

PERSPECTIVES

On the Professions

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"Ethics in Phase II Trials of Cancer Therapies"

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This issue of Perspectives began with Fay Sawyer, one of the founders of our ethics center, describing her recent health-care odyssey. Though Fay's long career at IIT included both editing Perspectives and developing and teaching one of the country's earliest courses in architecture ethics, nothing had prepared her for what she was describing. Indeed, as I listened, I could not say that much in life, including some years with lawyers and business people, had prepared me. Here, I thought, was a topic for Perspectives; so, I asked Fay to write down what she had told me. The result is the first of the five pieces that constitute the body of this issue. It is, in effect, a case upon which the other four comment.

Trial by Phase

After being diagnosed with a form of cancer incurable using any approved therapy, Fay found her way into a Phase II trial of a drug that promised help. The story of how she found the trial is disturbing. But the trial itself is the heart of the story.

What is a Phase II trial? In the United States, a promising therapy must be tested according to the Federal Drug Administration

(FDA) procedures before insurance companies will pay for it and, indeed, before physicians can use it in ordinary practice. The tests are generally done in three Phases. Phase I determines the maximum allowable or safe dose. Phase II determines that the safe dose can do some good. A reduction in tumor size of at least 50% is -- according to one on-line "cancer guide" -- the minimum necessary for a therapy to be considered effective. Ordinarily, this is the standard for a complete Phase II trial, not for any part of it.

For the test of most cancer therapies, only someone with advanced cancer makes a good test subject. Of those very ill people, medical ethics allows only those unable to benefit from any standard therapy to participate. Anyone participating in a Phase II trial of a cancer therapy is the medical equivalent of the military's "cannon fodder".

Only in Phase III is there an attempt to compare the effectiveness of the therapy against alternatives (including the alternative of doing nothing, "the control"). A therapy can pass Phase I and II and still not be good enough for FDA approval.

Four Comments

When something goes wrong within an institution, there are always at least four possible

explanations: the organization, its personnel generally, specific personnel ("a few bad apples"), or the victim. If we blame the organization, we suggest changes in procedures, for example (in this case perhaps), reducing the workload of the institutional review board (IRB), the committee that approves research protocols, so that it would have a better chance of catching a flawed protocol. If we blame the personnel generally, we suggest better selection or training, for example, choosing physicians who care more about patients than about research. If we blame specific personnel, we call for them to be fired or otherwise disciplined. If we blame the victim, we say, for example, that she should have insisted on reading the consent form before signing it, that she should have asked more questions, or that she should have become an expert on Phase II trials before entering one.

One of the nice things about Fay's case is that, given how much she did do, it is hard to blame the victim. Another nice thing is that the institution involved, though nameless here, is in fact one of the best teaching and research hospitals we have. Its mistakes--and it made some big ones--are unlikely to be its alone. Noteworthy, I think, is that none of our commentators seems to blame the specific personnel involved. All four focus instead

on changes in policy that would affect the way many medical institutions conduct Phase II research or on demanding more of physicians and other medical researchers generally. Apparently, our commentators recognize the general in Fay's particulars.

Michael Wolf, a social worker with long experience in hospitals, seems particularly distressed by the way the patient tends to become a mere bystander at every stage of the research process. His advice to everyone involved is: communicate more and better.

James Nelson, a philosopher long concerned with medical ethics, argues that everyone involved in medical research makes the line between treatment and research sharper than it need be. We must plan for subjects who might benefit from a research therapy even after they no longer have a place in the research.

Knut Ruyter offers a European view: indeed, you should plan, as we already do; what's stopping you?

David Ozar, a philosopher who has chaired a busy IRB, concurs with almost everything those before him have said -- but with his own emphasis on the researcher-physician's role in educating the patient. That emphasis leads him to argue that part of gaining a patient's informed consent to participate in medical research is making sure the patient knows all the alternatives. For someone likely to die of cancer, dying gracefully is one of the alternatives. There is care available that can avoid most of the pain associated with death from cancer, preserve the patient's dignity, and allow the patient to devote her last days to putting

affairs in order rather than racing from one physician to another in search of "hope".

Necessary Brevity

There is, of course, much more I could say to introduce this subject, for example, explain why none of our four contributors refers to the Code of Professional Responsibility of the American Medical Association (AMA), especially Opinion 7.07: "In clinical investigations primarily for the accumulation of scientific knowledge, adequate safeguards must be provided for the welfare, safety and comfort of the subject."

But since we have five pieces instead of our usual four, and no more space than usual, I will say no more.

-MD

"Clinical Trials of Cancer Therapy: A Personal Narrative"

Fay Sawyier, Philosophy,
Illinois Institute of Technology

After exploratory surgery, I was diagnosed with malignant pleural mesothelioma on December 28, 1999. My surgeon and his associates were pessimistic: "a few months, perhaps". The only hopeful thing they said was "good luck".

There matters might have stood had not my children urged me to get a second opinion. So, during the third week of January, my husband and I (the "we" in what follows) went to New York for consultations with three

oncologists: one at Sloan-Kettering, one at New York Hospital, and one at Presbyterian. It was at Presbyterian that we learned that in the same hospital where I had been operated on there was a mesothelioma clinic and program. When I asked Dr. Valerie Ruesch at Sloan-Kettering whether there was anything I should not do, she said, "Do not do nothing."

When we returned to Chicago, we saw an oncologist at Northwestern to ensure that if I had to be hospitalized again, it would be there (not at the hospital that had performed the exploratory surgery). We then made an appointment at the "meso-clinic" I had been referred to (at the hospital that had performed the surgery). My first appointment was February 10. By then, I was sure that neither surgery nor radiation would have any positive effect on my rapidly growing tumor. Accordingly, what was discussed at this initial meeting was a small variety of chemotherapies. One of these, called "multi-targeted-antifoliant" (MTA) was available only in a clinical trial and, therefore, on an experimental basis. MTA seemed to have few of the side-effects usually associated with "chemo" (nausea, weakness, and loss of hair). We said: yes!

