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Experts offer blueprint for improving a research staff education program

Education is the foundation for protecting subjects

For clinical trials administrators and investigators who desire best practices in human subjects protection, there can be no better place to start than with research staff education.

Education and training of research staff and investigators traditionally was provided in the form of a mentoring program in which a junior person learned from a senior person, says **Ruth Fischbach**, PhD, MPE, director of the Center for Bioethics at Columbia University in New York City.

"The mentor was supposed to be an advisor or teacher or role model or motivational friend and supportive advocate," she explains. "All the research values were transmitted from mentor to mentee. But now — particularly in busy labs where the principal investigator is off giving talks around the country or writing grants — sometimes the teaching is left to a junior person."

This is one reason there should be a formal education program for clinical trials staff, Fischbach and other experts note.

"We see education as the foundation for human subjects research, and clearly there can be no expectations of an individual to follow rules or ethical principles and policies if they don't know what the rules and principles are," says **Steven Peckman**, associate director for human subjects research at the University of California-Los Angeles (UCLA).

"So we consider education to be a cornerstone, and it is multifaceted," he says. "We work with all entities on campus, and we have specifically designed an education approach for different areas — not a one size fits all." **(See story on alternative educational strategies, p. 63.)**

Diversity improves effectiveness

The best approach is to offer a wide range of educational programs, suggests **Jeremy Sugarman**, MD, MPH, MA, a member of the faculty at the Phoebe R. Berman Bioethics Institute and the

department of medicine at Johns Hopkins University in Baltimore.

"Education should include discussion, lectures, web-based programs, and reading material," he adds.

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Editorial Questions

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Here are some suggestions for improving or developing a staff education program:

• **Offer basic training on human subjects research for new staff.** UCLA's education for new investigators and others begins with a session on the history of human subjects protection, institutional responsibility for protection of subjects, researcher responsibilities, and IRB responsibilities, Peckman notes.

"We talk about the construction of the IRB, who's on it, and how it works," he says. "We talk about the Belmont report, the Declaration of Helsinki, and how those principles inform what the IRB and investigators do," he says.

An educator provides investigators with real life scenarios in clinical trials and discusses the informed consent process and how to balance risks and benefits.

"We talk about the hot point issues of the day, such as how to create, submit, and carry out placebo-controlled trials," Peckman says. "We talk about conflicts of interest and the conduct of Phase I trials, which we do quite a bit of here at UCLA."

This first training session also includes a discussion of therapeutic misconception, and the educator may hand out articles written by experts on how people sometimes confuse a clinical trial with clinical treatment, he notes.

"What we see is the majority of complaints in human subjects trials is when there's confusion about the researcher and treatment," Peckman says. "Subjects should be very clear in their understanding of that before enrolling and during the trial."

Initial education also will cover Food and Drug Administration (FDA) guidelines, the regulatory and ethical framework for research, and how investigators can look at placebo-controlled trials in view of ethical principles and the risk-benefit analysis, he adds.

"There's an urban mythology that IRBs don't approve placebo-controlled trials," Peckman notes. "That's not true, but the placebo-controlled trial has to be ethically justified."

• **Use role-playing and other strategies to enhance learning experience.** It's estimated that people who are taught information in a lecture format will retain about 20% of what they hear, Fischbach says.

Alternately, when people are encouraged to actively participate during an education experience, they may retain 80% of what they hear because the process encourages their buy-in and

discourages daydreaming, she reports.

"A lecture is efficient for the instructor because the instructor has an idea of what he or she wants to convey in a short period of time and can do that without interruption," Fischbach says.

But it doesn't always work for the students, she adds.

"Especially with adult learners, we're finding that active participation in the learning process is advisable, and one strategy to accomplish this is using case-based, problem-oriented situations," Fischbach says. "You can use hypothetical cases or with discretion you can use the actual cases, protecting the identity of people."

The idea is to facilitate the students' relating to how solutions worked out in the theoretical situations may be applied to their own setting, she explains.

Role-playing is a strategy that lightens the educational atmosphere and may result in better understanding of human subjects protection, Fischbach says.

For example, one role-playing session involves the situation in which a postdoctoral fellow is shown an unpublished manuscript that the professor was asked to review. Ethically, the manuscript is not supposed to be shown to anyone other than the reviewer, but sometimes professors may see a solution that would assist a student and will show the person the manuscript for that reason, she says.

