

Ethical and regulatory challenges in a randomized control trial of adjuvant treatment
for breast cancer in Vietnam

Richard R. Love¹
Norman C. Fost²

Collaborative research among investigators from developing and developed countries are considered cost-effective investments (1). Guidelines for the ethical conduct of such research have been promulgated (2). In oncology, while several projects involving American investigators have been conducted, many opportunities have been lost (3). It is widely accepted that an American investigator involved in an international research project is expected to seek and receive approval from a federally approved institutional review board (IRB) in his home institution and approval from a similar ethical review committee in the foreign site.

In 1992-93 one of us (RRL) developed a proposal for a randomized controlled trial for adjuvant therapy of breast cancer in the Socialist Republic of Vietnam. The other (NF) was chairman of the IRB at the University of Wisconsin Center for Health Sciences, and asserts that this proposal consumed more time and provoked more discussion than all but 2 other protocols in his 23 years of service on the IRB, 19 as chairman. We present here an analysis of the major issues in this review process, to illuminate some of the ethical and regulatory complexities of international research.

1. Medical background, the proposed project, and proposed consent procedures

Standard treatment of breast cancer in the U.S. (and most Western/developed countries) includes various surgical procedures, usually coupled with "adjuvant" therapy, meaning therapy that is given after initial primary therapy, in this case surgery. Adjuvant therapy is given in the absence of any obvious evidence of cancer spread, to treat presumed microscopic disease. Common adjuvant therapies for breast cancer include combinations of radiation, chemotherapy, and hormonal treatments, including oophorectomy (removal of both ovaries) and tamoxifen.

In the treatment of premenopausal women with breast cancer, the place of hormonal therapies is incompletely defined. The physiologic basis is the observation that breast cancer growth is stimulated by estrogen. Thus, removing a major producer of estrogen, such as the ovaries, or providing a drug, such as

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

tamoxifen which opposes the cellular action of estrogen, would possibly be helpful in controlling the growth of breast cancer. While there is evidence that such hormonal treatments have benefit, these observations come from studies and analyses in which other variables make it difficult to determine confidently their relative contributions to improved outcomes (4).

While there is considerable scientific support for the conduct of breast cancer studies of the specific role of hormonal treatments in premenopausal women, it has been difficult to conduct such studies in the U.S. where the standard adjuvant treatments have been chemotherapy. Whatever the merits of hormonal treatments and the importance of studying them, it is generally acknowledged that mounting a placebo or no adjuvant treatment controlled trial in the U.S. is not politically feasible at present.

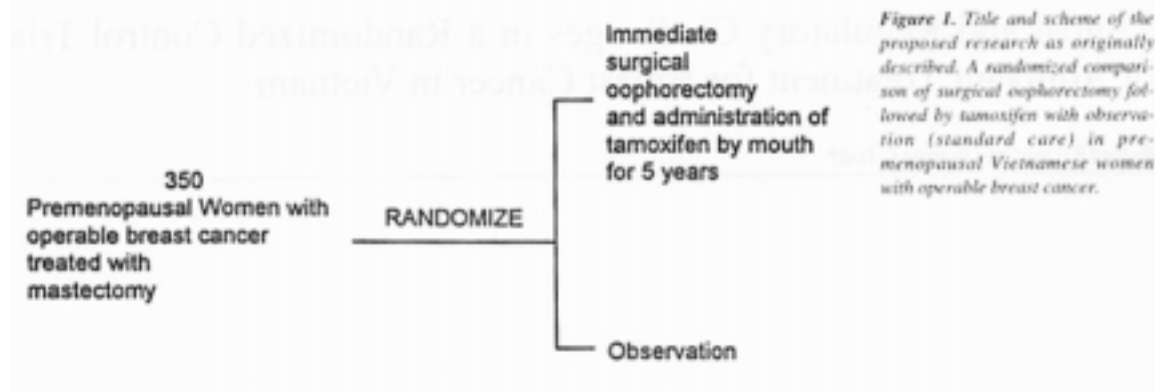
As a result of multiple visits to Vietnam, initially as a representative of the International Union Against Cancer, the first author (RRL) and principal investigator (PI) was familiar with the state-of-the-art of breast cancer care there. In the late 1980s and early 1990s, the economic situation in Vietnam and long-standing scientific isolation began to improve significantly after 30 years of hardship. As the PI consulted on individual patient cases and presented lectures, the limited experience of the Vietnamese, in both treatment strategies and Western scientific methods, was clear. The lack of resources and systems prevented any well organized care for these cancer victims. Systemic adjuvant treatments (such as chemotherapy or hormonal treatment with oophorectomy or tamoxifen) were only occasionally used, and then in manners unlikely to achieve any benefit to the patient (that is, not with full doses or according to schedules shown to be effective).