The medical group was eager to get patients into the trials. As soon as we indicated our inclination to take the MTA route, events happened fast. But what happened, by far the fastest, was the ritual of signing the so-called "informed consent form". Its several pages were waved in front of me but opened only to the page on which I was to sign. I was not given a copy. I only succeeded in obtaining a copy many weeks

later. I was then surprised to see how much negative information there was in it. I would indeed have signed - "consented" - anyway. My only alternative was death. But I strongly disapprove of turning an important moment of decision into an empty ritual.

After a CT scan and a pulmonary function test, I started MTA treatment on March 1, 2000. The protocol involves a "blood draw" (also known as "test") and a visit with the medical staff once every week. As long as I "pass" the test, there is chemo once every three weeks and a CT scan, pulmonary function test, and arterial blood draw once every six weeks. The chemo takes only ten minutes and has had no obvious side-effects. After the first chemo, I went to a lecture about Medieval Cosmology at Regenstein Library.

About six weeks after I entered the chemo program, I had my first informative meeting with my doctors. One cannot receive chemo without seeing -- and being seen by -- one's doctors, but that is for their information, not the patient's. They checked for lesions on my lips something or other in my throat, thyroid events, and so on.

Sometimes they listened to my breathing with or without a stethoscope. And, of course, there was the endless parade of "vitals" - temperature, blood pressure, and sometimes height and weight. During the entire time, the nurses and clerical staff kept changing. The chance of receiving the treatment intended on the day intended was partially dependent on the patient keeping her wits. I frequently joked that it is a good thing I have only cancer and not Alzheimer's!

At the first of these informative meetings, I learned that my tumor, which had been growing very fast, had not grown at all during the previous six weeks. Six weeks later I learned that, in fact, it had by then shrunk by 25%. Six weeks after that I learned that it had shrunk by another 10%. However, at the fourth of these meeting, I learned both that the hospital had lost my CT scans and that the oncologist, after consulting Eli Lilly (MTA's manufacturer), had decided to cut me off from any further treatments! After seven treatments, I was on my own again not because I no longer needed the MTA but because I no longer satisfied the research protocol. Unless one has a reduction in tumor-size of at least 50%, one must be "cut off"; 35% or even 45% reduction is not good enough. I was astonished. For some (intense) hours I pondered what could possibly generate such a protocol, finally concluding that pharmaceutical companies are eager to demonstrate that they do not kill more than they preserve (ergo 50/50). There may even be something to that conclusion. About this time, a boy in Ohio was killed by some experimental gene therapy.

But now the tale gets morally interesting. After the seven treatments I had received, my condition had improved enormously. Whereas earlier I had been breathless and nauseated (although functional), now I could swim, walk, talk, and eat. I pointed all this out to my (former) oncologist, who was totally unresponsive. I suspect that she was primarily dedicated to making a name for herself with new therapies. Notoriously poor with patients, meeting with me made the doctor nervous, even irritable.

My husband, friends, relatives, and I were understandably nonplussed by the arbitrariness of the cut-off. MTA was not obtainable except in a clinical trial. Cutting me off was a sentence of death. Even some of the other doctors at the clinic were dismayed that a patient who was doing so well (substantial tumor reduction and no side effects) should be deprived of treatment.

I contacted friends who had connections to the Federal Drug Administration (FDA). I contacted members of the Institutional Review Board (IRB) at the institution where I was being treated. And my husband, who is a lawyer, contacted the Director of Medical Research at Eli Lilly. When my husband called Eli Lilly, he was not threatening a lawsuit, only asking if it might not be possible for a patient, who was flourishing on their drug, to continue taking it. As someone else remarked, Eli Lilly should have me as their poster child.

This call may have been decisive. Soon after, another oncologist (senior to the one who had cut me off) phoned to say that he was taking over my case.

It is now mid-November. I am in my thirteenth cycle of MTA and continue to feel fine. I have not had the last CT scan results, but I am sure they will be much like the others. The consensus among the medical staff is that, as long as I continue to benefit, they will continue the MTA.

My training and inclinations are philosophical. I have told this story not to expose but to pose two questions, hoping for answers:

First, why that 50% cut-off in the protocol? Who gains and who loses by drawing the line for participation in a clinical trial there?

Second, what happens to other patients who may have results from MTA (or other clinical trial drugs) just as good as mine? Would they be cut off as I was? Would they be too intimidated by the doctors to do anything but go home and die? What happens to people who don't have a lawyer in the family to phone the drug company?

I am, of course, happy that I have had many extra months of good life. But I am also appalled that, if it had not been for my strength, my husband's legal skills, and my family's four generations-long association with the institution in question, I might well now be dead. That seems wrong. Too much has depended on the intelligence and clout of the patient. You shouldn't have to be Fay Sawyer to get fair treatment!

"Clinical Trials of Cancer Therapy: A Social Worker's View"

Michael S. Wolf, Northwestern University

Fay Sawyer's account of her experience in an early phase of the clinical trial of a new cancer treatment reflects a frequent debate in medical research, a debate setting the consumer against a more powerful adversary, the academic or pharmaceutical research investigator, whether physician or scientist. Such investigators

require a human population to determine whether an unproven treatment produces the desired effect and what undesirable "side effects" there may be. Generally, a standardized clinical trial, that is, an experiment that properly monitors outcomes in patients while controlling for extraneous factors, is necessary for the Food and Drug Administration (FDA) to approve of a new drug. Without a clinical trial, a new treatment will not be fully recognized as having the appropriate and safe attributes needed to be designated a therapeutic agent for the corresponding illness. Without that recognition, ordinary physicians will not use the medication and insurance policies will not pay for their use.