In the role-playing session, students were asked to turn down the professor's offer to see the paper without appearing to be ungrateful, Fischbach adds.

During the session, students came up with several original strategies for tactfully handling this ethical dilemma.

Some time later, Fischbach was told by a student how she attended this role-playing class and then returned to her lab where the lab director offered to show her an unpublished paper that he felt might help her. The student recalled one of the role-playing strategies and used that when she turned down the lab director's offer, recalls Fischbach.

The strategy worked, and the lab director then told the student he was grateful for her candor and hadn't thought about it that way, she adds.

Web-based training offers more flexibility

• **Provide web-based training when appropriately.** One of the chief advantages to a web-based education program is that it is a flexible learning experience for busy people.

"People are very busy and getting them to show up at a specific time is difficult," Sugarman says. "[Web-based programs] provide education that's available whenever anybody wants it."

The other advantage is that web-based education can be offered inexpensively and can easily be kept current over time.

For instance, Durham, NC-based Duke University, using a grant from the U.S. Department of Energy, developed web-based education modules on genomics and ethics that are available free of charge to the public, Sugarman reports.

Many other groups and organizations also offer web-based research education for free or at affordable prices as well.

UCLA and some other universities have web-based, human research certification programs that are institutional requirements for human research staff.

"Our research staff are required to take our certification course because it has a lot of information that's specific to UCLA human research negotiation and the IRB review," Peckman says. The web-based certification program is on-line at www.training.arc.ucla.edu.

Columbia University has a web-based seminar on conflicts of interest at www.ccnmtl.columbia.edu/projects/rcr/rcr_conflicts, Fischbach notes.

"The learner can click on the web page whenever there's time, and I think that convenience is very helpful," she says. ■

Learning can go beyond traditional classroom

Here are some innovative teaching ideas

Sometimes, the best teaching strategy is one in which the student is not even aware that he or she is a student.

At least that's the approach that one research educational program has tried and found to be successful.

"What I find useful in these situations is to try to recruit investigators to be instructors," says **Ruth Fischbach**, PhD, MPE, director of the Center for Bioethics at Columbia University in New York City.

"So they'll do their homework in preparing to teach, and this is a helpful strategy," she notes.

Educational content and approach should be tailored to the student audience, and with human subjects protection the audience can vary between medical students, postdoctoral fellows, faculty, IRB members, investigators, clinical trials staff, and others, Fischbach says.

"Often you overestimate what you think people know," she says. "So ask each group some basic questions to assess where they're at, and then base your teaching and education from there."

Determine knowledge gaps

Another issue is attracting principal investigators to educational seminars when they may not see that as a priority. One way to do this is to hold faculty development sessions that cover the latest changes in regulations or practice, Fischbach says.

"Most recently, we've had a successful conference at Harlem Hospital, supported by a National Institutes of Health [NIH] grant ward, to look at privacy, confidentiality, and conflicts of interest as relevant to an inner-city population," she says. "We invited Harlem faculty to be instructors, and we had lectures and workshops where the topics were coordinated."

This way, attendees would hear a lecturer speak about a specific topic and then have an opportunity to discuss it and relate it to their own situations during the workshop that followed the lecture, Fischbach notes.

During the workshops, participants would teach each other.

"Often someone there would say, 'I just had that happen last week, so how did you resolve that?'" Fischbach recalls. "So it would be a real workshop without just having people sitting around listening."

The workshops would use overhead devices and educational aids, and even include situations in which workshop participants could instantly vote through a handheld device on which they could select answers to questions or problems that are presented, she notes.

"You could ask a question of what they thought is the limit of equity holdings that a principal investigator can hold before having to disclose it to the IRB based on the NIH regulations, and then have participants select an answer," Fischbach explains.

Based on how many participants had the correct answer, the workshop educator could provide more or less instruction on this issue, she adds.

"This is a good strategy for getting people to talk, and if interesting issues come up they can bring what they learned home and discuss it over the family dinner," Fischbach says.

It's also important to vary the way education is handled in order to keep it timely, interesting, and effective.

At UCLA, one of the ways researchers are kept up to date on new policies and other timely information is through newsletters, says **Steven Peckman**, associate director for human subjects research at the University of California-Los Angeles (UCLA).

