Tamoxifen Turmoil

New issues emerge as healthy women volunteer to take a potent drug

By JANET RALOFF

The National Cancer Institute broke new ground 2 years ago when it launched a large-scale test of a synthetic hormone in healthy women. The $68 million trial is designed to see whether tamoxifen can cut the incidence of breast cancer — the leading cancer among U.S. women — in healthy individuals at high risk of developing the disease (SN: 5/9/92, p.309).

Tamoxifen is currently the drug of choice to prevent new tumors in women who have undergone breast cancer surgery (SN: 2/22/92, p.124). But the NCI trial raises the issue of whether researchers are justified in giving disease-free individuals a drug with the potential to induce life-threatening side effects (SN: 4/25/92, p.266).

Of the 16,000 North American women whom oncologists hope to recruit for the study, half will receive two tamoxifen pills a day for 5 years, and half will receive an inactive powder molded into identical-looking pills. Some 270 hospitals and clinics taking part in the breast cancer prevention trial have signed up 11,111 women so far.

But ethical questions surrounding the study have intensified, driven by recent policy and research developments.

Things heated up in February, when two trials of breast cancer survivors taking tamoxifen reported an apparent excess incidence of endometrial (uterine) cancer. In one of those studies, B-14, some women died of this cancer (SN: 2/26/94, p.133).

Then in April, Bernard Fisher of the University of Pittsburgh came under intense scrutiny (SN: 4/30/94, p.282) when NCI charged him with sloppy management of the National Surgical Adjuvant Breast and Bowel Project (NSABP). NCI has temporarily halted recruitment of patients into the breast cancer prevention trial, which, like B-14, is run by NSABP.

Finally, citing concern over tamoxifen's apparent link to endometrial cancer, physicians at Canada's Hamilton (Ontario) Regional Cancer Centre (HRCC) unanimously withdrew from the NCI study. When these clinicians explained why to the 80 volunteers enrolled there, 70 of the women also opted out.

Because the healthy women in the breast cancer prevention trial "cannot weigh the risk of this drug against a disease they already have, we're entering a very controversial and novel ethical arena," maintains Arthur L. Caplan, director of the University of Pennsylvania School of Medicine's Center for Bioethics in Philadelphia. These ethics involve not only the rights of healthy volunteers, but also medicine's special obligations to them, he contends.

Most individuals are invited to enter a clinical trial because they are sick and the agent or procedure under study may benefit them. But a disease prevention trial "flips who's the subject from the sick to the healthy," Caplan points out. "And it flips the intervention from one where you worry about whether the disease will kill you to where you worry about whether the intervention will cause harm, because you never know whether you would have gotten the disease."

Medical research can justify such "flips" if it offers healthy volunteers an extraordinarily high standard of risk notification and surveillance, Caplan believes. And while that's what NCI claims to be doing, Caplan says that's not always what women in the breast cancer prevention trial have received.

For instance, he charges, "[data on] deaths and side effects of tamoxifen have not been passed along in a timely way."

NCI notified prevention trial subjects in April of B-14's endometrial cancer findings. Observes Andrew Arnold, head of clinical oncology at HRCC, "there had been no mention of endometrial cancer deaths" attributable to tamoxifen 5 months earlier, when NSABP revised the prevention trial's protocol — a statement of research design, objectives, and risks. However, Arnold adds, "we know [NSABP] had [those] data" by that time.

But ousted NSABP director Fisher defended the program's data reporting in a September interview with ONCOLOGY TIMES. The B-14 study was only required to report new cancers yearly — and it did, he says. Moreover, he notes, while B-14's protocol required a reporting of deaths, "we weren't required and we never necessarily looked at the cause of those deaths." However, he adds, NSABP did report B-14 deaths "as soon as we knew that they were indeed due to endometrial cancer."

Though study leaders should not have to relay new risk data daily, Caplan says, participants "ought to know within a month or two that there's been a death or cancer of the uterus attributed to the drug they're taking." This definitely has not occurred, Caplan says.

The NCI breast cancer prevention trial also highlights the basic ethical dilemma any physician can face when conducting research on humans, points out surgeon C. Barber Mueller of McMaster University in Hamilton.

Clinicians possess a special license to do what it takes to heal a patient. Indeed, he notes, while diagnosing or treating illness, physicians may legally undertake actions that can result in pain, injury, even death. So medicine encourages the physician to become a risk taker, he says — but only within the context of trying to help an individual patient.

Clinical trials, in contrast, have as their goal what Mueller terms a "distributive justice." Here, subjects volunteer to accept the possibility of no personal benefit, and even of some personal harm, for the *community's* potential gain. This represents an inherent conflict of interest for clinicians dispensing drugs to healthy individuals. Most physicians resolve the conflict by thinking of anyone who is prescribed potent drugs as a "patient" undergoing treatment — and willing to take risks — rather than as a "subject" in an experiment, says Mueller.

Indeed, NSABP exhibited just that mindset when designing NCI's breast cancer prevention trial, according to a recently published 1992 Food and Drug Administration memo by Paul W. Goebel Jr.

Before entering a clinical trial, volunteers must sign a consent form indicating that they understand the potential risks and benefits of their participation. NSABP developed a model consent form that cancer centers could use or customize for their prevention trial recruits.

In his analysis of this model form, Goebel argues that "[u]se of the word 'therapy' to describe this [prevention] study is inappropriate, as it implies treatment of a disease." Indeed, his memo says, the "tone of the entire consent document conveys that the purpose of this

endeavor is treatment of patients" rather than diseasefree women.