Purpose

But what about Fay Sawyer? While the FDA tries to protect the U.S. consumer from unsafe treatments, patients like Sawyer who seek access to experimental or alternative therapies often discover that their individual needs are passed over to maintain the integrity of clinical trials. The immediate survival of one seems to clash with the 'greater good,' potential knowledge about the ability of a particular treatment to save lives or to cause significant, possibly lethal, harm. To Fay Sawyer, this clash came as a surprise when she learned that she would not continue to receive treatment because the research protocol established did not allow it.

Sawyer's case highlights four hard questions related to clinical investigation of experimental treatment, and the patients who have exhausted known remedies. First, how are patients almost without hope to be brought into the trial (especially, how is their

consent to be obtained)? Second, at what point does a "clinical trial" cease to be a clinical trial, and become ordinary medical treatment? Third, can we differentiate the role of research subject from that of patient in a clinical trial? And last, can the welfare of a single patient enrolled in a clinical trial and the welfare of the larger population of patients who might benefit from what is learned from it coexist under the umbrella of the clinical trial? Underlying these four questions are two others: First, why should a patient consider participation in early phase trials? And, second, how can medical decision making be carried on as part of the clinical trial process?

Informed Consent

A common complaint of many patients participating in medical research is directed at the informed consent procedure. An institution hosting research on human subjects will have one or more review boards to provide strict guidance for principal investigators. Before investigators can begin recruiting research subjects, they must develop a clear, understandable, and thorough consent form explaining all aspects of the research to the patient.

The clinical trial Sawyer participated in had such a consent form. At the time Sawyer signed the form, she (and her family) were rightfully more concerned with seeking a means to extend her life than with specific details in the form. With death seemingly imminent, she had little choice but to sign the carefully crafted form. Signing satisfied patient, family, and researcher.

Nonetheless, investigators using the method of clinical trials

should understand that the moment when a patient becomes a research subject is a sensitive one. Do the patient and family truly hear what is being said? Do they understand the benefits, risks, and procedures involved? For Fay Sawyer, the answer seems to have been no. Patient-researcher communication was inadequate.

While many investigators may go beyond what would be expected to inform their subjects, unfortunately, much of the burden of gaining information generally falls on the subjects and their families. It is apparent that significant miscommunication occurred between the clinical trial investigators and Sawyer, especially concerning the patient's basic understanding of her path through the trial. The consequences of that misunderstanding were undone only through the resourcefulness of the patient and her family.

Few other patients have such resources. In fact, many individuals accessing health services in the United States are not even functionally literate with regards to their health care. Many also have inadequate social support or face considerable barriers to access to community resources (for example, because they lack health insurance). Taking into consideration these factors among others, it is not enough to tell patient (and family) considering enrolling in clinical trials to become an informed consumer before enrolling. It is also not enough to ask the terminal or chronically ill patient to reflect on her own motivation for participating in a clinical trial (altruism or self-preservation). While both of these steps are needed, researchers should also consider their role in protecting

those individuals participating in the study.

No Promises

In an early phase clinical trial, investigators cannot assume that the treatment will have the desired effect or that there will be no serious but unexpected side-effects. Finding out about such effects is, in fact, the whole purpose of the trial. Because the treatment may or may not prove to be a good one, giving a control group (say, half the patients enrolled in the study) a placebo or alternative treatment is considered ethical. Researchers must control whatever factors could influence the relationship between the intervention (in Sawyer's case, the chemotherapeutic agent for cancer treatment) and the measured outcome (change in tumor size). They must ensure that the study will be robust and credible.

But when a patient, such as Sawyer, shows marked signs of improvement along the lines desired for the treatment, what should happen? Should the researcher acknowledge the effectiveness of the treatment and better treat their patient accordingly? But what about the study? It is certainly possible that further investigation will reveal side effects from the intervention, or that a reduction in tumor size is not the result of the treatment under study but of several other factors.

Yet once a therapeutic benefit has been detected, the somewhat "exploratory" clinical trial changes for both subject and researcher. The clinical investigator has an ethical obligation to note the benefit, and as in Fay Sawyer's case, to reconsider treatment options for

the patient -- with ample assistance from patient and advocates on her behalf. The clinical researcher must constantly keep in mind the welfare of each individual enrolled in the trial as a patient, but also strive to preserve the rigor of the design and conduct of the trial.

Fay Sawyer appears to have successfully made the research investigators understand her needs as a patient. While the process of making them understand seems to have been excessively difficult, frustrating, and complicated, the lesson her success teaches is a simple one, to be observed by both patient and researcher: communicate. Patients and families considering participation in early phase clinical trials need to seek out as much information as possible. They should direct questions not only to the researchers conducting the clinical trial, but also to physicians, psychologists, social workers, nurses, case managers, and other health professions, especially some not affiliated with the study. Open communication between an informed consumer and the researchers reduces the potential for confusion and misinformation.

Caveat

The clinical investigator cannot expect to have a research sample full of Fay Sawyers, subjects who will assert themselves and advocate for their own needs. Many patients take a submissive role in the presence of a physician or research investigator whom they identify as an "expert," especially in a field as difficult to understand as cancer treatment. Such patients are more likely not to ask questions or seek out information from the investigator or health-care provider. Researchers need to improve upon

their existing efforts to recruit subjects for clinical trials to do a better job of helping individuals considering participation gain adequate knowledge of what it means to be a subject in a clinical trial. The overall objective of research using clinical trials is to improve the health of those diagnosed with cancer. But that objective, however good, can and should, be pursued without devaluing individual patients.