Another educational approach is to hold small group sessions in which participants sit in a circle and discuss their current research, he says.

"A large group can't do that," Peckman notes. "We're focusing on group needs rather than a one-size-fits-all program."

Some alternative educational strategies used at Columbia University Center for Bioethics include showing films, followed by a discussion, Fischbach notes.

Films might include PBS shows on research or short takes that were created to illustrate research ethical dilemmas, she says.

Provide quick updates

"One thing that faculty have to be aware of is that if you continually provide educational experiences that are very boring, that are meaningless and not relevant to what people are doing then you will turn off your learners so fast, and the next time you have a session people will be very reluctant to come," Fischbach says.

At UCLA, research educational updates are coordinated with each department, Peckman reports.

"The department keeps track of what is going on with the research portfolio and tells us which things they need and want us to come over to talk about," he says.

"Often, we'll see trends and try to be helpful," Peckman says.

For instance, one common problem is assuring appropriate compliance with the privacy regulations under the Health Insurance Portability and Accountability Act (HIPAA), he notes.

"HIPAA applications are not being filled out with enough information for IRBs to make decisions, and that's delaying projects," Peckman says.

Also, the biggest area of confusion nationally involves the recruitment of subjects and the confidentiality of medical records, he says.

"Investigators who are not involved in the care

of a patient do not have the legal authority to go through medical records in order to identify and recruit subjects," Peckman says. "Just because they're a physician does not give them the right to do this, and there's a risk of a breach of patient confidentiality if they do it."

These issues should be covered in educational sessions designed to provide updates to investigators and to prevent some of the more common problems.

"Fifteen years ago, we didn't have to deal with the issues coming out today," Peckman notes. "The research field is changing, and the way we look at it ethically, philosophically, and legally also is changing." ■

NIH's genetic info data system goes on-line

System was launched this spring

The Genetic Modification Clinical Research Information System (GeMCRIS), a web-based data system designed to assist researchers and others involved in human gene therapy studies, manages information about science and safety of clinical trials in this field.

Three years in development, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) jointly launched GeMCRIS at the end of March.

"There were several reasons for developing GeMCRIS," reports **Allan Shipp**, director of outreach in the Office of Biotechnology Activities at NIH.

"It gives the government agencies that have oversight in this area a tool to do cross-cutting analyses," he adds. "So it helps us do our job of oversight of safety."

Investigators involved in human gene transfer protocols conducted at institutions with NIH funding for recombinant DNA research already are required to register with NIH. With GeMCRIS, they may electronically report their AEs to NIH through an AE-reporting module, says **Kelly Fennington**, project officer at NIH.

"When a principal investigator [PI] reports an adverse event, the system is loaded with information about the protocol so that the principal investigator doesn't have to retype that information," she says.

NIH and FDA officials worked collaboratively to develop an adverse reporting format that investigators and sponsors can use to report AEs. This form contains data elements agreed upon by both NIH and FDA so investigators can use one form to report to two federal agencies. This form also can be faxed or sent to their IRBs, their data safety monitor boards (DSMBs), institutional biosafety committees (IBCs), and other oversight bodies, Fennington explains.

The system does permit PIs to delegate the AE reporting to a clinical trials coordinator or to someone else involved with the study, Shipp notes.

"But we expect a signed letter of delegation, and we hold the principal investigator responsible for whether the information has been reported," he says.

Designed to make AE reporting easier

A key role of GeMCRIS is to facilitate AE reporting, making it easier for investigators to adhere to the requirements that serious adverse events are reported on an expedited basis, Shipp notes.

"Serious adverse events that are unexpected and thought to be related to the gene transfer intervention have to be reported within 15 days of a principal investigator's notification of a sponsor or within seven days if the event is life-threatening or involves death," he says.

"A registered principal investigator would have a user ID and password and would go to our secure GeMCRIS site," Shipp explains.

Once the identification information is typed in, the system presents the investigator with a form that asks for all of the information that is required by the NIH and FDA agencies, he adds.

NIH beta-tested GeMCRIS for a year before launching the system publicly, Fennington says.

