responsibility of an academic
institution is to support its researchers and not to protect its financial interests.

Research may actually be limited and slowed by outside funding because of the regulation necessary to avoid conflicts of interest. Parks and Disis note that extra time and resources will need to be allocated for institutional and extra-institutional review processes [1]. One review found that industry-sponsored academic researchers were more likely to experience delays in publication, often because of the need for confidentiality while filing for a patent [5]. Assigning all positions involving contact with human subjects to disinterested third parties increases the cost of research and assumes that disinterested parties exist and are available. As investigators become increasingly involved in patenting and licensing drugs, they may even disqualify themselves from participation in their own clinical studies [1].

Both academic investigators and industrial sponsors must be aware of the impediments to research that can arise when financial interests are involved. Parks and Disis point out that universities are not designed to be as secure or secretive as industrial laboratories, a fact that is to their advantage. Communication between investigators and exchange of information can lead to increased creativity and focused research, but it can also be construed as an information "leak" by an industrial sponsor. Yet if industry sponsors need to reconsider their collaborative research frameworks, universities too must be realistic in their expectations. Many tested drugs will not be safe and efficacious, and many joint ventures with industry will not return large profits for the university [1].

Although a connection between academia and industry can accelerate and improve clinical research through increased access to resources and increased communication between researchers, we can only avoid the ethical conflicts apparent in the Olivieri case through strict regulation. Unfortunately this regulation can impede the very research we want to accelerate. However, when the rights and safety of all patients are considered to be of paramount importance in the final cost-benefit analysis of academia-industry partnerships, such regulations must be clearly delineated and strictly enforced. Consequently, both academic institutions and the medical industry must be aware of potential pitfalls when they initially pursue a relationship.

References


Questions for Discussion

1. What should Olivieri have done to avoid conflict with the pharmaceutical company Apotex? What should Apotex have done? What was the role of the university and the Hospital for Sick Children?
2. Parks and Disis point out several ways in which industrial funding can impede clinical research. Are there others? Is it possible to modify their recommendations to lessen their impact on research?
3. What do you think when you see that a drug company funded the clinical trials for one of its drugs? What are some ways that a researcher can manipulate the clinical setting, patient population, or data in order to change the outcome of a trial? What can be done to minimize this kind of manipulation?
Alison Bickford is a graduate of Amherst College where she majored in neuroscience. She is currently a second-year student in the Medical Scientist Training Program (MD/PhD) at Northwestern University's Feinberg School of Medicine. Prior to beginning medical school, she spent a year working with Partners in Health in Siberia.

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Medical Education

**Research Ethics and Medical Education**

Research ethics should be included in the medical school curriculum so students and residents can fully understand the ethical implications of medical research.

Stephen Leapman, MD, and Sharon M. Moe, MD

**Introduction**

The question begging to be asked among researchers and educators in Academic Medical Centers is: what do we currently teach medical students and residents about the ethical issues surrounding clinical research activities, from conflict of interest to protection of the patients enrolled in research studies (clinical trials)? The answer unfortunately is "not much, but more than before."

Outside forces have made us look critically at our teaching programs. The Accreditation Council for Graduation Medical Education (ACGME) has adopted requirements for competency in, among other areas, professionalism, practice-based learning and improvement, and systems based practices. Learning outcomes for these competencies require residents to demonstrate a commitment to ethical principles of health care delivery, informed consent, confidentiality, conflict of interest, and ethical business practices [1].

**The Issues**

Medical trainees are often caring for patients who are involved in clinical experiments (pharmaceutical, new devices, new operative procedures, or otherwise). Yet many residents and most medical students do not know the differences between Phase I, II, and III trials, and some have had little exposure to study design, including randomized or blinded clinical experiments. Students often do not appreciate the time and effort necessary to move a new drug or device from concept through the discovery process and to the bedside. Ethical principles and the moral standards governing clinical practice are generally part of clinical curriculum, but few training programs and almost no studies have examined habits of practitioners or trainees as they relate to the ethics of clinical research activities [2-4].

Yet the ethical concerns that surround clinical research programs are multiple; they include: adequate assessment of the risks and benefits to the patient-subject; lack of understanding of the study protocol by physicians, trainees, and the patient-subject; the potential for coercive enrollment that is inherent in the power differential between the physician and the patient; the process and completeness of informed consent; use of placebos in research; protection of confidentiality; disregard of subjects' needs, wants, or understanding regarding their participation in the study; conflicts of interest for the investigator, institution, educators, and staff; and use of surrogates as decision makers for subjects with diminished capacities. Since the lines between academic medicine and industry are becoming blurred and the distinction between clinical research and clinical practice may be suspect, attention to a more robust education for students, residents, and fellows seems paramount.

**Potential Solutions**
Because these are the formative years of their professional identity, residents should be a part of clinical investigations and should examine the ethical issues that patient research raises. A curriculum addressing research practices allows residents to consider how the relationship between investigator and patient-subjects differs from that between caregiver and patient. The distinction between research and patient care is sometimes a fuzzy one. Through involvement in clinical protocols, residents can come to understand the drug development process, learn to interpret the results of studies, realize that drugs used for "off-label" purposes in clinical practice cannot be used in research without permission from the FDA, and understand that any systematic evaluation of patients to advance generalizable knowledge is research. Indeed, both chart reviews and off-label use of drugs, when either is specifically designed to answer a hypothesis and then gather findings, constitute clinical research. In addition, residents and fellows share the responsibility, along with investigators, to inform the general public about research practices. This is especially important if the trainees are called to advise patients about participating in clinical trials.

Students must also learn the role of the Institutional Review Board (IRB) and the importance of the informed consent process, including an understanding that consent forms are written succinctly and in simple English or the appropriate language for the patient. Such forms need to describe the essential features of the study with a clear understanding that the patient's care is not tied to participation in the study. In addition, patients must be fully cognizant that they may withdraw from the study at any time. There must be neither conflict of interest nor situations that could lead to a conflict of interest [5]. Residents could be trained in research protocols by opening IRB meetings to them so they could be active listeners even if they are not active participants. Simulated protocols and simulated IRB committees might also serve as educational techniques for introducing medical students and residents to the complexities of clinical research. Educational solutions such as these protect both the investigators (including trainees) and the patients.

Conclusions

In summary, residents and medical students must understand the essential components of participating in clinical research, including basic ethical principles and the historical basis for those principles, research design and the assessment of risk and scientific merit, and accountability of the investigator and the research team including potential conflicts of interest. With this new knowledge, trainees can ethically function as advocates for the merits of research participation to their patients and as advocates for patients to investigators on the all-important issues of subject selection and informed consent [4].

References

2001, Dr. Leapman became the first executive associate dean for Educational Affairs.

Sharon M. Moe, MD, is the associate dean for Research Support and medical director of the Clinical Trials Program at the Indiana University School of Medicine. She received her medical degree at the University of Illinois, Chicago and completed a subsequent residency at Loyola University and a fellowship in nephrology at the University of Chicago. Her current research interests relate to the pathophysiology and treatment of musculoskeletal disorders in patients with renal failure.

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Clinical Pearl

**Chronic Myeloid Leukemia and the Application of Rational Drug Design**

*Imatinib is a pharmaceutical therapy recently approved by the FDA to help treat chronic myeloid leukemia.*

Richard M. Stone, MD

Chronic Myeloid Leukemia (CML) is a rare disease (annual incidence in the United States of 2 in 100,000), but the understanding of its pathophysiology directly led to the development of one of the first truly specific anti-neoplastic therapies [1].

CML is characterized by an over-proliferation of marrow cells generally manifested by an elevated white blood cell count with a left-shifted differential. The appearance of the blood smear resembles what would normally be seen on a bone marrow aspirate: myeloid forms in all stages of differentiation including blasts, promyelocytes, myelocytes, metamyelocytes, and bands. Other typical findings include basophilia (or eosinophilia), thrombocytosis, and splenomegaly. Most patients present asymptomatically, often at the time of a routine CBC during a check-up or as part of the work-up of an unrelated problem. Constitutional symptoms such as fatigue, fever, or night sweats reflect the high cell turnover. Left upper quadrant pain from the splenomegaly could be another presenting complaint.

The course of CML is subdivided into different clinical phases reflecting the underlying pathophysiology:

- The chronic phase—the presenting phase in over 85 percent of patients—is typified by the features listed above. With a median duration of 4 to 8 years, this phase is compatible with normal activities.
- Barring an allogeneic transplant, the terminal acute leukemia (myeloid in 75 percent, lymphoid in 20 percent) blast crisis phase supervenes.
- This is sometimes preceded by an "accelerated phase," characterized by increasing constitutional symptoms and spleen size as well as poorly controlled counts.