"The Importance of Knowing Where You Are"

James Lindemann Nelson,
Philosophy, Michigan State
University

If you find yourself living on a frontier where very different views of life contend, it's hard to avoid consistent confusion. Professor Sawyer's illness brought her to just such a frontier. Malignant pleural mesothelioma introduced her to therapeutic nihilists, who seemed not to realize that patients can become research subjects, and to experimental enthusiasts, who seemed not to realize that research subjects needn't stop being patients. It was left up to Professor Sawyer to sort out the difference between being a patient and being a research subject and to intuit what it means to be both at once. No one seems to have tried to explain the frontier to her. Perhaps no one could.

The Magic 50%

Professor Sawyer says her tale gets morally interesting about half way through, but that's too modest; it's morally interesting right from the start. Consider the surgeons who diagnosed her disease. Their ignorance (or, just

possibly, inability to communicate) is remarkable. They failed to convey to their patient that her own grim sort of cancer was the target of a research group in their very own institution. When, by way of a New York City detour, Professor Sawyer did find her way to that meso-clinic back in Chicago, she was eagerly welcomed into the trial. Yet, all she recalls of her preliminary discussions with the re-searchers is that she chose (with understandable enthusiasm) MTA, an agent advertised as having few of chemotherapy's characteristically nasty side effects. Nothing about what would make her use of MTA part of an experiment rather than part of a therapeutic regimen seems to have stuck in her memory. Perhaps nothing was said. About the signing of the form attesting to her fully informed and voluntary consent to become a research subject, she relates only that it was an annoyingly empty ritual. The hollowness of the procedure didn't keep her from signing, of course-consider, as she says, her alternative. What was the chance that she would say anything other than an enthusiastic yes?

The signing of that subsequently fugitive form seems thickly insulated from anything else in her story. For example, neither the discussion of various chemotherapeutic possibilities that took place before the signature ceremony, nor the weekly 'test' that had to be 'passed' afterwards, seems to have had anything to do with what Professor Sawyer took herself to be about as she inked the consent form. When she finds that she has 'failed' the test - that despite the shrinkage of her tumor and the remission of her symptoms, she is no longer to have access to the

life-saving drug she is astonished. It is only then that she asks what could possibly generate such a protocol, concluding that the requirement that at least half of the tumor have vanished must be to show that the drug saves as many as it kills.

This conclusion seems to me both unlikely and enlightening. A 50% shrinkage rate as a cut-off for continued inclusion in the trial seems to have no interesting relationship to a 50% mortality rate attributable to the drug. My suspicion is that the cut-off was motivated by the desire to demonstrate a result robust enough statistically so that Lilly could claim that, for at least a subgroup of those who took MTA, tumor degradation could be decisively attributable to the drug and nothing else. Professor Sawyer's interpretation makes it plain, though, that she had not yet thought about the possibility of her exclusion from the trial on any grounds other than her own health. (Was that perhaps what she took the weekly tests to be determin-ing?) When she did come to realize just where she was - smack in the middle of a research protocol - her effort to make sense of things assumes that the side-effect-less drug she had been taking was a very dangerous, potentially lethal agent.

The Therapeutic Misconception

What's enlightening about her response, I think, is that it shows the depth of the "therapeutic misconception." What goes awry is that the ill subject does not grasp that what she has volunteered for really is research; it can be enormously hard to shake the erroneous belief that the intervention is designed to make the volunteer better, rather than contribute to anything as faceless

as the medical welfare of future patients. Professor Sawyer's reaction to being dropped from the trial shows how tenacious the misconception can be even for the most intelligent, well-educated, intellectually and socially confident people in our society, as well as how relatively deranging it can be when that misconception is shown to be what it is, a misconception.

At the time of her writing, Professor Sawyer was once again receiving MTA; she looked forward to doing so as long as it continues to help her. I hope that is a very long time indeed. She remains confused about why the protocol was structured as it was - where was the magic in that 50% figure -- and about the fairness of a system that demands extraordinary amounts of personal status and social power to secure what's needed to continue a life that remains richly rewarding, both to her and to those with whom she shares it. It is indeed hard to understand why no one has explained to her the scientific justification for the 50% figure; you would think that the research physicians, to say nothing of Lilly itself, would have been anxious to offer that justification, if only to keep her good will.

Professor Sawyer's question about the influence of power and status on access to the things that may keep us alive is tougher - no one seems to have a definitive answer - but the research-therapy boundary is not the only morally puzzling frontier on which we sometime find ourselves.

Some Related Questions

The question that I find myself left with here is whether there is any practical way to forestall the

therapeutic misconception? How can we reliably get decent informed consent - decent enough to make research on very ill human beings morally defensible? It seems clear to me that whatever effort was made to help Professor Sawyer see just what she was getting into failed miserably, and such a failure, with such a person, does not auger well for research with seriously ill people in general. I also find myself wondering, not whether it is fair that only the rich and powerful can gain access to such scarce and precious goods, but whether it is fair that even the rich and powerful can. What's the character of the contract between society, science, and the sick here?

We have a practice of withholding even promising pharmaceuticals from general availability until they've passed some pretty tough tests. In consequence, the standard formulary consists of agents whose benefits, and whose risks, are fairly well understood -- an enormous benefit to us all. Yet the consequence is also that some potentially very useful drugs are available only in research protocols and, within those protocols, only to those who satisfy research-driven criteria. Those who cannot gain access to the protocols, or who get randomized into 'control groups,' don't get the chance to benefit (or to run the risk of being harmed) by the intervention in question. Is gaining reliability at the cost of access thus constricted unfair?

Time to Muddy the Waters?