So far, the feedback has been positive, Shipp reports. "We received feedback that helped in designing the system in the beta-testing, including its ease of use as a reporting tool," he says. "As we developed this system, we conducted focus groups with different potential end users: one for investigators, one for patients, one for IRB/IBC members."

GeMCRIS also provides the public access to a rich set of data about gene transfer trials.

Clinical trials subjects, their families, investigators, IRB members, and others may see everything collected in the system except for the raw adverse event data. There is no need for registration or a

password to access this public information, Shipp notes.

"Previously, we had information about trials in our system, but it wasn't in an interactive database," he says. "It was a very rudimentary database, and the information was more limited than what you see in the GeMCRIS."

Once someone visits the web site, it's a simple matter of going through the site's search engine in GeMCRIS and then selecting from the available data, Fennington says.

Researchers, patients, and others are able to pull up information about clinical applications; investigational strategy, including what vector is used; the gene transfer product; route of administration; a scientific abstract that allows one to view the overall scientific strategy, and a nontechnical abstract that is written at a level that could be understood by an educated layperson, Shipp says.

For example, a clinical trial listed on the site for gene therapy to treat prostate cancer offers these descriptions in the scientific and nontechnical abstracts:

- **Scientific abstract:** "Direct introduction of therapeutic genes into malignant cells in vivo may provide an effective treatment of solid tumors such as adenocarcinoma of the prostate. The herpes simplex virus thymidine kinase (HSV-tk) gene codes for an enzyme which phosphorylates the nucleoside analog ganciclovir (GCV) into an intermediate that is incorporated into newly synthesized DNA and terminates further replication, leading to cell death. . . ."
- **Nontechnical abstract:** "Direct introduction of therapeutic genes into tumor cells may provide an effective treatment of prostate tumors. One strategy is to confer drug sensitivity to tumor cells by inserting a recombinant gene into them. This gene is from the common herpes virus and codes for the enzyme thymidine kinase (HSV-tk). Thymidine kinase converts the antiviral drug ganciclovir into a form that is toxic to rapidly dividing cells such as tumor cells."

GeMCRIS has several features that make it easy for investigators or their clinical trials representatives to report AEs.

For instance, when an investigator types in an ID number and password, the pre-formatted report pops up with all of the information that already has been reported about the particular trial, Fennington explains.

After the initial AE report has been filed, an investigator may return to GeMCRIS to type in follow-up information. "The previous adverse event information pops up, and all they have to do is type in information that has changed," she says.

If an investigator is interrupted in the middle of filing a GeMCRIS AE report, then it's possible to click on a "pending" icon so that the report is saved, but not entered as final data until the investigator returns and completes the report, Shipp says.

Standardized reporting

Another value of GeMCRIS is that it allows for reporting and analysis of adverse events in a more standardized way. Prior to GeMCRIS, adverse events were submitted in various formats and could not be standardized for analysis, he explains.

"Often, they were reported on MedWatch forms or templates or the back of a cocktail napkin or whatever," Shipp says.

Since the reporting previously was so open-ended, NIH officials often had to call investigators to obtain necessary details, he adds. "Through standardized vocabularies and data elements, reports are clearer and are more easily compared and analyzed."

It's a much richer data set than can be worked through in such a way that yields much more helpful information, tailored to the information needs of end users, Shipp notes. "GeMCRIS is an important new tool to make investigators' lives easier and to help us do our jobs better." ■

Canadian group studies ethical use of placebos

More stringent requirements recommended

When should placebos be used in clinical research? Can subjects with a medical condition be asked to consent to withdraw from their current medications and take an experimental medication — with the 50/50 chance that what they actually receive will be no medication at all?

Or should placebos only be used in trials of a therapy in which there is no acceptable alternative, or the currently accepted therapy is not effective?

That's the dilemma tackled by a group of ethicists, attorneys, clinicians, pharmaceutical representatives, and lay volunteers who agreed to work on Canada's National Placebo Initiative.

Launched in 2001, the initiative was charged with resolving an essential difference in the two placebo policies used in Canadian research and make recommendations for a common uniform placebo policy.

"The policy used by Health Canada differs significantly from the policy used by the three major funding agencies sponsoring clinical research," explains **Kathleen Cranley Glass**, LLB, BCL, DCL, director of the biomedical ethics unit at McGill University in Montreal, and a member of the committee charged with developing recommendations on the new policy.