The goals of therapy have been, first, to prolong the duration of the chronic phase and, second, to eradicate the disease if possible.

The diagnosis of CML should be strongly considered in a patient with leukocytosis unexplained by a severe infection, especially if accompanied by basophilia and an elevated platelet count. Such a suspicion should prompt an effort to determine if the diagnostic abnormality—the Philadelphia chromosome with the resultant bcr-abl fusion mRNA and protein—is present in the hematopoietic cells obtained from peripheral blood or bone marrow sources. One of several methodologies can be employed to detect this hallmark finding. The most typical is metaphase cytogenetics. Cells are allowed to divide and enter metaphase, and the chromosomes are counted. A foreshortened chromosome 22 constitutes the Philadelphia chromosome and indicates the presence of the bcr-abl transgene due to a t(9;22) balanced translocation. Interphase cytogenetics (fluorescence in situ hybridization or FISH) can alternatively be used to detect this fusion when fluorescent probes for each of the involved genes can be shown to colocalize. Finally, the gold standard is now polymerase chain reaction (PCR)-based detection of the fusion bcr-abl mRNA. The PCR technique can detect from 1/10,000-1/1,000,000 fusion mRNA molecules. Philadelphia-negative CML, an entity clinically resembling CML yet having no detectable bcr-abl fusion, probably has a variant pathophysiology and should be
considered a separate disease, particularly in the current therapeutic era.

The consequences of the bcr-abl fusion protein—a tyrosine kinase enzyme always in the "on" position—are unbridled signaling resulting in overproliferation of hematopoietic elements. This yields the high white blood cell counts, platelet counts, and the extramedullary hematopoiesis/splenomegaly typically seen at presentation. The disordered signaling also results in the turning on of downstream proteins, failure to undergo apoptosis (programmed cell death), and cytoskeletal changes [2]. Experiments have shown that the bcr-abl protein is necessary and sufficient to produce CML [3]. Inhibiting bcr-abl with imatinib caused specific anti-leukemic effects in cultured cell lines and resolution of murine bcr-abl–bearing leukemias, providing a high degree of pre-clinical rationale for use of this agent [4].

**Revolutionary Approach to CML**

Imatinib has indeed revolutionized the approach to patients with CML. The historical milieu from which imatinib entered the therapeutic armamentarium basically involved an allogeneic transplant for those young and fit enough to undergo the dangerous procedure and who had a histocompatible donor, whether sibling or unrelated. In patients under age 45 transplanted within a year of diagnosis, the treatment-related mortality is 10-20 percent with long-term disease eradication in about 60 percent [5]. Many of those who relapse can be saved with infusions of lymphocytes from the donor (adoptive immunotherapy) [6].

Other patients received "medical therapy" which evolved from the oral chemotherapeutic agents: first busulfan, then hydroxurea, and finally interferon [7]. Interferon, a naturally occurring protein, was the first agent to cause a significant diminution of disease burden, and was, perhaps in combination with low-dose cytarabine [8], considered the treatment of choice for CML patients not undergoing allogeneic transplantation. Interferon's use was associated with frequent side effects, including neuropsychiatric and constitutional problems which led to intolerance in up to 25 percent of patients [9].

Imatinib mesylate's activity was initially reported in a series of phase I trials [10, 11] conducted in patients in all phases of CML, and was confirmed in large phase II trials [12-14] in patients with interferon-refractory or intolerant chronic phase as well as in more advanced disease. The following conclusions could be drawn from these clinical studies:

- Although imatinib has activity in all phases of CML, it leads to a higher response rate in earlier phases;
- The drug is generally well-tolerated with mild side effects of diarrhea, gastrointestinal distress, and fluid retention being common but rarely severe or life-threatening;
- Cytogenetic responses are common in which few if any Ph-positive metaphases are detectable.

Imatinib was approved by the FDA in May 2001 for the treatment of all phases of CML. (Editor's note: imatinib mesylate is commercially marketed as Gleevec.) However, the results of the IRIS study [15], in which patients with recently diagnosed chronicphase CML were randomized to receive either ara-C plus interferon or imatinib have clearly established imatinib as the medical treatment of choice.

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The precise role of allogeneic transplant in the imatinib era remains controversial [16]. For patients over age 30-40, it seems reasonable to start imatinib and reserve transplant for signs of failure of this medical therapy as evidenced by persistence or re-emergence of a sizeable CML disease burden detected by cytogenetics or a rise in the number of bcr-abl transcripts assayed by quantitative PCR. For patients who are younger with a sibling match, a transplant could be reasonably offered as initial therapy or after a few months on imatinib to lower disease burden. While the emergence of imatinib resistance has been described, and is frequently due to a mutation in the bcr-abl ATP (eg, drug) binding site, a new generation of small molecule inhibitors which can inhibit these 'resistant' enzymes are emerging.

References


Richard Maury Stone, MD, is a graduate of Harvard Medical School. He completed his internship and residency in internal medicine at Brigham and Women's Hospital in Boston and then trained as a fellow in medical oncology at the Dana-Farber Cancer Institute. Dr. Stone currently cares for patients with leukemias, myelodysplasia, and myeloproliferative disorders and conducts clinical and basic science research related to improving treatments for these diseases.

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Health Law

Wright v. Fred Hutchinson Cancer Center: Maintaining Patient and Public Trust in Clinical Research

An ethical case explores a lawsuit against Fred Hutchinson Cancer Center of Seattle by patients who claimed they were not told of the full risks associated with a clinical trial they participated in.

Laura Lin, MBA, and Bryan A. Liang, MD, PhD, JD

Fred Hutchinson Cancer Research Center is the largest and most successful bone marrow transplant center in the world and receives more funding from the National Institute of Health (NIH) than any other independent US research institute. In the 1980s the center conducted a series of clinical trials using T-cell depletion in an effort to prevent graft-versus-host-disease (GVHD), a major cause of death in bone marrow transplant patients. Several of the patients enrolled in the trials died. After an inflammatory series of articles about the clinical trials in The Seattle Times [1], several families of patients who had participated in T-cell depletion clinical trials sued the center [2]. The patients' families claimed that clinical investigators at the center did not disclose to the patients that the experimental GVHD treatment was known to cause bone marrow treatment rejection, that they did not disclose relevant information to the Institutional Review Board (IRB) and intimidated the IRB in contravention of federal regulations, and that investigators had a financial interest in the outcome of the trial due to their ownership of stock in the company supplying materials for the trial.

Depositions taken from individuals involved in the trials and expert physicians who objectively reviewed the case and testified to its merits revealed that there were lengthy, detailed, and documented discussions with patients and their families that described the potential risks and benefits of the clinical trials, that there was extensive opportunity for patients and their families to ask questions and discuss alternatives and concerns about the trials, and that the written consent forms allowed patients to make informed choices about their treatment and trial participation. Further, the chairman of the IRB that had approved the trials indicated that the clinical trials were reviewed, assessed, and approved independently and without obstruction or intimidation by the trial investigators. Finally, although the company that granted a license to use several monoclonal antibodies for the trials was co-founded by one of the investigators and several physicians at the center owned stock in the company, the company did not sell or have plans to sell any of the antibodies for the clinical trials treatment, and they did not seek patent protection for the antibodies or their use.

The patients' families made the following legal claims:

- the set of federal regulations that define research requirements for informed consent in clinical trials, known as the Common Rule [3] was violated [4] and under the Civil Rights Act of 1983 families could sue for damages.
- the families were third-party beneficiaries to the contract between the center and the Department of Health and Human Services, which disburses federal grant funds on the condition that the research fulfills federal regulatory IRB criteria for ethical research conduct; and
- the families had their US constitutional due process rights under the 14th Amendment violated when the Center interfered with the IRB procedures because adequate research procedures had not been in place and the patients had suffered harm. They claimed that US acceptance of the Nuremberg Code (which describes the special need
for safeguards for human experimentation), Declaration of Helsinki (which discusses the disclosure standards for informed consent), and Belmont Report (which describes the inadequacy of medical malpractice standards to ensure informed consent in clinical trials and the need for additional safeguards), all indicated US acceptance of such a standard in due process jurisprudence.