The principal investigator conceived of the idea of a clinical trial as a means for technology transfer, education, and immediate improvement of treatment. The conversations and planning about a trial focussed attention on this as a scientific tool and on details of the state-of-the-art in cancer treatment.

The trial was seen as an educational tool to engage specialist doctors in working together to develop a *From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

consensus and system of care for their young patients with breast cancer. As the process developed, the possibility of major medical benefit to Vietnamese and other Asian women became evident.

The investigator proposed to conduct a randomized controlled trial of adjuvant surgical oophorectomy and tamoxifen in 350 premenopausal women with operable breast cancer, in collaboration with physicians at two major cancer hospitals in the Socialist Republic of Vietnam. The original presentation of the study design is in Figure 1. A comprehensive protocol was submitted to the IRB, including an extensive discussion of the rationale for conducting the trial in Vietnam. The specific benefits to the Vietnamese, and also to the international community, of the proposed trial were noted.



2. Differing standards of care

In developing the proposed research program, the investigator found himself uncertain about the application of American standards of informed consent in the Vietnamese setting. After detailed discussions with Vietnamese physicians and cultural experts (both professional and immigrants to the U.S.; for examples, one was an American Ph.D. medical sociologist who has led a non governmental Vietnamese liaison organization for many years, a second was a Vietnamese medical sociologist visitor to the university), it became clear the American standards would not be acceptable to Vietnamese physicians, political leaders in Vietnam, or the vast majority of Vietnamese patients. Western notions of

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

informed consent are inconsistent with and antithetical to a paternalistic style that is not only standard practice in Vietnam, but apparently preferred by the Vietnamese people.

In particular, it is not customary in Vietnam for patients to participate in their own medical decisions in the way that is normative in the U.S. and other Western cultures. Patients expect and look to their physicians to tell them the appropriate treatment. It is unacceptable for a physician to openly express uncertainty with regard to what is the best treatment. In practice, given a choice of options, patients virtually always defer to the physician. While this paternalism may be considered unfortunate, even to some Vietnamese, virtually all Vietnamese queried believed this is best for the patient. Thus while it might be technically possible, though difficult, to inform Vietnamese women about alternative ways of treating breast cancer, or options within a research protocol, Vietnamese people do not believe it is the right thing to do; and even if it were done, the "informed consent" which resulted would not be functionally relevant because patients, in fact, would defer judgment to their doctors. In addition, trying to force this mode of consent on the physicians risked losing their cooperation with the project because of the tone of cultural imperialism that it would convey. In light of these considerations, the PI initially considered waiving some elements of the consent process; namely, those that would convey uncertainty by the treating doctor. This would imply *not* disclosing alternative therapies and not disclosing that the patient's proposed treatment had been determined by a process of randomization.

3. The use of surrogates in the consent process

The authors anticipated that the IRB would have to consider a proposal for surrogate consent in two senses. First, particularly in view of the limited participation of the prospective patients in the consent process, someone had to represent them as a group in deciding to initiate the study. This could be considered especially problematic in view of the intention to use two treatment approaches neither of which would not be considered standard treatment in developed countries. We thought it important that

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

the "macro" decision not be made solely by U.S. agencies, such as the University of Wisconsin IRB. Second, since patients would not be participating actively, by American standards, in the decision to be a research subject, it was unavoidable that the decision would be made by a surrogate. This would typically be the patient's physician. Given the mixture of research and clinical motives however, we thought it prudent to seek an additional layer of representation for the patients. Towards this end, the PI convened two "surrogate groups" to review the protocol, with particular attention to the proposed consent process.