Currently, the research governance and standards for the review of clinical trials in Canada can follow one of two approaches. One approach is the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans,* published in 1998 as a joint policy initiative by the Medical Research Council of Canada (now Canadian Institutes of Health Research, CIHR), the Social Sciences and Humanities Research Council of Canada (SSHRC) and the Natural Sciences and Engineering Research Council of Canada.

The other approach, used by Health Canada, is to follow Canada's Clinical Trial Regulations and international guidelines, such as those produced by the International Conference on Harmonisation (ICH), a 1990 international agreement on human subjects protections developed by representatives from the United States, Japan, and Europe.

Essentially, the funding agencies have taken the approach of requiring "clinical equipoise" in research — permitting the use of placebo only when there is no "established effective therapy" for the condition being studied, Glass says.

The approach supported by Health Canada — and reflective of the ICH policy — is one that considers the "level of risk" and would allow the withdrawal of commonly accepted therapy to subjects, provided subjects are given full informed consent and will not face risk of death or serious injury during the trial.

To study the issue, Health Canada and CIHR established a joint initiative in the spring of 2001 and established the National Placebo Initiative and the National Placebo Working Committee (NPWC). The NPWC brought together an expert group of interested individuals who researched, discussed and debated the placebo issue in an attempt to arrive at a consensus around recommendations about the appropriate policy for Canada.

The members of the NPWC included a clinical trial nurse, a citizen representative, an ethicist, a health attorney, a patient advocate, a designated person with process experience in conflict resolution, a representative from the pharmaceutical industry, a principal investigator, a representative from the regulatory and public health sectors, a member of a research ethics board (the equivalent of IRBs in the United States), a statistician, and ex officio representation from Health Canada and CIHR.

The committee then established six subcommittees to address the different issues in the debate. These six subcommittees were dedicated to: citizen issues, scientific issues, ethics, legal perspective, regulatory perspective, and a research ethics board subcommittee.

Each subcommittee provided a section of the final report giving background, history, and perspective on the issues in its area related to placebo use and making policy recommendations based on its perspective.

The NPWC then combined all perspectives and developed overall draft policy recommendations.

Background

According to the background provided in the Canadian report, the beginning of the debate on the use of placebos in research largely began in 1964, when the World Medical Association published its *Declaration of Helsinki*: *Ethical Principles for Medical Research Involving Human Subjects*. The declaration recognized that research is often conducted in the context of clinical care, the report notes.

The declaration also addressed the issue of withholding established therapies by requiring that "in any medical study, every patient — including those of a control group, if any — should be assured of the best proven diagnostic and therapeutic method." While the word "proven" was the cause of some controversy and confusion, read literally, the requirement would have prohibited new research, since "unproven" therapies could not be tested. However, the intent of the statement is clear, that is, that effective therapy should not be withheld from patients seeking care, the report states.

For almost two decades after that declaration, research ethics followed a doctrine of clinical equipoise — the rationale that patients should not be disadvantaged by entering a trial in which treatment is randomized when there is no consensus in the expert community about the preferred treatment for the patient population under study, making the arms of the trial medically and morally

equivalent. This means that a placebo arm is acceptable if there is no established, effective therapy.

However, achieving a consensus among experts on what therapies are established has never been easy, Glass notes. And over the years it has become increasingly clear that clinical trials featuring the use of placebo — even when other common therapies were available — often were occurring.

The 1960s and 1970s saw an increase in the quantity of regulation surrounding all aspects of new medical products. In the 1980s, the *International Conference on Harmonization (ICH)*, a group including regulatory authorities and representatives from industry from the United States, Japan, and Europe, established the rules that currently act as guidelines for Health Canada regulators.

The ICH-E10 guideline limits the use of placebo controls to trials in which there is no known proven effective treatment that is "lifesaving or known to prevent irreversible morbidity."

In 2002, in a controversial move, the World Medical Association also added a "Note of Clarification" on paragraph 29 of the *Declaration of Helsinki*, allowing for the use of placebo controls even if "proven therapy" is available, "where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm."

NPI recommendations

The NPWC published its initial draft report in April and has since revised the draft once based on comments it received. The changes, though, were largely to clarify what was stated and no substantive changes in the recommendations were made, Glass says.