**Disposition: Wright v Fred Hutchinson Cancer Center**

The US district court for the Western District of Washington dismissed all of the patients' family claims, holding for the center and granting the center's motion for judgment in its favor.

At the outset, the court noted the standard for granting the center's motion:

> The Court…accepts as true the allegations of the plaintiffs'…and views them in the light most favorable to the plaintiffs. [Defendant's] motion[s]…will not be granted unless it "appears beyond doubt that the plaintiff can prove no set of facts in support of [its] claim which would entitle [it] to relief."

The court first noted that there is no private right of action for violations of regulations such as the Common Rule for informed consent in clinical trials because such breaches are not deemed violations of a "federal right" as defined by law. Next, it noted that there was no legal support for a private civil rights claim because neither statute nor legislation has defined a right of action for Common Rule regulatory violation.

Next, the court disagreed with the families' claim to third-party beneficiary status. The court held that parties that may benefit from a government contract are not generally assumed to be true third-party beneficiaries; that is, they do not have standing to enforce an agreement between parties in a governmental contract unless there is a specified and clear intent noted in the agreement or by the authorizing statute that defines the agreement. In this case, the parties were not intended under the agreement or any authorizing law to have these kinds of enforceable rights, and hence the families could not legally support their claim.

Lastly, the court addressed the 14th Amendment Constitutional claim and held that the families' due process rights were not violated. Under the 14th Amendment of the US Constitution, citizens are entitled to have adequate due process. This means that the government must have adequate procedures to protect the individual, but flawless implementation of the procedures is not required. However, if harm occurs due to imperfect procedure application, the state must provide an adequate post-deprivation remedy. The traditional state tort system is usually considered an adequate post-deprivation remedy. Because the families had access to adequate procedures—a standard IRB process—and had access to post-deprivation tort remedies, the court concluded that there was no due process violation.

The court later dismissed the patients' families' claims as well as their motions for reconsideration.

**Commentary**

The patients in any clinical trial have the fundamental right to assess and determine the extent of their participation through adequate informed consent. Under the AMA Code of Ethics Opinion 8.08, patients have the absolute right to self-decision regarding treatment modalities, and such self-decision can only be effectively expressed if they have all material information regarding treatment [5]. It is therefore the physician's duty to present the medical facts and circumstances in a manner that the patient can understand and to make clinical recommendations that are consistent with sound medical practice [6].

In the case of clinical trials, the obligation extends further. The AMA Code indicates that, when experimental, the "clinical investigation…[must be] part of a systematic program competently designed, under acceptable standards of scientific research, to produce data which are scientifically valid and significant" [7]. As part of this obligation, physicians are also required to indicate any potential or actual conflicts of interest in the outcomes of the trial: "any material ties to companies whose products they are investigating, including: financial ties, participation in educational activities supported by the companies, participation in other research projects funded by the companies, consulting arrangements, and any other ties" must be disclosed [7].
In this case, physicians at the Fred Hutchinson Cancer Center appear to have attempted to fully inform the patients about the potential risks and benefits associated with the GVHD T-cell depletion trials. Renowned, neutral experts in both clinical trials and clinical medical ethics appeared to agree that the extensive discussions and documentation were well within the bounds of acceptability for disclosure and offered adequate opportunity for patient concerns to be raised. Indeed, the extent of discussion and documentation presented in deposition was exemplary for clinical trials research, at least with regard to the scientific nature of the trials.

Although this court decided that the extent or relationship of physicians in the clinical trials to corporate interests did not need to be disclosed under federal rules, it can be argued from an ethical perspective that the relationship between the investigators and the company that supplied monoclonal antibodies should have been disclosed to all patients clearly and early. One of the investigators had co-founded the company and others owned stock in it. Transparency is the hallmark of trust, and it may have been that patient families, upon discovering these relationships, were understandably skeptical of official explanations. In particular, the lack of full and frank disclosure may have led to an increased reliance by the patients and their families upon the depiction by newspaper accounts such as in the Seattle Times and elsewhere, rather than by explanations the center or the physician investigators themselves provided.

Clinical trials with extensive informed consent have the potential to benefit the patients who engage in them as well as the present and future society. Any health care providers who seek to participate, and have their patients participate, in clinical trials must rigorously adhere to the Code of Ethics principles both in letter and in spirit. Indeed, physicians must avoid both actual impropriety as well as the appearance of impropriety. Only by doing so will patient and provider trust—the foundation of the therapeutic relationship—be maintained, and a partnership between the two promoted that will result in optimal outcomes for the patient today and in the future.

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Policy Forum

The Need for a Centralized Clinical Trials Registry

A centralized registry to provide information to consumers regarding the effectiveness of clinical trials is needed to help patients make informed decisions about treatment.

Christian J. Krautkramer and Shane K. Green, PhD

Imagine waking up one morning to headlines touting the discovery of a remarkable new drug, Somax. The acclaim is based on a clinical trial with thousands of participants, the unprecedented results of which have just been published in one of the world's top medical journals. Soon, television ads will offer the promise of improved health and well-being, with a reassuring voice encouraging you to seize the opportunity: "ask your doctor if Somax is right for you!" And why not? The study has been vetted by experts and the data and conclusions have been judged sound; Somax may be just the thing to treat your ailment.

Is this scenario too good to be true? It's hard to say, especially if you are not given the whole story. Yet under current clinical reporting guidelines, the manufacturers of Somax have no obligation to disclose "proprietary information," which may include data from other trials, even if those data suggested that Somax was less effective than other medications, altogether ineffective, or even potentially harmful to those taking it.

Global sales of pharmaceuticals amount to approximately $350 billion annually, so the makers of Somax have powerful economic incentives to withhold all but the most positive of findings; after all, there would be scarce market-share for a drug shown to have questionable efficacy or benefits that are outweighed by associated risks. Granted, the pharmaceutical industry is a business and is, therefore, entitled to earn a profit; these profits, in turn, help fund further biomedical research and innovation. There must be a point, however, at which that entitlement is superseded by the interests of the patient-consumer—caveat emptor should not apply to inherently vulnerable patients.

Though the above scenario is hypothetical, the underlying issue unfortunately is not. Concerns over the nondisclosure of negative or inconclusive clinical trial data came to a head this past August when an FDA review, prompted by a tragic incident, confirmed that pharmaceutical manufacturers had withheld study results that suggested an increase in suicidal ideation among children taking certain antidepressant medications (specifically, Paxil from GlaxoSmithKline (GSK), and Pfizer's Zoloft) [1].

The practice of nondisclosure, by no means limited to these recent high-profile cases, is finally garnering the attention it deserves, and long overdue steps are being taken to counter it.

Why disclose all clinical trial data?

Once a drug is approved by the FDA and reaches the marketplace, it is critical that all information on that drug's past performances be available to physicians and patients alike, for one simple reason: physicians cannot practice evidence-based medicine, nor can patients expect to benefit from evidence-based medical advice, if key evidence is suppressed. Indeed, it is the potential for the suppression of evidence (ie, negative clinical trial data) to cause harm to patients, albeit indirectly, that has brought this issue to the fore.
Disclosure is also important for those individuals who participate in the clinical testing (ie, pre-approval) of new drugs. When people consent to be subjects in clinical trials, they do so in spite of the distinct possibility that the experimental intervention may offer them no benefit, and, in fact, may cause them harm. Why? Healthy volunteers may be motivated to participate in Phase I trials by the promise of financial remuneration. Patients with seemingly incurable disease may enroll in Phase III trials in hopes that the experimental therapy available to trial subjects will succeed where conventional treatments failed. But many, if not most, participate in clinical trials with the altruistic intention of contributing to medical knowledge that may help improve human health and well-being [3].

By asking prospective subjects to assume the risk inherent to clinical testing so that others may benefit from the findings, researchers take on implicit responsibility to minimize that risk and ensure that the remaining, unavoidable risk is not taken in vain. Full disclosure of previous clinical trial data (ie, data from any and all prior trials of a given drug) is essential to meet these responsibilities, for several reasons.

First, the data from each phase of pre-market clinical trial testing (ie, Phase I, II and III) provides the foundation for the next phase of tests, or for more testing at the same level, in part by helping to mitigate risk to subjects in subsequent tests. If clinical trial data is suppressed, it cannot inform the design or conduct of subsequent trials and, therefore, cannot be used as it ought to be: to protect subjects from possible harm.

