PERSPECTIVES OF A COMMUNITY MEMBER ON THE IRBMED

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What on earth am I doing here?

That was the question in my mind some 25 years ago when in January, 1982, I attended my first IRB meeting. I had been asked to serve on the board by a friend and congregant, Dr. Ronald Bishop, then the head of what I believe was called Ethics in Medicine. Dr. William Coon was the chair of the board and he welcomed me graciously, as did other members of the board. But nothing really helped me to overcome a sense of profound ignorance of what was going on. The language was strange and unfathomable to me, and I wondered how long I could survive since I surely had nothing to contribute to the deliberations of this august group.

It was many months before I understood that my sense of ignorance was not only accurate, but the point of my being there. I was a community member, as it were a kind of resident ignoramus, someone who does not know what all the scientific members of the committee know, someone like the average person who might be asked to participate in a research study. My role on the IRB then and today is to put myself in the place of that person. If I were the one being recruited, do I understand enough of what is going on to make an informed and responsible decision?

Twenty five years ago the IRB was very different from today. We had a board of about 14-15 members. We dealt with far fewer protocols, about 1,000 a year if I recall correctly. We accomplished the work in one hour or less, often having time for Bill Coon to ask our “legal eagle,” Ed Goldman, to bring us up to date on new wrinkles in the law related to our work. Bill’s secretary, Sally, who also worked for other doctors, did the paperwork and filing. There was no staff provided.

In those days, there was only one other non-scientific person on the board, Ann Munro, who was the hospital ombudsperson. She and I did not review protocols. We only listened in the meetings, picked up what we could, and made our judgments. In contrast to today, we received no formal training in how to be an IRB member. Now there is excellent and ample training. We both saw a silly film about IRBs that I recall had little to do with the way our IRB actually functioned. At our request, we sat in on the recruitment of a research subject and the procedure that followed.

I also was directed to a lecture to be given by Dr. Robert Reed on the ethics of health care. As it happened, I was given the wrong date and found myself—seated right at the front where I could not escape—in a lecture about the liver. The liver is, of course, a very interesting organ, but the lecture did not further my knowledge of health care ethics. That came the following week.

What I learned from Dr. Reed and other sources suggested to me by Dr. Bishop and Dr. Coon was the ethical context of human subject research. Since I do not have scientific knowledge to bring to our board discussions, I try always to keep in my mind these fundamental ethical principles about how human beings should treat one another. The scientists as well as the lay people use these principles in making our decisions.

Perhaps the oldest principle in health care ethics is that of Hippocrates, who lived from 469-370 BCE. What is most important in his famous oath, for both clinical practice and research, is the statement that “I will keep them from harm and injustice.” There is no finer principle in health care ethics than that.

A second major principle is found in Immanuel Kant’s categorical imperative. One of the forms in which he stated this is directly related to the ethics of health care: treat every person as an end not a means, using people for your purposes only if they voluntarily and knowingly and free of coercion agree to let you use them in that way.

Do no harm. Respect the autonomy of other people. These are the two foundations of the ethical practice of medicine and the ethical research enterprise.

In the 20th century, with rapidly advancing scientific knowledge, there were challenges to these ethical principles. While some, perhaps many, doctors did experiments as ethically as Walter Reed, who offered consent forms to research subjects in Cuba, in Spanish, when he was studying yellow fever, others were less sensitive.

Between 1955 and 1970, the tragedy of the drug thalidomide, the episode at Brooklyn Cancer Hospital, and the Stanley Milgram experiment at Yale all raised ethical concerns in America about the way in which research subjects were treated, about drug safety and efficacy, about informed consent.

Two episodes were most important for the development of ethical guidelines and federal involvement in the regulation of research. One was the trial in December, 1946, of 23 German doctors and other medical personnel for their research on people whom the Nazis considered "life unfit to live:" Jews, Gypsies, homosexuals, Slavs, the mentally disturbed, and others. Guidelines emerged from that trial that have had a crucial role in shaping the course of health care ethics ever since.

Among these guidelines are the following:

- The voluntary consent of a research subject is essential.
- The research should be reasonable in terms of expected good results that cannot be obtained in any other way.
- The research should be based on the results of animal experimentation wherever possible.
- The researcher should avoid all unnecessary suffering and injury.
- The research should have a favorable risk/benefit ratio.
- Only scientifically qualified persons should conduct research.
- The research subject can end the research at any time, and the researcher should end the research if he or she perceives it to be harmful.