Overall, the committee has recommended more of a return to the doctrine of clinical equipoise and a shift away from the concept that participants in a clinical trial could ethically withdraw from their current medications if no serious harm would result, she adds.

It is the approach that Glass finds most appropriate, given that clinical research does most often take place within the context of clinical care.

"Obviously, I come from a background in ethics and the law, and do not have a background in pharmaceutical development, science, or medicine," she notes. "But I have studied the law and the ethical perspective, both here and in the United States, and I could not find any perspective which would allow a physician to step back from his or her moral obligation to provide care and permit the withholding of appropriate treatment — even if the patient/subject were to knowingly consent."

She was surprised, however, at the diversity of opinion within the members of the committee — particularly the patient and citizen representatives, both of whom expressed opposite opinions.

The patient representative supported an environment in which placebos could only be used when physicians determined that no other effective therapy for the condition was available. However, the citizen representative wanted the opportunity to participate in placebo-controlled trials under any circumstances, as long as full informed consent was given about the risks and the actual availability of other therapy.

"His attitude was that he should be given all of the information about the trial, its purpose, what other therapies were available, etc., then the decision about whether to participate should be left up to the individual subjects who might be enrolled," Glass says.

Experts across the spectrum shared the citizen representative's opinion, from regulators to clinical investigators to pharmaceutical representatives, she says.

"I think people honestly differ in opinion on this matter — aside from any financial incentives to further research," she notes. "It is not as if the pharmaceutical industry and others, motivated by profit, is pushing for more use of placebos."

The difference in opinion between the two community members of the committee indicates that the public also is divided on the issue, she notes.

However, Grass says, the committee ultimately felt that there had to be some limit to what patient subjects could consent to, and it was the responsibility of REBs and IRBs to first consider whether a placebo-controlled arm would be appropriate before allowing subjects to be asked to consent.

"Our approach believes that the first step should be for the REB to determine, 'Is this an appropriate study to conduct in humans? Is it morally appropriate to use placebo in this case?'" she notes. "The second step should be full informed consent, whereas the other approach places informed consent first."

The NPWC currently is working on a final draft

of the report to given to Canadian authorities.

The proceedings are being closely watched by the research community in the United States, which also is debating the ethical use of placebo, says **Howard Mann**, MD, associate clinical professor of radiology at the University of Utah School of Medicine and a member of the school's IRB.

Guidance from the U.S. Food and Drug Administration and the Office of Human Subjects Research Protections supports the broader "level of risk" school of thought promoted by the Health Canada approach and the ICH, though the use of placebos is still controversial, he says.

Advocates for the withholding, or withdrawing, of effective therapy under certain circumstances include ethicists such as Franklin G. Miller at the National Institutes of Health and Michigan State University's Howard Brody (who have both called for the abandonment of the concept of clinical equipoise in randomized controlled trials), as well as drug regulators in the United States and Europe, and pharmaceutical and biotechnology companies, he adds.

According to Mann, the most compelling aspects of the recent Canadian effort were: a clarification of the notion of "established effective therapy" by the clinical epidemiologist and trialist David Sackett and a call for the use of systematic literature reviews in establishing whether "established effective therapy" for a particular condition exists; and literature reviews to support the choice of a control intervention for a randomized controlled trial; and a detailed clarification (and revision) to the guidance concerning the permissible use of placebos in trials.

The NPWC approach, which sought input and perspective from members of the public not associated with the research community or the pharmaceutical industry, also was interesting, Mann says.

"The perspectives of patient and health care consumers is generally not solicited when considering the social value of proposed biomedical research, or in informing research design, such as the choice of appropriate outcome measures for trials," he points out. "This is a pity. We [in the United States] need to encourage the creation of consumer organizations, such as Consumers for Ethics in Research in the United Kingdom, that will provide substantive input into the formulation, design, and conduct of clinical trials."

The draft report of the National Placebo Initiative is available on-line at: www.cihr-irsc.gc.ca/e/services/19301.shtml. ■

Cancer researcher calls for trial process changes

Fewer animal studies, more human trials

Current methods for studying new cancer drugs are too inefficient and costly, resulting in unnecessary delays in the development of new therapies, a noted cancer researcher told colleagues at recent international meeting of surgeons in Australia.