Second, before clinical research can be undertaken, trial proposals are vetted by Institutional Review Boards (IRBs), which are charged with ensuring that the risk of harm to participants is not undue, unnecessary, or unmitigated. But IRBs are precluded from performing their function effectively if they are not privy to all available information concerning the experimental treatment, including data on past trial performance.

Finally, the potential for others to benefit from a trial subject's assumption of any unavoidable risk becomes moot if the data generated in the course of study are buried [4]. This is particularly objectionable in cases where actual harm is incurred by research subjects, whose sacrifices are worthwhile only if they are disclosed, thereby mitigating potential future harms to others [5].

**Recommendations of the ICMJE**

The International Committee of Medical Journal Editors (ICMJE), which comprises the editors of 11 of the world's top medical journals, has recently taken a significant step to combat the problem of "selective awareness" of clinical trials. In an editorial published simultaneously in all member journals [6], the ICMJE announced a new policy to the effect that, beginning next year, papers describing clinical trial results would only be considered for publication in member journals if the trial had been registered, prior to volunteer enrollment, in an open registry that met certain criteria.

Acceptable registries will be those that include a unique trial identification number, a statement of the intervention(s) and comparison(s) studied, the study hypothesis, primary and secondary outcome measures, participant eligibility criteria, key trial dates, target number of subjects, funding source(s), and contact information for the principal investigator(s). Moreover, the registry must be open to the public at no cost, be electronically searchable, and be maintained by a not-for-profit group (ie, registries operated by GSK or Eli Lilly & Co., for example, do not qualify). According to the editors, the only current registry that meets the criteria is [www.clinicaltrials.gov](http://www.clinicaltrials.gov), maintained by the National Institutes of Health.

This important policy, however, applies only to ICMJE member journals, and, while they are among the most respected medical journals in the world, there are hundreds of others that publish clinical trial results; hence, the ICMJE has recommended that all journals adopt similar policies concerning trial registration.

Though they represent a laudable initial step toward the ultimate goal of openness in clinical research, the recommendations of the ICMJE fall short of what is needed, for 2 main reasons: First, they do not mandate that the results of trials be entered in a registry, meaning that negative data could (and likely would) remain undisclosed; and second, the ICMJE does not advocate for a single, centralized registry, the lack of which will make it significantly more difficult for patients, physicians, and researchers to acquire and make use of all pertinent information on trials of a given drug or class of drugs.
Negative Results

For physicians to make informed clinical decisions as to the best treatment options available to their patients, they must be able to weigh possible harms against likely benefits [7]. Not surprisingly, information concerning potential benefits is easy for physicians to come by; journal articles, continuing medical education activities, and pharmaceutical company representatives provide a very detailed picture about which drugs constitute the cutting edge therapy for a particular ailment. In contrast, negative results (eg, those indicative or suggestive of serious side effects) sometimes remain unreported [8]. Merely registering clinical trials before they are conducted will not rectify this imbalance.

To succeed in addressing the issue of selective awareness, a registry must include descriptions of trials' outcomes, be they positive, negative, or inconclusive. This is not, however, as simple as it sounds; studies are often closed or not submitted for publication based on questionable experimental methodology, therefore trial results must not only be released but also explained in good faith or, at minimum, qualified. The inclusion of outcome reporting in a clinical trials registry would do little to change the frequency of publication of negative data in peer-reviewed journals, but it would bring the data into the public domain where it can be accessed by patients and physicians alike.

Centralized Registry

Multiple clinical trial registries, even if each meets all the criteria set forth by ICMJE, would necessitate that physicians, researchers, and patients locate and investigate many sources to acquire a full complement of available information. In addition to being unnecessarily inefficient, such an approach increases the risk that important information will be missed. A single, authoritative source of information on established and experimental therapies would drastically reduce that risk, and allow for far more efficient and effective data collection.

Hence, we support creation of a comprehensive registry, to include all trials conducted in the US and all international trials sponsored by US-based groups, housed in the National Institutes of Health (NIH), and accessible through the National Library of Medicine (NLM). The heart of the US clinical-research establishment, the NIH is already home to www.clinicaltrials.gov, which could, at least in theory, be modified to become a more comprehensive trial registry. Moreover, NLM is host to several searchable databases of medical literature, notably including MEDLINE, the world's most comprehensive, and most searched, medical journal database. Putting the trial registry in proximity (in a virtual sense) to the NLM databases would greatly facilitate one's ability to access all available data, published and unpublished.

There is currently a bill pending before the US Senate, S.2933 [9], and supported by the American Medical Association [10], that similarly recommends the creation of a clinical trials registry to be housed at the NIH. The registry would contain information on all publicly and privately funded clinical trials involving drugs, biological products, or devices, from start to finish, regardless of the outcome of the trial. Furthermore, registration of trials would be mandatory, with strict penalties for non-compliance. Support for this bill from the clinical research community and its benefactors—health care consumers—would add momentum and increase pressure to pass this important legislation.

Conclusion

To best serve their patients, physicians must be as informed as possible. To be truly empowered and provide genuine consent to treatment, patients must be as informed as possible. To reduce redundancy in experimentation, at great cost and potentially great risk to human subjects, clinical researchers must be as informed as possible. For all of these parties, a centralized, comprehensive clinical trial registry would redefine, to their benefit, what it means to be "as informed as possible"—what more justification could one require?

Conceivably, some individual or collective actors will, in the interest of prioritizing profits, continue to devote great effort to protecting trade secrets or burying bad results that could prevent a financial windfall. Therefore, pressure must be placed on the pharmaceutical industry, FDA, researchers, journal editors, and legislators to institute a singular, comprehensive, and mandatory registry for all clinical trials, as an essential means by which to ensure that new drugs...
help patients as well as pocketbooks.

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Genetic research is threatened by lack of samples, and public policy should be developed to encourage public participation.

Michael E. Berens, PhD, and Gary E. Marchant, PhD, JD

DNA samples are the life-blood of modern genetic research. By analyzing genetic variations in DNA collected from a population of individuals, and correlating those variations with health outcomes, researchers are ushering in a new era of more effective and personalized medical diagnosis and treatment. The enormous potential of genetic medicine is threatened, however, by growing barriers to the availability of adequate genetic samples, and this problem is likely to intensify as both the demands for such samples and the obstacles to obtaining them continue to grow. This commentary identifies key factors that are impeding research access to genetic samples and discusses some potential policy responses, including fostering a sense of civic responsibility to donate genetic samples for medical research.

Impediments to DNA Sample Collection

A series of real or perceived risks associated with research use of genetic information is discouraging the donation of DNA for research use [1]. First and foremost is the fear that the confidentiality of genetic data will not be adequately protected and genetic information will be used to discriminate against the DNA donor in employment, insurance, or other contexts. Another fear is that researchers will use the donor's DNA for research projects of which the donor does not approve. For example, members of various ethnic groups are particularly concerned that their DNA could be used to classify and stigmatize populations based on race.

Yet another impediment to obtaining genetic samples is the increasing demand for property rights in DNA samples by donors. As some genomics and pharmaceutical companies begin to prosper financially from genetic research, some donors of DNA claim they should be entitled to share in the financial returns. It was recently suggested, for example, that DNA donors should demand $50,000 per genetic sample from pharmaceutical and biotechnology companies [2]. Such high monetary demands would stop genetic research in its tracks. Other groups, including some Native American tribes and disease advocacy organizations, are also asserting property rights to their donated DNA samples, not so much for pecuniary gain but rather to prevent (mis)use of their DNA in research or commercial applications they do not support.

Policy Solutions are Needed

Effective policy responses are needed for these real issues. The most important imperative for promoting genetic research is to put in place carefully crafted legislation that protects the privacy and confidentiality of genetic information without unduly hindering genetic research. Whether actual or perceived, the specter of discrimination from unauthorized disclosure and use of personal genetic information undermines public confidence in donating DNA for medical research.

Measures that build public trust in genetic research are also needed. Trust is much easier to destroy than create. A few highly publicized transgressions by researchers can tarnish and undermine trust in the entire genetic research enterprise. The research community should put in place institutional mechanisms that attempt to predict, prevent, and
respond appropriately to potential controversies, minimizing the frequency and impact of these trust-destroying incidents. While Institutional Review Boards (IRBs) play a critical role in preventing potentially unethical or inappropriate conduct, they should be supplemented by broader and more comprehensive ethical and legal advisory mechanisms that can support the overall mission and approach of the institution. A recent report on best practices for human tissue repositories by the Rand Institute recommended that each institution that collects genetic samples establish "a bioethics advisory board or other governance and oversight advisory board to provide another layer of review [in addition to IRB review] for privacy and confidentiality procedures" [3].