The more immediate event that sparked a change in the research world in this country was the revelation in 1972 of the infamous Tuskegee Study, a forty year study of untreated syphilis in Negro males by the US Public Health Service. The purpose of the research was not told to these men, the risks were not revealed to them, and when penicillin became available as a successful treatment for syphilis, they were not informed of it.

As a direct result of the Tuskegee Study becoming public knowledge, Congress appointed the Belmont Commission, whose mission was "to

identify basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects." Their report, completed in 1976, drew a distinction between medical practice—"interventions that are designed solely to enhance the well-being of an individual patient…and that have a reasonable expectation of success"—and research—"an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge."

Federal regulatory authority grew out of the Belmont Report. More important to me as a community member are three fundamental principles that guide the way health care research is done.

The first principle I will mention is justice. There must be an equitable selection of research subjects, not just your subordinates or family or vulnerable people. There must not be the undue coercion of high pay. Justice also means that there should an equitable distribution of burdens and rewards, so that one class of people are not subjected to the risks of research while another class of people reaps the benefits of the research.

A second of these principles is respect for persons. This means, among other things that we should treat each person as an autonomous agent, being sure that persons with diminished capacities—children, the mentally ill, those with dementia, and others—are protected by having a responsible agent who can speak on their behalf.

Respect for persons means the use of an informed consent in which the following elements are present: a clear explanation of the procedures to be used, making sure to distinguish between which are experimental and which are standard practice; the discomforts and risks as well as the possible benefits of the research; alternative procedures that might be more advantageous or equally so to the potential subject; an offer that is honored to answer any questions; a clear statement that the subject can withdraw at any time consistent with protecting the welfare of the subject.

Respect for persons means that potential subjects must be able to comprehend what is going on, that they are not a captive population where coercion could be a factor, and that confidentiality is protected. Respect for persons means individual autonomy.

The third Belmont Principle is beneficence. This is drawn out of the Hippocratic notion that we should do no harm. A careful weighing of the risk-benefit ratio is required so that the peril and pain involved is measured against the potential good for the subject or for those with similar conditions to the subject. Beneficence requires asking if the answer to the research question is really important and whether it might be obtained in some other way, such as in lab work or by animal experimentation.

Beneficence means good research design, competent investigators, continuous monitoring and systematic assessment, and the consideration of not just physical and mental aspects of the risk-benefit ratio, but also legal and psychological and economic aspects.

Justice, autonomy, and beneficence. I remember them with the acronym, JAB (as in jabbing a needle into your arm). I try to remember JAB when I review protocols or when I am listening to others' reviews and trying to decide how to vote.

My work on the IRB was pretty much as I have described it for 13 years, until the retirement of Bill Coon. At that time, we were just a few months past an FDA audit that cited us for 28 violations, in no small part, I think, because the IRB literally had no support staff and a tiny budget. I alone was paid for each meeting I attended, $25.00 (an amount that has increased to $75.00 now). As far as I am aware, that small amount and the cost of the lunches was the total expenditure by the Medical Center for the IRB. Change had to happen if the IRB was to continue to thrive. As we learned from others' experiences, if the IRB did not thrive, the research enterprise at the University of Michigan Medical Center would be put at risk.

The next six years was a period of significant change and much difficulty. Dr. Sumer Pek served as chair for three years. He brought us into the computer age, sought new ways of understanding our mission, and developed procedural guidelines and templates that won national praise.

Dr. Pek was followed by several others for short periods of time. During these years from 1995-2001, the length of meetings expanded until we rarely finished in less than two and one-half hours and often went as long as four hours. I can remember being given for review as many as 18 protocols in one week! I saw other members with several times that number.

When Drs. Vernon Sondak and Robert Cody took the leadership of the IRB, slowly but surely things began to improve, partly because of increased support from the Medical Center. Soon we had two boards meeting, and then four, and now five, with two co-chairs and four vice-chairs. The number of protocols mounted each year—Jan Hewitt cites more than 5,000 applications each year now-- and the number of members on the IRBMED also mounted. I counted 77 on the directory of members dated January 2, 2007, although Jan reports more than 90! There are 27 staff members.