Of course, Professor Sawyer's chance of benefit from MTA was hardly hypothetical. Perhaps what her case shows is that we need to consider a modification of that

contract between society, science, and the sick. We now end trials prematurely if an experimental intervention causes a subject to die. We also end the trials if the subjects receiving the active intervention are clearly responding much better than are the subjects in the control group. Why, then, should we not, as a matter of course, change the protocol if an experimental intervention seems to be saving a particular subject's life? Such subjects could well be removed from the trial if the interaction of drug and disease does not meet protocol targets, but continue to receive the treatment as long as they seem to benefit.

If the therapeutic misconception was a problem before, would not adopting this sort of proposal make the problem worse? On the contrary, fusing research and therapy may be just what's needed. If we recognize that protection from risks is not the only goal of ethical medical research, that there is nothing unethical or otherwise improper about research benefitting specific research subjects, the best response to the therapeutic 'misconception' may not be trying to get people to understand that they are not to benefit from their involvement. The best response might be to acknowledge, from the start, that it is possible that some subjects might benefit from their involvement -- and even to shift procedures so that it is more likely that they will. Sometimes, the best way to live on a frontier is to make it a little more like home.

"Cancer Research and Therapy: A View from Norway"

Knut W. Ruyter, Director,
National Committee for
Medical Research Ethics,
Norway

Trials of new cancer therapy are as well known among Norwegians as among Americans. Generally, we have also had similar ethical issues: whether seriously ill patients ought to be randomized into placebo-controlled studies, whether re-searchers ought to inform patients thoroughly about alternatives to trial therapies (such as non-treatment or mere palliative care), whether researchers should have follow-up responsibilities for patients, including for non-medical services (such as social services and hospice), and so on. While Fay Sawyer's case illustrates issues common to our two countries, it may also bring out some important differences.

Tempting offers

The eagerness of researchers to enroll patients in trials is well known. New trials can be interesting. They can further careers. But they cannot be carried out without a certain number of patients. Without that number to serve as research subjects, the study must be postponed or abandoned. Researchers therefore have a tendency to jump at any patient fitting the criteria for inclusion in their study.

Though eagerness is a virtue in researchers, it does have a downside. It tends to infect patients, making their "consent" resemble a spontaneous outburst of hope (someone will help me!)

more than an informed decision to participate.

I cannot say that the ritual of consent that Sawyer described does not have its counterpart in Norway. An ethics committee only reviews the consent form and accompanying written information before the trial begins. The committee cannot monitor how consent is actually obtained. Nonetheless, the ritual Sawyer described is ethically unacceptable.

In Norway, we have tried to buttress the requirements for informed consent by strongly recommending that patients have at least twenty-four hours to consider participation in a trial on the basis of written information. We stress that the information is to help the patient decide wisely, not to help the sponsor limit legal liability. So, for example, we discourage listing every recorded side effect. That's excessive. Sawyer was surprised at the amount of "negative information" the consent document contained because the information did not seem designed to help her decide whether to participate. (To see our guidelines, in English as well as Norwegian, visit on our web site: www.etikkom.no.)

But no formal precaution, not even the twenty-four hour "cooling off" period, can prevent the consent procedure from becoming a mere ritual. Only the researchers themselves can do that.

Cut off

Next, I would like to address the decision to end the research subject's participation in treatment when the tumor, though shrinking, did not shrink enough to satisfy

the research protocol. What I say here about the protocol depends on the description Sawyer has given of it. I have not studied the protocol itself.

Given Sawyer's description, I am pretty sure the protocol would not be approved in Norway. We do not, of course, require researchers to keep a patient in a trial when she falls short of the criteria for inclusion. But we would not approve a protocol unless the research sponsor agreed to continue treatment for research subjects who, though disqualified by the protocol, still show significant benefit from the experimental treatment. Our guidelines stress the responsibility of follow-up, access to treatment, and plans for preparing researchers to respond to related medical problems, especially when subjects are from vulnerable groups, such as seriously ill cancer patients. If sponsors (or researchers) are not willing to take on this responsibility, they cannot do the research.

Physician or mere researcher?

Another disturbing issue in this case is the unresponsiveness of the researcher -- who is also a physician -- to a patient for whom being dropped from the study seems a death sentence. The physician should have done more, much more, for her patient. I earlier stressed the importance of medical follow-up for every individual patient included in the trial. Equally important in this case is the physician's duty to act as a physician, not only as a researcher, even when the patient is a "mere" re-research subject.

The ethics committee does not evaluate the moral virtues of

researchers, but health-care institutions that do research with patients should consider such evaluation a vital part of its quality assurance. If I were asked about an unresponsive researcher like this in Norway, I would recommend a transfer to a laboratory where there would be no direct contact with patients. Patients need a caring and empathic physician.

The researcher in this case reenforced the stereotype of the aloof, one-sided, and uncaring researcher. In the long run, such researchers damage the fragile confidence that even they rely on to attract subjects. Much of the willingness of people to become subjects of medical research is their assumption - and hope - that the physician-researcher will act as their physician during the research -- that, at the very least, the physician will take the patient's interests seriously enough to offer the best available therapy. Cold and disinterested physicians should do patients the favor of finding something else to do.

Clout

Sawyer reports that, in desperation, her husband called the medical director of the sponsoring pharmaceutical company to get her back in treatment. That call seems to have worked. Sawyer was soon "taken over" by another oncologist who, undoubtedly, had been prompted by the director. That was good for this patient.

But, as Sawyer makes clear, this exercise of "clout" -- her husband's status coupled, no doubt, with the company's fear of bad publicity -- is morally disturbing: what about all the

other vulnerable patients that do not have a husband who is a lawyer?

Using clout to be heard is unfair, but still common even in Norway, with its "socialized medicine" (as we are happy to call it). It is, of course, true that using clout is a natural human response in such desperate circumstances. Anyone who would not have availed himself of it under the circumstances would have seemed less than human. The husband's phone call is in itself understandable, even honorable, certainly not blamable.