Nonprofit research intermediaries that collect and anonymize genetic information and then release it into the public domain without intellectual property restrictions for researchers can also help alleviate real or perceived concerns about the collection and possible misuse of genetic information by private companies who might be seen as being unduly influenced by their profit motive. Another promising innovation is the collaboration between research institutions and organized donors of DNA. For example, the PXE Foundation has established an unique collaborative model in which it partners with researchers to study PXE disease, with the researchers receiving access to the foundation's genetic database and the foundation sharing in the decision making, review, and benefit sharing of the research.

A New Civic Ethic of DNA Donation

Public attention has focused largely on the risks of donating genetic information. These risks are important and must be addressed. But the public discourse should also focus on the positive side of genetic research and donation. Each of us, as well as our relatives, friends, and colleagues, has the potential to benefit personally from advances in genetic research that can help treat deadly and common diseases such as cancer, diabetes, neurodegenerative disorders, and developmental aberrations. The personal benefits we can expect to receive from genetic research may impose a social obligation to participate in facilitating the genetic research that can bring these benefits to fruition.

Eminent British philosopher John Harris recently wrote about the social obligation to participate in genetic research:

Someone who benefits from research but refuses to participate in it is clearly acting unfairly by free-riding on the contribution of others. Where people volunteer to participate in research (at least where the risk and dangers to them are minimal), they are doing what any reasonable and decent person should be willing to do—both because of the overwhelming utility of the research and because they wish and expect to receive the benefits of research in their turn [4].

Harris makes clear he is not talking about an enforceable legal obligation to donate one's DNA to research but rather a moral obligation. Similarly, bioethicists Ruth Chadwick and Kare Berg have argued for a duty to participate in genetic research based on ethical principles of solidarity and equity [5].

Bringing about this shift in public perception will require a broad and sustained public education effort, much in the way that the media, government, businesses, and other institutions promote the ethic of blood donation. Equal or greater efforts will be needed to instill a moral duty to donate genetic material for research—a public good like blood donation—from which we all benefit. Medical researchers and practitioners will need to be in the vanguard of creating new social mores in favor of contributing genetic material for research, but for the full promise of genetic research to be realized, the entire community must share the benefits and accept the responsibilities involved.

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Medicine and Society

Gatekeeping and the FDA's Role in Human Subjects Protection

The FDA bears the responsibility to monitor clinical trials and protect human subjects from harm.

Daniel Carpenter, PhD

Introduction to Human Subjects Regulation

Clinicians and clinical researchers are well aware of the importance of human subjects regulations in medical research. Just about any study conducted at a university medical center, a hospital, a contract research organization, or elsewhere must now pass the muster of an Institutional Review Board (IRB). IRB approval is necessary before the project is begun, in some cases before investigators can even apply for funding. This is as true of social science projects in anthropology, economics, epidemiology, political science, and sociology as it is of clinical or experimental research in medicine and psychology. The aggregate activity conducted under human subjects protections is staggering: every year thousands of IRBs in the US examine over 20,000 research proposals, and hundreds of thousands of experimental subjects and patients are presented with their legal human subjects' rights and sign consent forms stating that they understand these rights as they participate in the experiment [1].

Exactly how we got here and exactly what keeps us here—the evolution and maintenance of human subjects protections in clinical research—are not well understood. Our casual understanding, available from some published histories and a brief tour of the World Wide Web, is that current human subjects protections in medical research followed from the Nuremberg Code of 1947 and the World Medical Association's Helsinki Declaration of 1964 and have been supported by the evolution of ethical standards in the medical profession. These impressions are half-true but miss the more important feature of human subjects protections: their authorship and enforcement by the US Food and Drug Administration (FDA). The breadth and rigor of human subjects regulations that govern US clinical research are attributable mostly to the FDA rather than to the AMA or the National Institutes of Health (NIH) [2].

The Role of the FDA

The FDA is the primary author and enforcer of human subjects protection in the United States. The agency's role as gatekeeper to the prescription pharmaceutical and device markets in the US, combined with the implied powers that come with that role, make the FDA the most consequential force for human subjects protection. The FDA's veto power over product development gives pharmaceutical firms and researchers compelling incentives to cleave tightly to federal regulations and rigorous ethical standards. Just as important, the FDA has interpreted its authority over clinical research quite broadly, issuing detailed and comprehensive rules and aggregating inspection forces to monitor clinical investigators, laboratories, and IRBs and even to interview human subjects enrolled in clinical trials. The FDA has a life-or-death say, not just about products but also about IRBs, clinical investigators, and individual studies.

The FDA was involved early and often in human subjects protection. The FDA's Investigational New Drug Regulations of 1963 included requirements for informed consent and human subjects protections in clinical trials with investigational new drugs [3]. In 1971, 3 years before Congress passed the National Research Act (P.L. 93-348)
requiring institutional assurances of human rights protection and IRB review, FDA regulations already required IRB approval of all studies involving investigational new drugs or biologics [4]. After harmonization of these regulations with NIH/Health and Human Services in the 1980s, the federal government's Federal Policy for the Protection of Human Subjects (the "Common Rule") was adopted in 1991. In many ways, the Common Rule codified practices and collected rules that were adopted decades earlier by the FDA.

The FDA's formal capacity in regulating clinical research is uniquely complemented by the day-to-day field and enforcement activities that the agency devotes to human subjects protection. No agency at any level of government conducts more inspections of clinical researchers and IRBs than does the FDA. Again, this practice began quite early. After a trial monitoring program was run and observed from 1972-1974, the FDA launched its Bioresearch Monitoring Program in 1977, which included inspection of clinical investigators, biopharmaceutic laboratories, toxicology laboratories, and IRBs [5]. Such inspections reports consume the time of more than 30 FDA employees at headquarters and in field offices. When deficiencies are found, the FDA may issue a warning letter to institutions detailing "significant deficiencies" in IRB oversight. If the deficiencies are serious enough, the FDA can disqualify both the IRB and the clinical investigator.

Exploring the Significance of FDA Regulation

Just how intensive or exhaustive is FDA oversight? Data are insufficient to permit a good answer to this question, but some patterns from the past 2 decades can be gleaned from FDA and congressional reports. From FY1986 to FY1995, for instance, the FDA's Center for Drug Evaluation and Research conducted 1712 inspections of establishments for compliance with FDA informed consent requirements. From 1991 to 1995, the FDA issued an average of 158 IRB inspection reports per year. In the early 1990s, such inspections uncovered numerous violations of federal rules, most of them minor. Almost half of IRBs (48 percent) inspected from October 1992 to September 1994 failed to keep adequate minutes of their meetings, while more than one-third (36 percent) failed to promulgate adequate written procedures. Almost half (48 percent) were found to have operated without a quorum of members present.

From January 1993 to November 1995, the FDA found violations serious enough to merit a warning letter in 31 cases. The agency has never disqualified an IRB, but in response to FDA findings of serious noncompliance with federal regulations, research institutions have disbanded their IRB more than 60 times in the past 2 decades. The FDA can also disqualify clinical investigators for serious or repeated violations of agency regulations. This too has happened only rarely—just 19 times from 1978 to 1994, according to one FDA report—but this number understates the reach of FDA regulation. Over the same period more than 110 clinical investigators were sanctioned or have signed consent agreements with the FDA, a serious and embarrassing admission of negligence in clinical research that can hamper researchers' ability to attract further funding. The threat of reputation harm is sufficiently harrowing for clinical researchers and medical centers that even rare sanctions present sufficient incentives for most researchers to rigorously maintain human subjects protections [6].

The FDA cannot, of course, disqualify physicians from medical practice, nor can it prohibit universities from engaging in research. What backs up the FDA's human subjects regulations is its authoritative gatekeeping role in the pharmaceutical and medical device marketplaces. Since 1938, by federal statute, no new drug may be marketed or prescribed in the United States without prior approval from the FDA. Universities, medical centers, and research organizations that violate FDA regulations will simply lose business from sponsors that must conduct clinical studies to receive FDA approval. Since research funding is the lifeblood of any research endeavor, FDA sanctions can do enormous implicit and explicit damage to the careers and livelihoods of researchers and research organizations that violate federal law.

Before approving an Investigational New Drug (IND) application, the FDA requires researchers to submit and sign a formal statement that they will uphold prevailing ethical standards and that their institution's relevant parties will be notified of their study. FDA officials have the power to reject or terminate INDs (and hence terminate clinical studies) when the proposal presents an "unacceptable risk" to human subjects.