We meet in our separate boards at different times and by and large are unaware of the work of the other boards. The increased number of boards and reviewers, along with increasing the number of expedited reviews and single-member reviews, has made for a vastly more efficient process without diminishing the ethical review the IRB is mandated to do. We spend our time discussing protocols that are challenging and raise difficult questions, while simple reviews—for example, a protocol that has enrolled no subjects since the last annual review—are dealt with outside regular board meetings.

Old-timers like me have the honor of serving on two of the five boards, while newer members sit only on one. On each board, according to 46.107 of the federal guidelines, there is at least one member "whose primary concerns are in scientific areas" and at least one member "whose primary concerns are in non-scientific areas." 46.108 requires that at every meeting at least one non-scientist be present.

The composition of the board has changed over the years. Not only have we grown in numbers, we also have a very different make-up. When I joined the board in January, 1982, there were two women on the board, Dr. Donita Sullivan and an attorney whose name I do not remember. Today there are at least 29. There were no pharmacists on the board back then, and someone who suggested having one was laughed at. Today there are two PharmDocs from Investigational Drug Service on the IRBMED, one of them a Vice-Chair of one of our boards. There were no nurses on the IRB in 1982, but several now.

We have a stronger IRB because of these changes, one that is truly reflective of the diversity of opinions and judgments regarding medical research and one that reflects a diversity of specialties involved in health care.

According to the Human Research Subject Participant Protection Program Operations Manual dated April, 2005, the Mission of the IRBMED is as follows:

> "The Institutional Review Board's first and most important function is to protect the rights and welfare of human research subjects. The safeguarding of subject rights and welfare must take precedence over the goals and requirements of any research endeavor. This mission is mandated by federal regulations, and the approval process cannot be overturned by the institution."

Periodically, an IRB member will remind us of this mission, "to protect the rights and welfare of human research subjects," lest we get caught up, even the non-scientists, even the community members, in the brilliance of a research proposal that seems to have such glowing potential for human good, but also has an edgy ethical side to it.

Here are some of the ways that community members speak of this responsibility.

Fran Lyman makes the point that being a community member is considerably more difficult today than it was before, a point I can validate from my 25 years experience. Machines are more complex, drugs have proliferated beyond counting, and the regulations from the Feds seem to change almost weekly.

I think Fran would agree with me in saying that research subjects are also confused by the multiplicity of medical options and the constant changes that make it difficult to understand what is going on. In that sense, in our confusion and uncertainty, we still represent a typical research subject.

Joan Lowenstein, whose board deals primarily with cancer, wrote that "I often think about friends or relatives who have had cancer. I think about what my own reaction would be if I were diagnosed with cancer." She goes on to speak of the importance of the perspective of those who are not scientists "in determining whether ordinary people can understand the benefits and risks."

Pamela Redding, who is the prisoner advocate on the IRBMED and who served on an IRB in Hawaii before joining us in 2003, makes the point that

"I have nothing to gain professionally from membership so I feel free to say what I feel is right." Those of us from the community—a lawyer, a librarian, a nurse, a professor, and several ministers—do not have the pressure we experience in our own chosen professions to look good. We can afford to look foolish by asking "silly" questions, just the kind a research subject might well ask.

Pam also makes a good point in saying that "the beauty of the IRB design is that it brings together a wide range of perspectives." Our five IRB boards have a diversity of medical specialists, other health care workers at the Medical Center like nurses and pharmacists, and community members from different walks of life. Each of these persons contributes something special to the decision-making process from the vantage point of our own perspective. I like to think of us as interdependent since different ones of us know different things.

That interdependence extends to sometimes having a second reviewer go over the protocol, sometimes means that a person with special competence who is not on the IRB will be asked to join in the review, and sometimes lay members will be asked to read an informed consent to see if it makes sense to them.

Duke Morrow has written of his role as "that of looking at research (especially informed consent) through the lens of a potential subject/patient/medical services consumer" and views this as important because not all of the IRB members can understand what it is like to sit in the patient's or research subject's chair. Especially is this true, he writes, "with conventional insurance and medical decisions being made with cost as a significant factor." Duke feels that we need "more clarity in costs to the subject."

I still support the old notion I was taught when I joined the IRB that research should not cost the subject anything. I am aware that the line between treatment and research is sometimes difficult to establish, and that there are some maladies for which research is the treatment. But in an age of skyrocketing costs in health care, those who volunteer for research under any circumstances surely deserve not to be charged for it!