That's dangerous, Mueller says, because it may imply that a volunteer stands to benefit from her involvement in the trial. And with clinical trials, there should be no expectation of individual benefit. When such an expectation is implied, he says, "it constitutes duress" — a form of coercion prohibited by the Nuremberg Code and many other post-World War II guidelines for experiments involving human beings.

There are other subtle — and most likely unintentional — examples of coercion in the consent document, Goebel charges. For instance, he says in his memo, because the consent form downplayed tamoxifen's toxicity while emphasizing its benefits, it resulted "in undue influence being placed on women to enter the trial." The consent form also refers to recruits in the first person. This, while making the document more personal, "tends to transfer responsibility for insuring informed consent from the investigator to the subjects," he adds.

Finally, Goebel's memo says NSABP can't claim it provided recruits full disclosure of their risks when "no mention is made that determination of the *safety* of tamoxifen for this use is one of the purposes of the study."

Goebel's memo "is a devastating indictment," Caplan says, and "probably the most disturbing document I've seen associated with the study."

FDA officials asked to approve the consent document apparently disagreed with Goebel's critique. A few days after the Oct. 28, 1992, memo was issued, they told NCI the consent form was fine.

The Hamilton center's withdrawal from the prevention trial raises several additional questions. For instance, Arnold notes that in a May 22 letter, physician Donald L. Trump — NSABP's acting executive director — urged the Hamilton clinicians to reconsider withdrawing from the trial. Arnold says he was asked to consider "the message which your institutional withdrawal could send to others."

Trump elaborated on his concerns in an interview with SCIENCE NEWS. "If I'm considering dropping out as an institution," he said, "I think I have not only the ethical obligation for assuring that my patients [subjects] are protected, but I also have an additional ethical obligation to the integrity of the study. Because what I do as an institution may affect women 3,000 miles away who have entered a study that now may be compromised by my decisions about the facts."

And, he said, "I'm reasonably certain that decisions were made [by HRCC] without benefit of the latest analysis of the risk-benefit profile" and other pertinent information, "such as the minutes of the End Results Safety, Monitoring, and Compliance committee." This panel of scientists and physicians from outside NSABP periodically reviews the prevention trial and its data. In fact, Trump says, the members have "reviewed information about other [nonbreast] tumors that might be associated with tamoxifen and have unanimously in the last 6 months on two occasions recommended that the trial continue. They found it was safe and ethical and a trial that was important to complete."

"I don't want to spoil trials," explains Arnold, "but there were extraordinary circumstances." As data on the risk of endometrial cancer emerged, he recalls, "we became very uncomfortable giving tamoxifen to women who didn't have cancer."


Dan Skripkar

Personally, he says, "I've no doubt that tamoxifen prevents breast cancer." But he notes that questions remain, not only about the magnitude of that effect, but also about whether any cancers that do develop in women taking the drug will prove more aggressive than normal (SN: 9/25/93, p.207).

This illustrates the understandable conflict between physician as healer and physician as experimenter, Mueller says — a conflict that may be resolved only by making clinical trials distinguish clearly between the two. He would like to see such trials undertaken only by individuals with no direct responsibility for a subject's care. Other physicians would then be appointed to look out for the volunteer's best interest — even if that meant eventually counseling a subject to withdraw midway through a trial.

The Canadian center's withdrawal landed NSABP in an even thornier ethical dilemma: having to decide whether to let dropouts know if they had received tamoxifen.

During double-blind studies such as this one, neither the recruits nor the experimenters know whether subjects are receiving the active agent or the inactive placebo. Only after the trial is over will researchers learn who got which.

Sometimes volunteers also learn at this time whether they got the active agent; other times they don't. There is no rule. But Trump did say that NSABP does not plan to inform volunteers of their status when the prevention trial ends.

Caplan argues that in studies like this one — where a potent drug is dispensed to healthy volunteers — there ought to be a scheduled disclosure to each subject.

Why? These women may have been placed at increased risk of certain adverse health effects — enough so to warrant close medical follow-up in subsequent years.

Indeed, most women who withdrew from the prevention trial at HRCC this year asked Arnold to track down their status. He relayed that request to Trump in May and again in June. But it was only during a July 8 phone call that Trump finally agreed, he says — and then only for those who requested their status in writing. In late August, Arnold forwarded to Trump some 60 letters making such a request.

Asked whether dropouts from other centers also can learn whether they received the drug or a placebo, Trump said, "we've operated under the assumption that if the patient [subject] does want to know, we would give her that information." However, he added, "we're not advertising that."

Caplan argues that the breast cancer prevention study's reliance on a powerful drug to treat healthy women constitutes a unique venture in U.S. medical research. But he also suspects it won't remain unique for long. "And that's why it's important that it get close scrutiny," he maintains.

Because of the special obligations medicine has to the healthy volunteer — someone who participates in a trial for altruistic reasons, and often in the hope of benefit — special safeguards, reporting standards, and reviews may be necessary, Caplan says.

He says it's tempting to try to turn such responsibilities over to institutional review boards (IRBs), panels at individual medical centers charged with approving human studies. However, he adds, many IRBs would not be up to the task. With participation largely voluntary and budgets sometimes nonexistent, he says, "they just don't have the resources to do much more than they are doing today" — usually screening proposals and approving new studies.

If that's true, says Caplan, the federal structure for managing this new breed of clinical trials may need an overhaul. □