What is blamable is that the company would only make an exception for a patient who had clout - but not for all the other patients who were in the same position as she was. Fairness is an important part of research ethics; researchers should at least try to treat relevantly similar cases alike.

One can of course speculate on the motives of the company. I will not, except to say that I would be disappointed if the company's medical director thought primarily of the reputation of the company before calling the researchers. Pharmaceutical companies have long worked with medical authorities to develop international guidelines for good clinical practice (often abbreviated ICH-GCP). These establish an international standard of acceptable scientific and ethical practice. They have a whole chapter on research ethics. I would like to think that the phone call reminded the medical director that cutting a patient off of an effective treatment is not in accord with international standards.

Independent Review

What Sawyer's case shows is that an independent review is necessary in clinical trials, to assure fairness to all subjects and, especially, to protect the most vulnerable ones. Ethics committees are supposed to provide that independent review. In this case, the ethics committee seems to have failed (as ethics committees sometimes do). The failure suggests the importance of another kind of review, such as a patient advocate might provide. But will those most in need of independent review know how to access such an advocate any more than they know how to access the ethics committee? "I have only cancer, not Alzheimer's" is no joke.

"In the Face of Death: Four Ethical Issues"

David T. Ozar, Center for Ethics, Loyola University of Chicago

Fay Sawyer's "Clinical Trials of Cancer Therapy" raises at least four ethical issues. From the point of view of contemporary standards of ethical research in the United States, one of these issues is an (ethical) "no-brainer." Two more should be. Only the fourth, about which Professor Sawyer says nothing, is ethically complex.

The No-Brainer

The way in which the re-searchers dealt with Professor Sawyer (and her husband) during the informed consent process fell far short of ethical practice. Rather than actively educating the potential research subject about the proposed research -- what is known about the therapy to date,

its likely risks and benefits, and so on -- the researchers simply handed Professor Sawyer the consent form. She was not even invited to educate herself. Apparently, the researchers thought that the purpose of giving Professor Sawyer the form was to have her sign it, not read it, understand it, or otherwise seek to resolve thoughtfully any questions she might have about participating in the research.

True, Professor Sawyer (or her husband) may already have communicated to the researchers that she viewed herself as having no real alternative to participation. But lack of any real alternative does not excuse researchers from making sure each research subject understands all the relevant information. For even if Professor Sawyer were disposed to view any increased likelihood of life-extension from the research as of more benefit than any non-experimental medical alternative available to her, she might reasonably have concluded that, all things considered, entering the research program was not the best choice for her. She might, for example, not have wanted to suffer any of the therapy's possible side effects.

Professor Sawyer does indicate that she was already aware that the side-effects of the experimental regimen were not very burdensome; so, it might be argued that she already had learned of and weighed the risks involved. But a researcher's obligation to a potential subject is personally to educate or, at a minimum, to verify that the subject's previous education has been sufficient to weigh not only all the risks but also any factors that might limit possible benefits.

In sum, the researchers, in winning Professor Sawyer's consent, failed to conform to the most elementary contemporary ethical standards regarding informing research subjects and receiving their informed consent.

The 50% Test

The eventual exclusion of Professor Sawyer from the research because her improvement did not pass the 50% test raises a different ethical issue. It was because of this issue that the previous paragraph stressed providing information about factors limiting the possible benefits. Unless specifically informed otherwise, few research subjects would guess that their continued participation in a Phase II trial could be limited by not improving fast enough. So, the absence of any reference to that limitation in the informed consent form was a serious ethical failure on the part of those who drafted it and of any IRB that reviewed it. The researchers' failure to alert Professor Sawyer to the possibility of exclusion from the study if she did not improve fast enough only compounded the wrong inherent in the form itself.

At a deeper level, there is also the ethical question that Professor Sawyer poses about the 50% rule. Is the purpose of the rule simply to protect the pharmaceutical company by giving the public the impression that Phase II trials do more good than harm? There are serious ethical flaws with that basis for the rule. Could there be a good defense of the rule in terms of scientific methodology? Perhaps, but no one who interacted with Professor Sawyer seems have suggested one, not even those who finally offered her continued use of the experimental

medication. Without more information about the reasons for the rule, making a final judgment is difficult. But the 50% rule surely deserves careful ethical analysis. If there is no good reason for the rule (that is, no reason related to its benefit to present or future users of the drug), then the rule itself is very likely unethical.

Professor Sawyer points out that because of her own (and her husband's) education, organizational savvy, and position (especially her husband's status as a corporate lawyer), she was eventually able to get the 50% rule set aside in her case. She asks what would happen to someone who was not so savvy or so well positioned. The answer is pretty obvious, raising questions of equity of access to treatment that affect all medical institutions. In addition, it is not clear whether the justification of the 50% rule was challenged even by those who eventually set it aside in her case. If restoration of her access to the drug was merely the effect of her leverage, those who authored or administered the rule never seriously considered the ethical question it raises, another ethical lapse.

Respect for the Patient

Beyond the issue of equity already raised here, there is an issue about the way in which both the individual researchers and their institution treated Professor Sawyer after she consented to become a participant in the research. They did not treat her as a patient, only as a potential source of scientific knowledge. But in fact Professor Sawyer would not have been a potential source of scientific knowledge for them if she were not already

their patient. Both biomedical researchers and their institutions owe each potential subject the recognition that she is a patient first and only secondarily a research subject. Neither individual researchers nor their institutions may set aside the obligations that health care professionals have to patients because the patient in question is also a subject of research. It is only after a potential subject has freely chosen to become someone whose participation in the research is used for the benefit of others that any aspect of her treatment may be ethically viewed as secondary, and that only insofar as the secondary status is necessary for the successful conduct of the research and only if the patient-subject (or, in the case of a patient with compromised capacities, an appropriate surrogate) has freely consented to every such amendment to the standard physician-patient relationship.