Surrogate groups have been useful in prior research projects involving complex medical and ethical questions (5,6). The process involves identifying a group of laypersons who resemble the prospective research subjects as much as possible. The surrogates are asked to review the proposal, including the consent forms, in an informal, open-ended session, for the purpose of eliciting candid opinions about the study and consent form, as well as to gain impressions as to whether prospective subjects, fully informed, would want to participate, or if not, what the reasons might be. The theory, and the result of prior studies, has been that surrogates will be more open in their criticisms and concerns because they are freed of the common constraints of the patient role. Patients are too often inhibited in questioning physicians for a variety of reasons: illness, dependency, fear of reprisals, embarrassment, not wanting to take up the doctor's valuable time, and possibly misplaced altruism -- the feeling that the patient's duty is to help the doctor. In summary, the purpose of the surrogate groups was twofold: first, to provide the investigator and the IRB with independent opinions about the project as a whole, including the medical and consent aspects; and second, to provide some protection for individual patients by ensuring that their interests would not be violated by participation in the study.

Toward this end, the PI convened two surrogate groups and sought input of several expert peer reviewers.

3.1 Surrogate Group 1: Educated, American-living Vietnamese

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

Immigrants

The PI assembled a group of 4 Vietnamese immigrant women, two of their husbands (one Vietnamese, one American) and a visiting Vietnamese Ph.D. sociologist, which met over 2Ω hours. The PI indicated that he needed their help to decide the best way to conduct a Special Breast Program for Vietnamese women in Vietnam.

The PI asked them to pretend that they were in Vietnam and developed cancer, or to imagine that their sisters were in this circumstance and sought their advice. This was an understandable request to the group, because some had a medical background (one woman a pharmacist, one a nurse) and a third woman had a sister who had died of breast cancer in Vietnam. The full spectrum of issues normally covered in the consent process was presented: purpose, selection of subjects, procedures, benefits, risks, alternatives, confidentiality. The PI discussed the American way of informing women about the choice of treatment, and group members presented their understanding of the Vietnamese way. They described a paternalistic system in Vietnam, which they believed was best, under which a physician would tell the patient that one or the other treatment was best and recommend it. The PI openly discussed the review process for such programs in the United States and said that he was exploring the possibility that if the group approved, that foregoing some elements of individual informed consent might be possible. This discussion led to further very detailed questioning about the treatment choices, benefits, risks and treatment in the West for such cases, as well as direct questions about the principal investigator's interests, and possible benefits for Vietnamese women. This latter subject was answered by saying that the overall goal of the program was educational, and that the clinical trial portion of the program was a very challenging undertaking whose

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

scientific success was uncertain.

The PI asked each individual for his/her opinion about the appropriateness of conducting this program in the Vietnamese way, that is without presenting the alternative treatments and randomization details to individual women, and each agreed that they believed this way was the best way and said they would approve of a program conducted under these conditions.

3.2 Surrogate Group 2: Moral Leaders: Directors of the Vietnamese Women's Union

During a visit by the PI, he arranged to meet with the leaders of the Vietnamese Women's Union which represents women's interests at all levels of Vietnamese society as a functionally independent entity.

The PI met with the vice president and the chief of the International Relations Department of the Vietnamese Women's Union for 1½ hours. While all conversations were translated, both leaders had a Ph.D. from an English-language university and spoke excellent English. The group openly discussed physician-patient communication in Vietnam, and after their comments and negative assessments of individual informed consent, the PI asked the two leaders for their opinion of a plan to treat Vietnamese women in the proposed program without individual informed consent. The PI explicitly stated that without their personal approval this program could not be undertaken. These leaders appeared to well understand the ethical and regulatory problems the PI faced and accepted responsibility for passing judgement on the appropriateness of this program.

At the conclusion the vice president consulted with her colleague and then stated her approval of the program, to be conducted in the Vietnamese way, with the responsible *From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

physician telling the patient post randomization that one or the other treatment would be given.