Conclusions
Determining whether FDA regulation of clinical trials is maximally effective in protecting human subjects is beyond my aims here. A certain answer to this question may be impossible, and better information would require intensive study of tens of thousands of clinical trials conducted over the past few decades. One thing that is certain, however, is that to the extent that any institutional force in the United States will be responsible for strengthening or weakening human subjects protections, the necessary and effectual action will probably be observed in the Food and Drug Administration.

The emergence and enforcement of human subjects protection in the US has been the product of efforts by many organizations, institutions, and individuals. Neither the NIH nor university research committees nor medical associations (as general as the AMA and as specific as the American College of Cardiology) can be ignored. Yet to think of the FDA as just one more player in the political and scientific arena of human subjects protection would also be inaccurate. With its gatekeeping power over medical products, its considerable inspection force, and its long-held statutory authority, the FDA is arguably the most powerful player in clinical research.

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1. For some rough estimates of the number of IRBs, number of federally sponsored or regulated clinical trials, and number of human subjects participating, see the report of the General Accounting Office (GAO), Protecting Human Research Subjects, March 8, 1996 (GAO/HEHS-96-72), pp. 2, 6. In the past half-century, the total number of human subjects in medical and pharmacological research easily exceeds 10,000,000 and is perhaps much larger.

2. Casual and academic treatments of human subjects protections, including informed consent and the evolution of institutional review boards (IRBs), generally ignore or accord trivial treatment to the role of the FDA. For example, the National Cancer Institute's "A Guide to Understanding Informed Consent" (available at www.cancer.gov) discusses the Nuremburg Code, the Declaration of Helsinki, the 1979 Belmont Report and the unified 1991 Federal Code for the Protection of Human Subjects, but not the FDA.

3. In ongoing historical research, I have found evidence that many ideas and statements in the 1963 IND regulations were in fact hatched in the FDA's Bureau of Medicine in the late 1940s and 1950s, long before the thalidomide tragedy of 1960-1961. See Carpenter D, Moore CD. Robust action in a bureaucratic cohort: FDA scientists and the Investigational New Drug Regulations of 1963. Paper presented at the Yale University Conference on American Political Development, October 2004.

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Op-Ed

Ethics, Education, and Integrative Medicine

Physician knowledge of complementary and alternative medicine can help patients make informed decisions regarding treatment plans.

Victoria Maizes, MD, and Randy Horwitz, MD, PhD

The Evidence Question

The increasing number of patients who use complementary, alternative, and integrative therapies raises new ethical challenges for physicians. These challenges arise in part because some of the therapies recommended in integrative medicine (IM) have not been assessed with the rigorous scientific testing recommended to validate conventional allopathic treatments. The dominant approach to medical research is the randomized double-blind clinical trial originally developed for evaluating the efficacy of new medications versus placebo. This pharmaceutical model is not well suited to integrative research for a number of reasons including: the requirement that identical, rather than individualized treatments be administered, a single modality focus that ignores the real-world multiple treatment approach used in clinical IM practice, and the lack of outcome measures which assess nondisease-specific (wellbeing), global, and multidimensional/multisystem changes that many IM practitioners report seeing in their patients [1].

To evaluate the utility of IM prior to the availability of broad, multidimensional health outcomes trials, a sliding scale of efficacy is used. The greater the potential for harm, the stricter the standards of evidence to which the treatment is held. Where no satisfactory conventional therapy has been shown to be effective, the IM physician considers appropriate alternatives and discusses the potential risks and benefits with the patient. A therapy that lacks substantial evidence for efficacy can be recommended in good conscience if the potential benefit is based on theoretical grounds or clinical experience and the risk to the patient is negligible. The physician explains the basis on which the recommendation is made to the patient in an honest, forthright, and supportive discussion.

Defining Integrative Medicine

Integrative medicine is defined as healing-oriented medicine that takes account of the whole person (body, mind, and spirit), including all aspects of lifestyle. It emphasizes the therapeutic relationship and makes use of all appropriate therapies, both conventional and alternative [2]. In IM, the patient is a partner in his or her health care, with the physician taking the role of the informed, beneficent guide. The physician seeks to understand and respect the patient's beliefs and goals as well as his or her physical and psychological health and ailments. This is accomplished by asking a broader set of questions and listening carefully to the responses [3]. The welfare of the patient is considered paramount, and the physician tailors her actions to result in the best possible outcome for the patient. Allopathic and integrative medicine share the same ethical framework; integrative medicine training reaffirms the importance of beneficence, nonmaleficence, respect for patients, and patient autonomy.

In the United States, up to 88 percent of patients with chronic illness use some form of complementary or alternative medicine (CAM) [4]. The majority of patients do not share their use of CAM with their physicians often fearing the physician's scorn or skepticism [5]. Communication is central to the therapeutic relationship. The ethical principle of nonmaleficence may be violated unintentionally if physicians fail to take a complete history and patients refuse to fully and honestly disclose health information. The most prominent example of this possibility is physicians’ failure to ask
patients about their use of dietary supplements, botanicals, and vitamins. Because of the widespread use of these compounds in the US, the potential for drug-herb interactions should be explored through a thorough history by the physician.

In addition, skepticism or negative statements on the part of the physician may diminish a patient's hope or damage his or her belief system. This represents a more subtle violation of the ethical principle of beneficence. The impact of reduced hope should not be underestimated. Research reveals that the strongest predictor of mortality is neither lab tests nor physician assessment but rather the patient's own self-rated health status [6].

Case Studies

The University of Arizona's Program in Integrative Medicine (PIM) has been offering fellowship training in IM since 1997 and has trained more than 100 physicians [7]. The following cases are examples of specific ethical dilemmas that have arisen in the PIM training clinic. These cases serve to highlight the often challenging position of the physician seeking to balance allopathic and integrative medicine.

- A patient selects complementary and alternative medicine (CAM) when allopathic treatment offers better options and where delay in treatment presents risk. For example, a young man with testicular cancer prefers to try alternative approaches first despite the high success rate of conventional medicine for this potentially life-threatening cancer. This places the physician in the position of exploring and probably challenging the patient's belief system.

- A patient is offered a high-risk allopathic approach when a lower risk integrative approach is available. For example, a teenage boy with a 3-year history of headaches, neck pain, and a new onset tic disorder was treated with narcotics, antidepressants, betablockers, antipsychotic medications and epidural anesthesia. Osteopathic manipulation using the strain-counterstrain technique eliminated the pain in 2 visits. Physician ignorance of osteopathic (and other integrative) approaches is, of course, a significant problem and can lead to violation of the patient's right to full disclosure of all possible treatment options.

- A middle-aged, previously vibrant, professional man with a 6-month history of foot dystonia of unknown origin asks his physician when he will be able to use his treadmill again. The treating neurologist suggests that he give away the treadmill, stating he will never use it again. The negative prediction (a sort of "medical hexing") diminishes hope and counters the patient's belief that he will recover.

- A doctor practicing alternative medicine, with financial interests in the sale of his supplements, recommends multiple expensive dietary supplements to an elderly woman with hypertension. Despite her limited income she feels uncomfortable saying no. Selling products creates the potential for conflict of interest. If it is done at all, it is best separated from the therapeutic encounter. The physician's financial incentive must be made clear to the patient.

Conclusion

Patients' use of CAM and IM highlights existing, and presents some new, ethical challenges to physicians in training. Broadening the health history to understand a patient's belief system and motivation, as well as the full range of therapies he or she might be using is a first step to good care [8]. Developing a clear awareness of how one's "own personal, cultural, ethnic, and spiritual beliefs may affect [his or her] choice of recommendations regarding patients' treatment decisions" is another [9]. Greater self awareness is a stimulus of ethical behavior and can be developed through case discussions, reflection, and group process. Finally, broadening medical training to encompass the integrative paradigm provides a forum where ethics, science, and patient preferences are all considered in service to the best of medical care.

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Research Ethics in Literature

The Doctor's Wife is a classic novel that explores the complex human interaction between a researcher and his or her human experimental subjects.

Helle Mathiasen, Cand mag, PhD

Bioethics is a relatively young area of concern and field of inquiry, less than forty years old in its present incarnation—though many of the questions to which it leads are in fact ancient. In the mid-1960s, following the disclosure of several abuses here and abroad, ethical attention first focused on the use of human subjects in medical experimentation. Intense public discussion established the importance of voluntary and informed consent, and institutional arrangements were subsequently developed to protect vulnerable patients against the potentially excessive zeal of otherwise worthy experimenters.