There is hardly any resemblance between Professor Sawyer's description of the way in which the researchers and their institution treated her and the way in which ethical physicians and an ethical hospital would treat a patient, especially a patient with a life-threatening illness. The ethical failings of the researchers and their institution are not strictly speaking failures to do research ethically but failures to provide medical care ethically. They are nevertheless failures that all researchers who are health care professionals and whose research subjects are also their patients must attend to. Bio-medical researchers cannot escape their duty as health care professionals by claiming that those who are their subjects have physicians of

their own and that they, as researchers, therefore owe them nothing beyond what any researcher owes any human subject.

An Overlooked Alternative

There is also a much subtler ethical issue in this narrative regarding experimental treatments offered to patients who are terminally ill and for whom there is no non-experimental medical intervention that offers any likelihood of life-extension. The ethical issue here parallels, but is even more complex than, that faced by health care professionals who must determine when to speak to a terminally ill patient about hospice care. In addition to the experimental and non-experimental treatment alternatives (and the alternative of doing nothing at all) likely to be explained to a potential research subject in Professor Sawyer's situation, there is also the possibility of palliative care alone. A fully informed patient needs to be able to weigh this alternative along with the others.

There is a growing understanding within the health care community that, for some terminally ill patients, there comes a time when the best course is to cease life-extending interventions and focus the patient's own efforts, and the efforts of those in supporting or caring roles, on the goal of dying well rather than on living longer. For such patients, appropriate palliative care is a valuable intervention. Since the potential subjects of biomedical research are the researchers' patients already, a full discussion of alternatives should ordinarily include a caring and sensitive

conversation about palliative care. True, such a conversation would be sharply counter-cultural in many research settings. Indeed, there are probably many biomedical researchers whose work and lives are so focused on life-extension that they would find it extremely difficult to offer mere palliative care as a reasonable option and would, therefore, do a bad job of explaining it. Nonetheless, we need to think about what a good conversation between a researcher and a research subject like Professor Sawyer might look like. It is in this spirit, rather than to find fault with the researchers in Professor Sawyer's narrative, that I raise this fourth issue.

"Announcements"

CONFERENCES: The Eighth Annual International Conference Promoting Business Ethics will be held at the Institute for Business and Professional Ethics, DePaul University, October 24-26, 2001. Contact Prof. H. Peter Steeves, Philosophy Department, DePaul University, 2219, N. Kenmore Ave, Byrne Hall, 4th Floor, Chicago, IL 60614, ph. 773-325-1153, email psteeves@wppost.depaul.edu.

Design Thinking Research Symposium 5: Designing in Context will be held at the School of Industrial Design Engineering, Technological University Delft, The Netherlands, December 18-20, 2001, to consider the idea that the design process is somehow beyond designers, part of a wider nexus of shared responsibility, culture, language, and

<p>organization. For more information, visit the conference website: http://www.io.tudelft.nl/-research/dic/. Contact Henri Christiaans (h.h.c.m.christiaans@io.tudelft.nl) or Peter Lloyd (p.lloyd@io.tudelft.nl).</p> <p>The Eleventh Annual Meeting of the Association for Practical and Professional Ethics will again be held at the Omni Netherland Plaza in Cincinnati, Ohio, February 27-March 3, 2002. Call for papers to follow. Contact: Brian Schrag, APPE, 618 East Third Street, Bloomington, IN 47405-3602, ph. 812-855-6450, fx. 812-855-6450, email: appe@indiana.edu.</p> <p>CALL FOR PAPERS: The International Journal of Politics and Ethics, a new journal published on behalf of the Frank Maria Center for International Politics and Ethics at New England College, is intended as forum for diverse interests and attitudes in all matters related to politics and ethics, including their intersection. It is designed to encourage the exploration of matters of theory as well as broad issues arising from empirical contexts and the practical application of theory. No topic of critical interest is excluded from consideration. Within its preview are such topics as: comparative and international politics; political philosophy and ethical theory; public policy and analysis; cultural, intellectual, legal, and political history; legal theory; and interdisciplinary material that discusses substantive social, political, and ethical problems of public concern. Each issue contains full-length articles, book reviews, and occasionally correspondence. The final issue of each volume is dedicated to a</p>	<p>special theme, to be announced in advance. The journal is open to the work of all scholars wherever they may be. Interested contributors are encouraged to visit the journal's website (http://www.nec.edu/academics/cipe/ijpe.htm). Articles may be submitted electronically as an email attachment. Offers to review are welcome. Contact Patrick Hayden, Editor, IJPE, Department of Philosophy, New England College, HENNIKER, NH 03242 (email: phayden@nec.edu).</p> <p>Seton Hall Law School Health & Policy Program, The American Society of Law, Medicine & Ethics and Seton Hall University School of Graduate Medical Education in cooperation with Gibbons, Del Deo, Dolan, Griffinger & Vecchione present New Directions in Human Subject Research: Looking Beyond the Academic Medical Center November 9, 2001. For more information, call (973)642-8871 or e-mail HeLPP@shu.edu</p> <p>The University of Alabama at Birmingham's Continuing Education Center is hosting a Training In The Responsible Conduct of Research Conference November 16-17, 2001. The conference features both plenary speakers and breakout sessions devoted to teaching specific topics in the responsible conduct of research. Educational resource material will be provided. Sessions run from 8:45 a.m. to 4:30 p.m. on the 16th and 8:00 a.m. to 12:40 p.m. on the 17th. For the full agenda go to www.uab.edu/ethicscenter. Or contact Professor Harold Kincaid, Center for Ethics and Values in the Sciences, University of Alabama at</p>	<p>Birmingham, Kincaid@uab.edu (205) 934-4805.</p> <p>The Thirtieth Annual Conference on Value Inquiry, Values in Health Care: Past, Present, and Future, will be held in Milwaukee, Wisconsin, April 4-6, 2002, with keynote addresses by Dan Brock, R.G. Frey, and Bernard Gert. Submissions should be related to questions of value in health care broadly defined, including: moral, political, or legal issues in health care; public health or health care policy; psychiatric ethics; research ethics; the use and role of technology in health care; genetics; reproduction; and the role of values in clinical practice. Submissions may be for paper presentations, poster sessions, panel or roundtable discussions, or workshop sessions. Abstracts should be approximately 750 words, and paper presentations should be approximately 20-30 minutes reading time. Submissions will be reviewed as they are received. Early submissions are encouraged. Deadline for submissions is: Friday, January 11, 2001. Abstracts may be submitted electronically in MSWord format to: tmay@mcw.edu, or mailed to Thomas May, Center for the Study of Bioethics, 8701 Watertown Plank Road, Milwaukee, WI 53226-0509.</p> <p>The 2002 International Symposium on Technology and Society, Social Implications of Information and Communication Technology, will be held in Raleigh, North Carolina, June 6-8, 2002. Its purpose is to bring together information and communication technology (ICT) professionals, computer science and engineering educators, teachers and scholars in the humanities and social</p>
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sciences, policy makers, students, and ICT users for the purpose of establishing critical dialogue on the social and ethical dimensions of ICT. Papers on any of the following topics would be especially welcome: electronic publishing; intellectual property rights in the digital era; social implications of wireless technology; equitable access for the disadvantaged and the disabled; national and international ICT policy; information security and privacy; free speech and censorship; social implications of electronic commerce; ICT and democratic processes; gender issues in ICT; misuse of ICT; distance education; web-based resources for teaching ethics in computing; ICT and high-risk systems; and ICT in developing countries. Submit a one-page abstract for a paper, or a proposal for a paper session or panel discussion, to the Conference Chair (email preferred): Joseph R. Herkert, Division of Multidisciplinary Studies, Box 7107, North Carolina State University, Raleigh, NC 27695-7107, ph. 919-515-7993, fx. 919-515-1828, email joe_herkert@ncsu.edu. Deadline for submission is December 13, 2001.