3.3 Expert Peer Review

The development of the program proposal involved many Vietnamese and international physicians. For these physicians the program was scientifically acceptable, and for the Vietnamese treating physicians, presentation of alternative treatments and the concept of randomization to individual women was not an appropriate approach. It was understood and accepted that should a patient be randomized to receive surgical oophorectomy treatment and refuse this, that no coercion would be applied and the individual's request would be respected.

Extensive corroborating documents and letters were submitted to the IRB to support these surrogate group and reviewer assessments.

4. The IRB review process: medical aspects

In addition to review and approval by the IRB, approval was also required by an institutional scientific review committee. In this report issues raised by either committee regarding the scientific design will be covered. The scientific review committee conducted two formal reviews and two votes. The IRB had 10 meetings over a period of six months, developing a file that is 6 inches thick.

A common initial precept from which reviewers viewed the proposed research can be summarized as follows: "The proposed study includes two treatment approaches, neither of which is standard treatment in the investigator's country, the United States. One arm --oophorectomy and tamoxifen -- at least has the virtue of being a plausible approach for adjuvant treatment, worthy of investigation under acceptable conditions. The other arm -- no adjuvant therapy after surgery -- should be considered inadequate anywhere. It is exploitative of the women in Vietnam not to provide some

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

systemic adjuvant treatment. This would be problematic even with high standards of informed consent. In light of the stated Vietnamese standards for consent, it is unacceptable."

We believe this analysis was flawed for several reasons. The educational and analytic process eventually brought the majority of reviewers to an understanding that both proposed treatments were reasonable choices, given the standards of care and circumstances in Vietnam, and that, for many reasons, American perceptions of the standard of care were not universal. It is impossible to know which of the many points and arguments were persuasive in this process. We review here the main themes.

4.1 Different medical approaches may be justified depending on local circumstances

Medical standards obviously vary among societies for a variety of economic, cultural, and technical reasons. Treatment of kidney failure with transplantation may be an appropriate use of resources in the U.S.; it would be highly debatable in a developing country whose entire annual health care budget might be less than that of a single American hospital. The annual per capita income in Vietnam is estimated to be \$360 US, and this is approximately the annual level of remuneration for senior physicians working at the cancer hospitals there. The standard use of chemotherapy as adjuvant therapy in the U.S. (a course of which is estimated to cost \$3000 per patient) is not appropriate in the Vietnamese setting. Thus it does not follow that the systematic absence of chemotherapy in Vietnam is an unwise policy.

Because of these background differences, a clinical trial might have a treatment approach unacceptable in one country which would be quite acceptable in another. A key question is whether the local standard of care is being followed. This was clearly true in the present proposal. A woman who was randomized to the observation group -- no adjuvant treatment -- would be no worse off as a result of being in this study. The study would expose such a woman to no risk beyond that to which she would have been exposed were she not in the study. On the contrary, being in the observation group offered the possibility of substantial benefit, namely, more careful follow-up and planned treatment, standard for

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

recurrence of cancer, if and when that should occur. The attention to the details of diagnosis and treatment in all research study participants (because of eligibility review and required recording of data) is commonly associated with higher quality care.

Some committee members argued that the women undergoing oophorectomy were being exposed to more risk than American women being treated for breast cancer, either with standard treatment or in clinical trials. Whether or not current chemotherapy regimens involve more or less risk of harm than oophorectomy, with its virtual certainty of infertility, is surely a subjective judgment. But even if the adjuvant program proposed were clearly more toxic than adjuvant regimens in the U.S., it would not follow that they would automatically be unethical for that reason alone. For a population at very high risk for recurrent disease because of the limited effective care available, higher risks might be appropriate. One example of this principle comes from the debate about clinical trials for a vaccine against the HIV virus. Assuming that such a vaccine might have considerable risk, it would be irrational for a population with an extremely low prevalence of HIV infection (Idaho, for example) to take such a risk: subjects would be more likely to be harmed than helped from such a vaccine. In contrast, in a country where HIV prevalence was extremely high (as in central African countries with adult HIV positivity rates of 30%), the potential benefit from even a very risky vaccine might exceed the risks. By analogy, given the poor prognosis of breast cancer in a country where no adjuvant treatment was available, it would not be irrational for a woman to assume a risk of adjuvant therapy that might be higher than that from a standard treatment in another country. In this case, in any event that standard treatment (chemotherapy) was one the investigator was incapable of providing. Some members suggested that the PI conduct another study, comparing more traditional American chemotherapy adjuvant regimens. This, of course, begged the question of whether the American standard treatments were an optimal approach. Among reasons for studying hormonal treatment was the array of concerns about the relative desirability of the traditional

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

adjuvant therapies.