During a presentation at the 2004 Annual Scientific Congress of the Royal Australasian College of Surgeons, held May 2-7 in Melbourne, Australia, **Jonathan Lewis**, MD, PhD, a former cancer researcher at Memorial Sloan-Kettering Cancer Center in New York City and the New Haven, CT-based Yale University School of Medicine, called for changes in oncology clinical trial design.

"The methods by which we clinically develop drug candidates are dismally out of step with the tremendous progress in basic science and our ability to discover promising new compounds," Lewis told attendees. "The issues are cost and time. The current approach results in clinical strategies that prolong the time it takes to get to a possible 'yes' answer. Instead, we need to shorten the time it takes to produce a 'no.' The ability to quickly rule out unpromising compounds or ill-conceived indications could cut 50% or more off the typical time and money devoted to cancer drug development."

According to Lewis, research has shown that studies indicating a compound's efficacy in treating cancer in animals do not reliably indicate how well humans will respond. Yet, researchers still waste valuable time and money conducting many laboratory studies before attempting to move into early clinical trials.

"The current way of having a very rigorous process of step-by-step of cancer drug development is scientifically correct — we have no argument with that," Lewis says "I think, though, what has become very clear is that the use of the lab to understand how the drugs are going to work in humans has been shown in cancer to be worth very little. Animal models are much less predictive of what is going to happen in humans."

Laboratory research should be focused on determining whether a particular drug is too toxic for use in people. Once those questions are answered, however, he believes smaller, focused human trials will yield better information.

"The main issue, in the lab, is to make sure of the absence of any major toxicity. You have to be very sure of that in the research lab," Lewis explains. "But I think worrying about efficacy and so on, we put too much emphasis on that. If we have something that is valid, biologically, getting it into human studies sooner makes a lot of sense."

Once a drug is moved from the laboratory to clinical trials, scientists should use genotyping to identify certain people who would be expected to benefit from treatment, allowing investigators to conduct faster, smaller early trials that would yield more specific information.

Laboratory scientists currently do this with compounds by studying them in homogenous populations of laboratory mice, Lewis points out.

Genetics role

Research is increasingly showing that genetics plays a large role in predicting how patients will respond to different treatments. Patients with the same type of cancer will often respond very differently to the same treatment, he says, and genetics are a large part of the reason why.

For example, researchers at Dana Farber Cancer Institute and Harvard Medical School[1] recently discovered that certain patients with non-small cell lung cancer (NSCLC) respond dramatically to the drug gefitinib (Iressa). These patients' cancers harbor a malfunctioning version of a protein known as EGFR. Researchers in Japan have reached similar conclusions. Patients with NSCLC whose tumors do not contain the gene mutation that produces the altered protein do not respond as well.

The Dana Farber researchers are trying a new approach to studying cancer therapies. Scientists scan the DNA of cancer cells for mutated genes that instruct cells to produce abnormal versions of growth proteins known as tyrosine kinases. The theory is that drugs known to block such proteins could slow tumor grown while leaving normal cells intact.

To test the theory, researchers analyzed tumor samples from patients who had been successfully treated with Iressa and four patients whose tumors did not respond. All of the responders had the mutation; none of the nonresponders did.

In the future, scientists should be able to use such genotyping to target which patients are most likely to respond to an experimental treatment and then study the drug in these patients first.

Lewis is the founder and chief executive of a new company, ZioPharm Inc., which plans to develop and commercialize anticancer compounds. ZioPharm intends to embrace this new approach, he says.

"Of course, there is no question that the gold standard, prior to [a drug's] approval, is and has to be the large, randomized Phase III clinical trials," Lewis says. "But if one moves to those too quickly, it proves to be inefficient. What we are going to be doing, is trying very hard to get a more homogenous group of patients, first."

Lewis contends that too many ineffective drugs get moved too quickly from Phase II to Phase III studies, which are larger and very costly to conduct. When a drug shows little or no promise in Phase III trials it is often abandoned, when, if problems had been discovered earlier during smaller studies, the compound could either be revised or abandoned early.

"We are seeing too many bad therapies going too far," he notes. "We do see things fail after several trials. At the same time, there is often an emotional thing in clinical research that goes on that keeps pushing things forward at tremendous cost and effort, only to fail in the end."