PUBLICATIONS: In 1970, Katherine Anne Power went underground to avoid capture for her role in the murder of a police officer. Placed on the FBI's "Most Wanted List," she surrendered in 1993 and served six years in prison. In Spring 2001 she graduated from Oregon State University with an MA in Philosophy. Powers has written of her experience with health care in prison in the spring issue of *Reflections*, the newsletter of the Program for Ethics, Science, and

the Environment. To receive a free copy, contact: Courtney Campbell, Philosophy Department, Oregon State University, Corvallis, OR 97331, email ccampbell@orst.edu.

Kenneth F. T. Crust, Editor of the *International Journal of Philosophical Practice (IJPP)*, announces that IJPP's first issue is now available on-line for subscribers. Non-subscribers may reach the abstracts and subscribe using the secure subscription service (<http://ijpp.net/Abstracts.asp>).

FELLOWSHIPS: The Harvard University Center for Ethics and the Professions invites applications for Faculty Fellowships in Ethics for the academic year 2002-2003. Fellowships will be awarded to outstanding teachers and scholars who wish to develop their ability to address questions of moral choice in such areas as business, education, government, law, medicine, and public policy. Fellows participate in the weekly seminar of the Center, which discusses problems of teaching and research in ethics. They have access to a wide range of activities in all of the professional schools at Harvard, as well as the Faculty of Arts and Sciences, including opportunities to participate in courses, colloquia, curricular development, collaborative research, study groups, case-writing workshops, and clinical programs. A significant part of their time is devoted to conducting their own research in ethics. The Fellowship extends from September through June. Applicants should hold a doctorate in philosophy, political theory, theology, or related disciplines, or a

professional degree in business, education, public policy, law, or medicine. Preference will be given to applicants at an early stage in their careers, normally no more than ten years from the terminal degree in their field. The deadline for application: December 1, 2001. Contact: Center for Ethics and the Professions, Harvard University, 79 John F. Kennedy Street, Cambridge, MA 02138; ph. 617-495-1336; fx. 617-496-6104; email: ethics@harvard.edu; website: <http://www.ethics.harvard.edu>.

The University Center for Human Values supports teaching, research, and discussion of ethics and human values throughout the curriculum and across the disciplines at Princeton University. With seminar and lecture courses, public lectures and symposia, a publication series and the scholarly work of its faculty and visiting fellows, the University Center fosters ongoing inquiry into important ethical issues in private and public life. The University Center invites applications from all disciplines for the Laurance S. Rockefeller Visiting Fellowships. These fellowships will be awarded for the academic year 2002-2003 to outstanding scholars and teachers interested in devoting a year in residence at Princeton writing about ethics and human values. A selection committee of University Center faculty evaluates applicants on the basis of: 1) the significance of their proposed research and its relevance to the purposes of the University Center, 2) the quality of their previous research and their ability to benefit from the activities of the University Center, and 3) the contribution they are likely to make to higher education.

in the future. Deadline: December 5, 2001. Contact: Amy Gutman, Director, University Center for Human Values, 304 Louis Marx Hall, Princeton University, Princeton, NJ 08544-1006, ph. 609-258-4798, email: values@princeton.edu.

The Center for the Study of Ethics in the Professions (CSEP) was established in 1976 for the purpose of promoting education and scholarship relating to ethical and policy issues of the professions. *Perspectives on the Professions* is one of the means the Center has of achieving that purpose.

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