4.2 Traditional adjuvant treatments had questionable application in Vietnamese women, particularly those residing in Vietnam

Many members of the IRB apparently had an unduly positive impression of the present state of treatment of breast cancer in the U.S. The PI was obliged on repeated occasions to review the poor (40-50%) five-year survival of similar patients in the U.S. regardless of treatment. To the present time, there is no single or routine standard adjuvant therapy in the United States. While chemotherapy is more standard than hormonal therapies alone, the details and combination of optimal programs are hotly debated. These details assume major importance in different circumstances such as are present in Vietnam.

Even if there were a clear single preferred adjuvant therapy standard for American women, there was difficulty convincing committee members that, since studies supporting this standard were conducted almost exclusively on American or European women, their relevance to Vietnamese women was questionable (4). There is a complete absence of published data, rigorous or otherwise, on the efficacy, toxicity and costs of breast cancer adjuvant therapy in Asian and particularly Vietnamese women. Additionally, there are data which challenge direct transfer of Western-proven therapies. Specifically, epidemiologic studies have demonstrated significantly lower estrogen hormone levels in Asian women (7). The impact, therefore, of lowering estrogen levels with oophorectomy or of interfering with estrogen effects with tamoxifen may be significantly lower in Asian women. Further, hormonal therapies are suggested to be most effective when tumor cells exhibit certain biologic characteristics such as presence of estrogen receptor proteins, which may be less often present in the more advanced stage cancers detected in Asian women.

Since this study was initiated, additional information has become available which further demonstrates the difficulty of transferring Western experiences with adjuvant chemotherapy to Asian

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

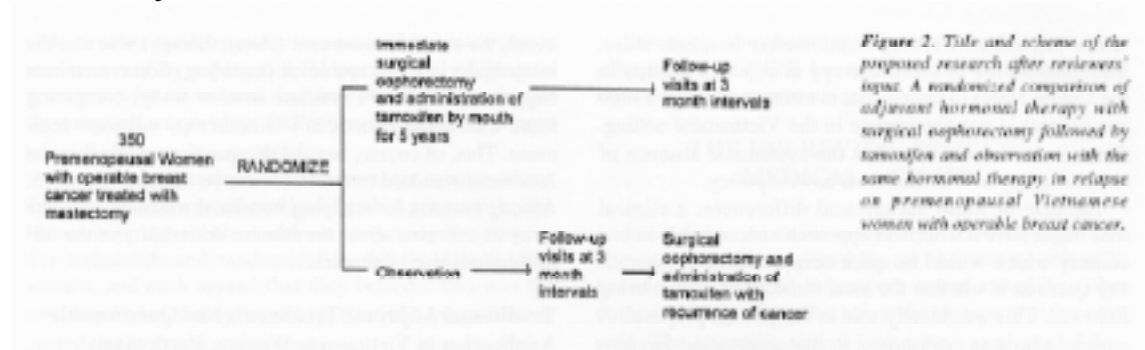
women. First, a long-term follow-up study of Italian patients showed that only those receiving >85% of planned therapy benefitted at all (8). Only 20% of all treated patients met this standard. It is extremely unlikely that many treated Asian women could meet this standard of therapy. Second, a study in Chinese women has shown no benefit of adjuvant chemotherapy (personal communication to RRL, Jonathan Sham, November, 1996).