This quotation is taken from the introduction by Leon R. Kass, MD, to a recently published anthology of readings on bioethics, entitled *Being Human: Readings from the President's Council on Bioethics* [1]. The President's Council on Bioethics encompasses 17 distinguished scholars and editors, including PhDs, JDs, and MDs, from some of the most prestigious educational institutions in the United States. What most differentiates this anthology from similar publications, however, is the fact that excellent stories, poems, memoirs, and philosophical treatises have been selected by the editors to illustrate a variety of issues in bioethics. Arguably, a textbook of medical ethics could teach similar lessons, but stories and poems call forth in us that which is most human: our complex interconnectedness.

As a longtime instructor in literature and medicine, I am delighted to find here excerpts from the classics—Homer, the Bible, and Shakespeare—as well as selections from the autobiography of Frederick Douglass, part of a story by Perri Klass, MD, and many others. These selections are valuable because they illustrate medical ethics concerns in a way that is accessible to scholars and laypersons. Everyone loves a good story: this book has several of them. But bioethicists and medical practitioners interested in a deeper understanding of the complex human interaction between a researcher and his or her human experimental subjects can also turn to complete works of fiction.

A classic novel in the field of research ethics is *The Doctor's Wife* [2] by Japanese author Sawako Ariyoshi (1931-1984). This story is based on the discovery by Japanese surgeon Hanaoka Seishu (1760-1835) of an effective anesthetic before any such breakthrough took place in the West. Ariyoshi has based her narrative on the records, diaries, books, and biography of Dr. Hanaoka Seishu but has added fictional characters, events, and dialogue. Informed consent and overzealous scientists are never mentioned directly in this historical novel, but these themes and characters are dramatized in a way that captivates our attention. We are guilty of anachronism if we attempt to place Ariyoshi's narrative in the framework of modern medical ethics, but we can learn much about the motivation and relationships of researchers and their subjects through this compelling story.

The plot centers on a poor Japanese family from a small provincial town who send their son Hanaoka (Umpei) Seishu to medical school in Kyoto for 3 years largely because his mother, Otsugi, has determined that he is destined to be a great man. Under her guidance, his sisters and other women in the family sacrifice their happiness to pay for his education. His mother also finds him a samurai wife, Kae, a 21-year-old innocent girl who, at first, is infatuated with her strong-willed mother-in-law.
After graduating from medical school, Umpei sets out to discover an anesthetic that will put a patient to sleep during an entire operation; the ambitious young doctor wants to be able to remove malignant tumors in breast cancer patients without killing the patient. He starts experiments to develop this anesthetic from mandarage (Datura alba Nees) and gives it first to stray cats and dogs. Then one of his sisters, Okatsu, develops breast cancer. Wishing to die, she asks her brother to give her an overdose of the anesthetic, but he refuses. Next, she asks him to operate on her without anesthetic, saying, "If I should die, I would still feel satisfied knowing that I might have been helpful to you" [3]. But he refuses because she is a blood relation. After Okatsu's death, their mother Otsugi offers herself as an experimental subject: "Everyone close to you, Umpei…except a fool, can see that your research would be complete if only you could test the drug on a person. I am the mother who gave birth to you, so I, more than anybody else, understand what you want to accomplish" [4]. Kae, the doctor's wife, knows her now-hostile mother-in-law is referring to her as the fool, so she proceeds to offer herself for the experiments, pleading, "Please try it on me" [4]!

After 10 years of animal experiments, the doctor chooses to try the drug on his mother, with the result that she falls into a deep coma. Umpei remains calm, as he explains to Kae that he has only put a little mandarage in his mother's drink; most of it is alcohol. She will sleep it off, he says. Next, the doctor tries a much higher dose on his wife, who suffers great pain and falls into a coma for 3 days: "Kae, however, was satisfied that she had outdone Otsugi and did not mind her weakened condition, although she did not recover her strength for some time" [5]. Her desire to compete for her husband's attention and to defeat her proud mother-in-law by tolerating greater physical pain and risk is strengthened when Koben, the daughter of Umpei and Kae, dies. After this event, Kae herself only wishes to die: "Having lost Koben, her own life seemed less significant, and the donation of her body to her husband's research seemed like a worthy action. Whatever her reasoning, she in fact craved the medicine….If only she could fall unconscious again!" [6]. Supervised by her husband, Kae ingests a large dose of the anesthetic and falls into a coma for 3 days. After a second experiment, Kae goes blind.

Having discovered and perfected the anesthetic, Dr. Seishu performs and teaches surgery on anesthesia and becomes a legend in his own time. At the end of the novel, Umpei's unmarried sister Koriku, who is dying, reflects aloud to Kae, "My brother became famous and people think you and Mother are wonderful" [7]. Koriku indicates that despite the success of his work, Dr. Seishu took advantage of the rivalry between his mother and his wife by pretending to ignore it so that he could make the leap from animal to human experimentation.

Several factors contribute to the doctor's success in using human subjects for his research: the women's rivalry; the women's inferior status; their depressive mental states and masochistic tendencies. Though they volunteered, the women could not have given informed consent, because the doctor did not communicate with them about the dose, nor did he himself know how much would be needed to produce general anesthesia with little-to-no harm to the patient. Doubtless, the 2 women observed how the cats and dogs suffered and died during the 10 years Dr. Seishu experimented on these animals, but they were so desperate for attention and recognition, and so depressed after their respective daughters' deaths, that they were willing subjects for the dangerous procedures.

Today, ethics committees and supervised experiments have improved the protection of vulnerable patients. One would certainly hate to think that Ariyoshi's story could happen now. However, her superbly crafted narrative leaves us wondering how bioethical principles can be enforced in the case of experiments on vulnerable people, such as prisoners, children, the mentally ill, and the elderly. The ever-present question is: what price must be paid for progress in medicine, and by whom?

References


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Medical Humanities

My Story: Living with Narcolepsy

A 34-year-old ED nurse discusses how her life has changed after developing narcolepsy with severe cataplexy.

Tricia Higgins, BSN

Editor's Note

Tricia Higgins is her own clinical trial with a cohort of 1. Tricia has been diagnosed with narcolepsy with severe cataplexy. This dual diagnosis is characterized by the inability to maintain voluntary wakefulness, abnormal REM, and sudden paralysis or weakness in muscle tone without loss of consciousness. If left uncontrolled, her symptoms make it nearly impossible for her to live normally. Her ability to live a higher quality of life is made possible by a cocktail of medications that were all developed for purposes other than narcolepsy. Patients and physicians facing uncommon or atypical disorders like Tricia's must consider a complicated series of decisions. Most therapeutic regimens and pharmaceutical developments are based on treating the underlying mechanism of a disease, a pattern that is growing more pronounced following tremendous advances in basic science and translational research. But what happens when that paradigm fails? How do things change for both patient and physician when determining an accurate diagnosis—let alone treatment—can take years? What happens when it is not possible to address the mechanism of a disease, when the clinical focus must be shifted to treating symptoms? The ethical and professional challenges to the treating physician are very real, but so too are the thoughts and reactions of the patient. In her own words, this is Tricia Higgins' story.

When I was 34 years old my world started caving in. I was a mother of 3, wife to a wonderful man completing his third degree, homemaker, emergency room nurse, and good friend to anyone in need. I was a volunteer in my children's classrooms and a CCD teacher at our local Catholic Church. Yet suddenly I was the one in need, a role I hated from the beginning and still hate today.

It all began while I was giving instructions to a mom who had brought in her sick child to the Emergency Room. Suddenly, I found myself on the floor looking up at the ceiling lights. I hadn't felt weak, or sick, but I couldn't get up. Slowly the feeling passed and I was back to work trying to forget the event. A day or so later while at work I once again slumped to the ground. After my third fall I decided to make an appointment with my primary care doctor. I explained to him that I always know where I am when I fall but I just can't move. My only consistent symptom is exhaustion; other than a stiff neck or a bump on my head, I could usually go on with my routine. On my way out of his office, I fell again—exactly the same fall, no warning, no aura; I just remember coming to and looking up at the lights.

When I was admitted to the hospital for the first time, the medical work-up began. I had the usual tests of EKG, carotid Dopplers, echocardiogram, routine blood work, all of which were essentially negative. I did fall while on a cardiac monitor but no arrhythmia was present. Eventually, the cardiologist and neurologist agreed to send me home.