Fran Lyman adds her concern about "studies that don't even pay the parking costs of patients."

Ann Damon writes that “what is done (in the name of research) is fascinating, interesting, exciting, and frightening…” She writes of her “curiosity and concern” as a community member. Curiosity at what medical research is studying and doing and what good it does. Concern about what is done to research subjects, about the level of their understanding of the research, about wanting good outcomes from the research, about the tie-ins between the good that research does and commercial ventures that grow out of the research. What really is in the best interest of the subject is the essence of her concern, and this manifests itself in asking questions like, “what does that mean, exactly?” The readability and thus the understandability of informed consents is a key concern.

In that regard, I looked over the “Simplification Guide to Medical Terms”, intended for use in drafting informed consents so that potential subjects can understand them. Most of the explanations of medical terms are indeed simple and clear, such as pregnancy being a clearer term than cyesis and seeing double being a clearer term than diplopia. But I am not sure I would feel better informed if I read that amnionitis is really just inflammation of the amnion or read that Addison’s disease is a serious disorder in which there is decreased cortisol and aldosterone in the body. Sometimes it is very hard to make medical terms clear in simple, layperson’s language.

I think that all of us who serve as community members on the IRB are deeply moved by the brilliance, the hard work, the creativity, and the compassion of the doctors and nurses and pharmacists and other staff people on or associated with the IRB. I think all of us are impressed with the dedication of these people, who all work a lot harder at it than we do. I think we appreciate the respect that is shown to us, even though we are not scientists and really are not very knowledgeable about medicine. I think to the limit of our ability we community members all try to represent a potential research subject confronted by the white coat: how would that person feel, what would that person want to know, how can we protect that person even as we strive to support the research enterprise.

I certainly would not have served on the IRB as long as I have if I did not believe in the research enterprise and in the integrity of those who engage in it. As a minister I have seen many people relieved of suffering, cured of a bad illness or difficult condition, given more years to live than was possible when I began in ministry some 35 years ago. I am grateful for all that has

been done, but I am also aware that the medical profession is as subject to ethical lapses as any other. I know from clergy misdeeds that no one is exempt. I know from being close to the review of one investigator who stepped over the line that, painful as it is, doctors are willing to police their own. The IRBMED is necessary and I am glad to serve on it.

There is, of course, room for improvement, and I am certain that everyone in this room and everyone associated with the research enterprise at this Medical Center has ideas on how to do that, the community members included. Here are some of the thoughts of me and my colleagues about how to make the work of the IRBMED even better. I am presenting our views without identifying who offered which idea and with only limited judgment about their merit.

One of us has expressed concerns about the objectivity of the IRB since the overwhelming majority of its members are "insiders" and colleagues of the investigators whose protocols they are reviewing. The non-science community members simply cannot understand the medicine, and a good review of an informed consent requires an understanding of the risks involved. The ones who do understand the risks, the medical and nursing and pharmacy and technical staff "have a vested interest in, and connection to, medical research, many (if not all) work for the same institution as the researcher whose proposal they are considering, that researcher is often a colleague in varying degrees of immediacy, that researcher is proposing research that could bring money or notoriety or prestige to the institution…"

This individual suggests that "if we replaced all the docs on my board with docs who had no connection to the hospital, and whose only connection to medical research was wanting to be able to take better care of their patients, the line for what is OK for an IRB board would move, more than barely, towards better protecting the patients, without any harm to medical science or its progression."

The system as it is, this person comments, is "frankly, heavily slanted towards approving research."

My own sentiments are somewhat different. While I have certainly observed some medical reviewers who were unable ever to find a flaw in any protocol they reviewed or voted on, I have seen others who have been meticulous in carefully weighing the risks to the research subjects, carefully examining

informed consents to see if they really are readable—one in particular used to request my reading of consents on a regular basis—and painfully willing to accept that sometimes docs go astray and have to be called back in line or even disciplined for ethical misbehavior.

I have shared this person's views because it is at the very least a recognizable risk in the human sense when we invite our colleagues to sit in judgment on our work. That kind of review is a hard thing to do, especially if our review turns out to be critical of what the colleague is doing. But I am not sure that pure objectivity is ever attainable, and I see week by week docs making sometimes stringent assessments, without personal animosity, to improve the quality and the ethical fairness of the research that is done.