A crucial point in this aspect of the discussions with the IRB was clarifying that the research project had to be understood as part of a broader context, namely, to define an effective treatment for the most common presentation of breast cancer in Vietnam which could be widely applied in that country. It was also important to convey the larger health priorities in Vietnam, particularly the control of communicable disease. In this context, the investigator's proposal was considered consistent with international guidelines for research in underdeveloped countries in that it was "responsive to the health needs and priorities of the community in which it is to be carried out" (Guideline 8, ref 2). The approval of the Vietnamese Ministry of Health, leaders of the Vietnamese Women's Union, and the director and physicians of the National Cancer Institute of Vietnam suggested that Vietnamese themselves were convinced of the project's relevance to the country's patient needs. This goal explicitly acknowledges an important value in all clinical research -- generalizability -- and implicitly addresses another value -- prudent and efficient use of resources.

There was a particular irony to the suggestion that the proposed trial constitutes exploitation of Vietnamese women. From the investigator's perspective, the clinical trial was the most effective way to prevent exploitation by explicit entrepreneurs. Large international pharmaceutical companies are aggressively marketing systemic antineoplastic therapies throughout Southeast Asia, in the absence of data on their impact on the population, and often absent clear disclosure of the marginal benefits of these therapies, even when given in the best circumstances in Western medical institutions.

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

Reviewers eventually accepted the arguments for the basic elements of the clinical trial. The initial major discomfort with the observation arm was eventually resolved by acceptance of the point that these patients would be no worse off as a result of trial participation, and might in fact be better off because of improved general care. In response to suggestions, the investigator revised the study title and schema to emphasize the regular follow-up care and the planned treatment with oophorectomy and tamoxifen for those patients assigned to the observation arm who later developed recurrence of their cancer (Figure 2). The investigator argued that this design -- encouraging observation patients to receive the same therapy as adjuvant patients -- represented an improvement over the designs in most Western studies of adjuvant treatment.



An additional issue concerned whether the circumstances were in place to allow conducting the proposed clinical trial to a satisfactory conclusion. In such research endeavors, a dominant value is this: that the trial has a significant likelihood of producing valid and accurate conclusions. This issue is perhaps not addressed frequently enough with respect to all research proposals. The investigator acknowledged that his was a high-risk proposal in this regard and identified the various components of the circumstances which warranted a conclusion that a successful trial might be accomplished.

Finally, there was extensive discussion about the formal and informal use of outside consultants. As noted, the investigator had presented supporting documents from outside experts, in response to

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

requests from the IRB, and documentation of the response from the surrogate panels. These documents, deemed by some to be tainted by the investigator's central role in obtaining the information, were received with mixed reactions. One lesson is that ground rules for outside reviewers need to be clearly established for controversial proposals. The review process did lead to the creation of an international multidisciplinary trial data monitoring committee for the study. The agreement of a group of five reputable senior university-based oncology investigators with expert knowledge of breast cancer and clinical trials, three of whom are women, facilitated acceptance of the proposal by reviewers.

5. The review process: standards for consent

The second central issue in the review process concerned informed consent. While the international guidelines for research in underdeveloped countries suggest that "every effort will be made to secure the ethical imperative that the consent of the individual subjects be informed" (2), commentary with these guidelines states:

"For example, when because of communication difficulties investigators cannot make prospective subjects sufficiently aware of the implications of participation to give adequately informed consent, the decision of each prospective subject on whether to consent should be elicited through a reliable intermediary such as a trusted community leader. In some cases other mechanisms, approved by an ethical review committee, may be more suitable."

Other language in the CIOMS guidelines (2), however, suggests that their authors were considering educational "difficulties" (such as literacy) most in suggesting acceptable circumstances for alternatives to individual consent, and not cultural differences such as the investigator was confronted with in this proposal.

In his initial presentation on proposed consent procedures, the PI argued that surrogate consent
*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

could be justified under the CIOMS international guidelines (2). Levine, a leading authority, and others had noted, prior to the publication of the CIOMS document, that "representatives of research subjects (in the host country) should have a presumptive claim to ethical guidance" (9) and "existing international ethical codes for clinical research simply do not provide guidance to trans-cultural, ethical quandaries." The PI went on to argue that the standard practice in Western countries of obtaining individual informed consent from each subject was not appropriate and probably not meaningful and feasible in Vietnam, given the widespread resistance to this notion by patients, doctors and political and community leaders (see section 2, above). He requested that the IRB waive the requirement for informed consent, at least with respect to the subject of randomization.