I remember falling a total of 17 times over the course of 2 months before I was convinced that I needed a more drastic treatment. I was started on Tegretol, an anticonvulsant, but my falls continued, so my dosage was gradually increased. I experienced lots of nausea and vomiting when I started Tegretol, but eventually I stopped falling. I was thrilled. I didn't like the diagnosis of complex partial seizures, but the prescribed medication stopped the falling. I agreed to stay on the Tegretol for a 1-year trial, but by the time the year was up, I was ready to quit because I hated the side effects. I
was slowly taken off the Tegretol, but then I started falling again. When I was placed back on the medication, the side effects returned, this time with an additional elevation of my liver enzymes. Finally I decided the treatment was worse than falling. It was at this point that the trial and error of using different combinations of medications began and this gave a whole new meaning to the words "medical practice."

After the Tegretol experience, it was suggested that I seek professional help from a psychiatrist. There was consistent underlying depression that seemed to resurface after each subsequent fall. I missed work occasionally, but I continued to work part-time. I didn't know it then, but my neurologist thought that the falling was somehow under my control. After a trial of Depakote and Neurontin, I had a severe outbreak of hives and had to be taken off both medications. The falls continued as did the side effects from other medications, now including tinnitus, extreme photosensitivity, and headaches. While at a routine appointment with my neurologist, I had a seizure in the CT department. I was readmitted to the hospital and referred to a neurosurgeon and another psychiatrist. I was restarted on Tegretol, and the nausea and vomiting started all over again. I remember the neurologist coming into my room while I was on the bathroom floor heaving into the toilet too weak to get back into bed. He just stared at me and asked what was wrong. After talking with the psychiatrist, I was discharged and sent home.

Here was my reality: falling at home was no big deal. Mostly I would sleep until I felt more alert. Falling at work proved to be more of a problem. I no longer transported patients by myself. I could no longer hold a baby alone in my arms. I also made sure that I stood with my back directly up against a wall.

Sometimes I would go for weeks without falling, but then they would become more frequent. I was never able to predict their onset. Medications would be added, all of them causing more undesirable side effects. I was ordered to stop doing the late night shifts at the hospital, to see if a regular routine was what I needed to keep from falling. I continued this way for 5 years, seeing a neurologist intermittently while the falls continued.

I was eventually referred for further testing to Brigham and Women's Hospital in Boston. After I was monitored over a period of 7 days, the attending neurologist arrived with a psychiatrist and explained that the falls I was having were not electrical seizures. They said it was a psychiatric disorder—non-electrical seizures and somatization—that caused me to fall. They explained that all I had to do was follow up with a psychiatrist, discover what was triggering my emotions, and then I would no longer have problems falling. They told me that my condition was treatable as long as I was willing to believe that I could get better. When asked if I could come off the anti-convulsant medications they hesitated. I said if these events were non-electrical in nature then I want to stop all medications. The doctors discouraged this since they knew that the falls were clearly less frequent when I was on medication. After they left, I couldn't believe that I was doing this to myself. I cried and cried. Alone in my room with the lights off and no one to talk to, I wanted to end it all. Just thinking that I was doing this to myself was unforgivable. I wanted to die. I was the root of the problem.

I followed up with a psychiatrist and explained the physicians' findings in Boston. I told him that the reason I was falling was some underlying emotion, and, once I discovered what I was trying to suppress, I would be cured. The psychiatrist did not agree with this conclusion. I told him that he had to agree with the conclusion or I would never get better; I begged him to make me better. He explained that he still disagreed with the other physicians' conclusions and thought that no one had come up with a correct diagnosis yet.

I was slowly able to compose myself and go back to work, but secretly I felt like a fool. I felt like a fake and a liar, but I kept most of these feelings to myself. The falls continued, but as long as they were not at work, I figured my job was not in jeopardy—and then I fell carrying a portable monitor up a flight of stairs on my way to a code in the ICU. My co-workers said they needed to count on me, but they never knew when I was going to fall. I felt totally defeated. It had been my decision to keep working, and now I no longer had that option. I started teaching courses at the hospital, but then I began to fall in the classroom.

At this point my life was spiraling out of control. Each fall would send me into a deeper depression until I was eventually placed on antidepressants. I was also started on medication for unexplained parasthesias and peripheral neuropathies. I began having trouble with sleep paralysis and terrible nightmares. I felt tired all of the time.

By 1999 I had been falling for 7 years, and my primary care doctor asked if I was getting enough sleep at night. I
looked at him as though he had lost his mind; until recently I had worked shifts in the ER; I had 3 active boys, and my husband was in law school at night. I told him every mom I know is tired. Then he said he wanted to enroll me in an overnight study for sleep disorders. I was adamantly against it. Every test I had taken had been normal; I was convinced this one would be normal too and would be another waste of time and money. I said I could not handle being tested again only to be told the results were negative. After much coaxing he scheduled the test in a hospital where I knew no one. I cried going to the hospital and begged my husband not to leave me. The sleep lab was in a prominent psychiatric hospital, and I was afraid that my husband was going to abandon me because, by this time, I too was convinced that I was losing my mind.

Within 2 days of the test, my doctor reported that at last I had a diagnosis that explained my symptoms. He said that I had narcolepsy with cataplexy. Once I started reading about narcolepsy, I knew that this was it; this was what I had been dealing with. Excessive daytime sleepiness, vivid dreams, automatic behavior—I could have written the book. I was able to accept the diagnosis of narcolepsy and the constant modifications needed for my treatment. I now wear a mask to bed to help with sleep apnea, and I think the quality of my sleep has improved. The use of Ritalin has improved my alertness during the day. Taking Prozac and Nortriptyline for the paraesthesias has also helped the cataplexy. It has taken many trials of various combinations of medications to help decrease my symptoms, but with my current regimen, including Xyrem, my cataplexy is better than it has ever been.

As I contemplate just how my life has been impacted as a result of narcolepsy, the first thing that comes to mind is how everyone thinks that it's comical. They laugh and then realize when they are laughing alone that I am serious about this disorder.

This illness has cost me my job, my friends, my self-confidence, my dignity. Work, the place we all go to make some money, pay the bills, and keep our children in school, that place where we feel like we make a difference in people's lives—for me that place was in the hospital as a nurse. I would gladly accept the challenging patients. I used to feel fulfilled even when I was fatigued at the end of a shift. My coworkers could always count on me for overtime or extra shifts. I would cover for someone who needed to be home with his or her kids due to illness. I was always there when something extra was needed, and I rarely took a break. Now I am no longer employed; I have been on disability for 4 years, forced out (or so it felt) because I had no control over my cataplexy and subsequent falls.

For me, cataplexy presents itself with total loss of muscle control. I will just fall to the ground, without premonition, without aura. I am always aware that I am on the ground, and I can hear what is going on. I am unable to move or speak for a period of seconds to minutes. It is the loss of control that bothers me so much. It is the unpredictability. And then it is the explanations to others when I am able to respond and speak. I am used to it, but it is hard to convince those around me who aren't not to panic.

Along with excessive daytime sleepiness, this is what plagues my days. But don't think that it is just my days that are affected. At night I often find myself screaming at a hypnogogic hallucination that I swear is really happening and invading my nighttime sleep. Many nights my husband has to wake me and assure me that there are no creatures coming to get me. Sometimes just before drifting off to sleep, or just before waking up, I will experience sleep paralysis. You want to move but you can't. You want to call out but you cannot speak the words. I used to think I was dying, and was afraid to fall asleep.

The excessive daytime sleepiness is difficult to describe. It is so painful to stay awake sometimes that my body actually hurts. It is struggling to do the housework, make the meals, stay ahead of the piles of laundry. It is missing appointments, being late to meetings, forgetting chores. It is being unable to drive and relying on others to give you and your children rides to events. It means lots of bike rides to the store when you forget something.

And it is the isolation. You only go out when you have to. Even walking brings its own set of risks. I am constantly worried that a fall will result and that the depression will resurface. It is easier to be reclusive because then no one knows what is going on with me. Hibernation and cataplexy in my own home can stay a secret. Just when I think it would be easier on everyone else if I were no longer here to burden my family, a ray of hope, a sliver of sunshine gives me inspiration to move forward.
Tricia Higgins is a native of New Jersey who currently makes her home in Morristown. She obtained her BSN from Catholic University in Washington, DC, and worked professionally as an emergency room nurse.

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