Another of my community member colleagues has concerns that too little attention is paid to the risk-benefit ratio in considering whether to approve a protocol, perhaps this person indicates, because "IRB members find risk-benefit ratio assessments to be one of the most difficult tasks involved in reviewing research protocols." It is difficult because it involves probabilities, and often we "may have no good estimate of the relevant probabilities." Perhaps there ought to be a clearer presentation of why a particular risk assessment has been chosen for protocols where it is not obvious.

The suggestion is made that a study might be done to assess how many research protocols could be called "losers." Such language would be used after "the books are…closed on that project." The evaluation might read as follows: "This research project yielded some good benefits (direct or indirect or both), and it has also incurred some human costs (the SAEs), and we judge that the costs outweighed the benefits. This project turned out to cost too much. It was actually a loser." Such a study "might be a useful learning experience for us in an IRB."

Several of my colleagues mentioned the issue of costs and payments. It is one to which attention could be given so that a standard of fairness of pay and fairness of what costs if any should be born by a research subject could become clearer.

It would certainly help research subjects if informed consents could somehow be made shorter and clearer. How to do this is the question, given the considerations of explaining what is really going on—the "informed" in informed consent—and the various regulatory requirements including

our much beloved HIPPA rules. These things beef up the consents. So maybe it is not length so much as clarity and presentation that matters. A good graphic designer might help with a better lay-out of the information to make it more readable.

A science editor—like a former community member who helped greatly with some complex research protocols, the late Martha Elder—could help provide the simplified language needed for an untutored reader without sacrificing the truth of what is going on. In some protocols bar graphs showing the percentage of risk/benefit of certain procedures might be helpful, and maybe visual depiction of the risks where that is appropriate.

Finally, as is done in many academic journals and even some magazines, an abstract at the head of the consent form that is no more than half a page long and that tells what the protocol is about would be very helpful. Having taken part in several research projects myself, I know the importance of a clear, informed consent to help me in the decision process of whether to take part or not.

Several years ago I heard a long-time member of the IRBMED say to a former member who asked how things were going that he had a concern that rules and regulations had replaced ethical considerations in our deliberations. I share that concern to a degree, even as I know the inevitability of such a change happening. Laws supposedly reflect ethics. Given the power of the laws that govern our IRBs and the consequences of violating those laws, it is understandable if our conversations often are about the federal regs and not about ethical issues. I try to remember and I think we all should that our mission is to "protect the rights and welfare of human research subjects." That is an ethical far more than it is a legal mandate.

Another suggestion made was to have a community non-science member sit in on the IRB Chairs meeting. That was not my suggestion and I am not volunteering!

From what I have heard at board meetings, there is no small amount of frustration with e-research. Short of abandoning that whole venture—which I admit some of us might relish—I have not a clue as to how to fix it, only to say that a great deal of time is taken up with the system itself and figuring out how to use it and what to do when it does not work that might well be

spent reviewing and reflecting on protocols. Once it is fixed, if that day ever dawns, upgrades should be forbidden.

I will conclude with one last function that I have always felt was an important part of my role as a community member, and that is reporting to the community on what is going on in research. I do not mean a report in any detailed sense that would violate the confidentiality of our meetings and our work. I mean a report in the sense of making clear to the wider public that ethical research is going on, that the members of the IRBMED are hard-working, ethically sensitive, extraordinarily smart people who are serving the common good in important ways.

When I was active in the ministry here in Ann Arbor, I invited several members of the IRB to speak to my congregation. I spoke myself about health care ethics on several occasions, and included in my annual ethics course at the church a full section on ethics in health care with an emphasis on research ethics. I am now teaching that course in the Osher Lifelong Learning Institute in Ann Arbor. In the first month of my retirement, I addressed the Turkish Endocrine Society on "The Rights and Welfare of Human Research Subjects.

I have felt it a real honor and a great challenge to serve on the IRBMED. I have made good friends with several board members. I have enormous respect for the work that these men and women do. I have been impressed across the years, especially in the last dozen years or so, with how much effort has been put into trying to improve the work that we do. I try to let the world know my feelings. That is one thing that, regardless of my ignorance of medical and scientific matters, I can do as a community member of the IRBMED.

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