A majority of IRB members rejected this request for partial waiver of consent, based on three concerns. First, there was a concern that such an approval could place the institution in jeopardy with the Office of Protection from Research Risks at the National Institutes of Health, the agency with oversight authority for IRBs. Second, IRB members were troubled by the remoteness of their relationship to the treating physicians in Vietnam, implying insufficient knowledge to trust their communications with the patients. One of the strengths attributed to the local control implicit in the IRB system has been its familiarity with the physician/investigators whose integrity is critical to the ethical conduct of experimentation involving human subjects. Third, reviewers felt that only through a written document could they insure that subjects were being informed about critical elements of the research program. While the PI offered assurances that subjects would be informed about critical elements, such as their inability to bear children after oophorectomy, the IRB insisted that presentation of this information in a written document was necessary to assure that such information was transmitted.

The negotiation about disclosure of randomization was more difficult. As stated earlier, the surrogate groups felt strongly that talking about the concept of randomization was wrong for Vietnamese *From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

patients. Indeed, the language expressing this concept in the Vietnamese language is especially confusing, even to educated Vietnamese. The surrogate groups felt there would be *de facto* deferral to physicians over treatment choices, and thus presenting this issue in a written document was functionally meaningless and would serve only to confuse and upset physicians and patients. These arguments were not persuasive to the IRB reviewers, who insisted on the inclusion of this information in a written document. There was a negotiated agreement to use a form which was brief compared to traditional consent forms, and which omitted some speculative or minimal risks.

5.1 Consent monitoring

The IRB committee also required an independently conducted consent monitoring study. This was accomplished in 13 consecutive subjects queried three months after entry into the study (Table 1). The responses showed a high degree of awareness of the critical elements of the study -- research, conducted by both Vietnamese and American doctors, and treatment which would prevent future child bearing. As the table shows, subjects were evenly split in answering whether they or the research plan decided treatment and whether they should follow instructions regarding treatment or could refuse proposed treatments.

With respect to the treatment decision (Question 3), the fact that half of the queried women said that they decided (answer B), in contrast to their physician (answer C), suggests a greater degree of perceived autonomy than might have been expected. The consent monitors thought there was an alternative explanation, namely, that the third answer (treatment was decided by randomization) involved concepts that were completely foreign and virtually meaningless to many women, so they picked the second answer ("I decided") by default. Some sense of perceived autonomy is revealed also in the answers to question 5. Seven subjects said, yes they could refuse the immediate surgical treatment.

However, a great majority of women subsequently enrolling in the study have not shown such

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

willingness. As of November 1996, 186 women have entered the study and been randomized to immediate oophorectomy and tamoxifen; of these, 17 have refused this treatment (9%); and of this small group, 10 (5% of the total) received tamoxifen alone. While this number of refusals possibly suggests more autonomy than the foregoing opinions and discussions predicted, in fact all but 2 of these refusals occurred in one institution where different medical and social/political factors and one physician contributed to this situation. The PI's impression is that, in fact, the majority of these refusals were not autonomous but actually a result of physician directives.

6. Conclusion

A randomized controlled trial of hormonal treatment -- oophorectomy and tamoxifen -- as adjuvant therapy for breast cancer was designed for several purposes: (1) to introduce research techniques to the Vietnamese health care system so physicians there could learn to conduct their own studies; (2) to improve the treatment of Vietnamese women with breast cancer by introducing therapies in a systematic way; (3) to assess the benefits and risks of hormonal therapy in this population.

The study presented two major difficulties for the U.S. institutional review board. First, both the experimental intervention (oophorectomy and tamoxifen) and the control arm (standard treatment as it existed in Vietnam) were initially considered ethically unacceptable. After extensive discussion, using surrogate groups in the U.S. and Vietnam, and consultation with experts in the treatment of breast cancer, the IRB accepted the study design, with slight modification, as ethically acceptable. Second, a proposal to use a consent process that was designed to meet the cultural norms and personal values of Vietnamese patients, physicians and political leaders was considered unacceptable by the IRB. After extensive discussion, again including surrogate groups and Vietnamese political leaders, there was agreement on the appropriate content of the consent process and consent form. In its final form, this included the key elements of informed consent, as required by U.S. standards, though with somewhat less detail than is

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

typical in a U.S. consent form. Consent monitoring suggested that the study participants understood the key elements: namely, that they were part of an American sponsored research project, and that oophorectomy would result in permanent infertility. Some patients *appeared* to understand that they could refuse to be in the study, or to have their ovaries removed. It is unclear whether they understood that their treatment was determined by randomization.

A negotiated agreement acceptable to the investigator and the IRB was reached. It is our impression that the vast majority of patients who have enrolled in this study have not consented in the way that is envisioned by mainstream ethical thought in the United States, and as is contemplated by the writers of the U.S. regulations. On the other hand, those Vietnamese patients who wish to make autonomous choices have sufficient information and freedom to do so.

Some might ask what harm would have been done by using the standard American consent form, and by insisting on a consent process more in line with American expectations. At the least, the study would have been extraordinarily difficult to conduct, possibly impossible. Failure to respect the cultural norms of the Vietnamese people, including physicians, patients, and political leaders, would have seriously undermined the complex negotiations that are required for any large-scale randomized clinical trial. The final outcome allowed for respect of both perspectives: traditional Vietnamese physicians and patients have been able to relate in the way they apparently prefer, and more Westernized patients are able to express their autonomous choice. We believe the process was essential, not only in mounting the study, but in facilitating respect among all concerned for what appeared at first to be incompatible views.

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

Table 1
Results of Consent Monitoring

1. Were you aware that the proposed treatment for breast cancer is part of a research project?
 - a. 12 Yes
 - b. 1 No (*but suspected*)
2. Who is doing the research?
 - a. 0 Doctors from the United States
 - b. 1 Doctors from Vietnam
 - c. 12 both of the above (*one included Australia*)
3. How was it decided which treatment you will receive?
 - a. 1 My physician decided which treatment is best for me.
 - b. 6 I decided which treatment I prefer.
 - c. 6 The research plan determined my treatment (by random selection).
4. Will this treatment affect your ability to have children?
 - a. 0 It will help me to have children if I want them.
 - b. 13 If my ovaries are removed, I will not be able to have children ever again.
5. What happens if you do not want your ovaries to be removed?
 - a. 1 I can refuse, but then the doctors will not take care of me any more.
 - b. 5 I must follow the instructions of the physicians, including having my ovaries removed if they tell me to.
- c. 7I can refuse to have my ovaries removed and still receive the other treatments without penalty.
6. What do you have to pay for?
 - a. 6 My breast surgery
 - b. 1 Vitamins and other drugs
 - c. 0 Transportation expenses to the clinic
 - d. 6 (*No answer given, but noted patient has social insurance.*)

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.

References

1. Feachem RGA, Kjellstrom T, Murray CJL, Over M, Phillips MA. The health of adults in the developing world. The World Bank, Washington, DC, 1993.
2. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for biomedical research involving human subjects. CIOMS, Geneva, Switzerland, 1993.
3. Magrath I, Litvak J. Cancer in developing countries: Opportunity and challenge. *J Natl Cancer Inst* 85:862-874, 1993.
4. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic or immune therapy. 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 339:1-15, 71-85, 1992.
5. Fost NC. A surrogate system for informed consent. *JAMA* 223:800, 1975.
6. Fost NC, Farrell PM. A prospective randomized trial of early diagnosis and treatment of cystic fibrosis: A unique ethical dilemma. *Clin Res* 37(3):495-500, 1989.
7. Key TJA, Chen J, Wang DY, et al. Sex hormones in women in rural China and in Britain. *Br J Cancer* 62:631-636, 1990.
8. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. *N Engl J Med*. 332:901-906, 1995.
9. Christakis NA, Panner MJ. Existing international ethical guidelines for human subjects research: some open questions. *Law Med Health Care* 19(3-4):214-221, 1991.

*From the Departments of Medicine¹, Pediatrics² and the Program in Medical Ethics², University of Wisconsin Medical School, Madison, WI 53706. (Dr. Fost is currently the DeCamp Visiting Professor of Bioethics at Princeton University.) Supported in part by NIH grant # CA 64339.