Such a system increases the costs of research and exposes many subjects, unnecessarily, to drugs that won't help them, he contends.

Statistics from the U.S. Department of Health and Human Services indicate the low productivity of cancer research dollars, Lewis says. The statistics show a 5.3% drop in cancer mortality between the years 1995 to 2002, but heart disease mortality dropped 14.4% during the same time period.

Not as simple as it looks

Changes do need to be made in the clinical trial process for cancer treatment, agrees **Mark J. Ratain**, MD, a specialist in hematology and oncology and chairman of the committee on clinical pharmacology at the University of Chicago Hospitals. And too many drugs get to Phase III trials.

However, Lewis' proposals have some flaws, he notes.

First, while animal efficacy studies may not be very beneficial for small-molecule drugs, the same cannot be said for other therapies, he states. He would want to see some demonstration in animal models that the drug would be active in a living being before moving into human trials.

"Just because it works in cell culture doesn't mean it is going to work in humans; but, then, I don't know what he specifically he is proposing," he says. "And there are too many drugs in clinical

trials now to say that we ought to have more drugs move to the clinic faster."

It is important to keep the Dana Farber research in perspective, he adds. The scientists there were studying the effects of Iressa in patients after the drug had already been approved by the U.S. Food and Drug Administration, and the researchers knew ahead of time which patients had responded and which had not responded to treatment.

It would be much more difficult for scientists to scan the DNA of prospective trial participants before they really knew what they were looking for, he adds. "That is great if you know the answer before you start. I didn't hear anyone saying we should look for EGFR somatic mutations before we give patients Iressa. That correlation was discovered after the drug was approved. If we knew the answer before we started, we would have done it that way."

Operating on assumption

Even if you suspect there are certain patients who will respond to the drug better, you are still dealing with a hypothesis that must be tested. And in oncology drug development, history has shown that many drugs do not work the way they are initially expected to.

Researchers often proceed using many assumptions about what a particular drug will target and how it will work, only to have later clinical trials show the drug works, but against other targets — either instead of or in addition to its intended target — and in different ways, Ratain says.

For example, drug developers initially did not expect Cisplatin to be effective against testicular cancer, and the drug was nearly abandoned because of the high rates of renal failure among trial subjects taking the drug. However, a patient with advanced testicular cancer was included in a Phase I trial and unexpectedly responded well to treatment.

Several other drugs have been shown to work in ways that scientists did not originally expect, and in populations they did not expect.

"I don't think we know anywhere near as much as we'd like to think we know, and there are so many assumptions that are being made that people accept without thinking about," he says. "Assumptions can range from targets, to dosing, to paradigms, to statistics. There is a lot of hand waving out there that is costing a lot of companies a lot of money."

Ratain says pharmaceutical companies and other drug developers should be more reluctant to take compounds to Phase III trials before there is solid evidence that the drug works.

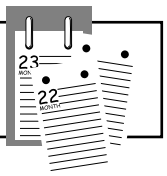
However, he contends that more people, with different conditions, should be included in Phase II trials, in order to more quickly determine how well the drug will work.

"Sometimes you just get lucky. That has been the history of cancer drug development," he continues. "There are few examples where the research was carefully planned and the careful plan worked. There have been numerous examples where it was carefully planned and it didn't. I think your chances of being right are often no better than your chance of just being lucky. I would say cast the net far and wide on top of your data and follow your leads and follow your gut."

Reference

1. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small cell lung cancer to gefitinib. *N Engl J Med*. Published on-line April 29, 2004. In press. To be published in the May 20 print edition of the journal. ■

CALENDAR



• **Mayo Clinic Fifth Annual Current Issues in Clinical Research, "Improving Clinical Research: Local Practice and National Issues,"** Aug. 26-27, 2004, Mayo Civic Center, Rochester, MN. For more information, call (800) 541-5815 or (507) 266-3074 or visit the web site at www.mayoclinicaltrial services.org/mact/mact-education.asp.

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CE/CME objectives

The CE/CME objectives for *Clinical Trials Administrator* are to help physicians and nurses be able to:

- review pertinent regulatory mandates;
- develop practical clinical trial oversight strategies;
- review best practices shared by facilities that successfully conduct clinical trials. ■

CE/CME *questions*

Physicians and nurses participate in this medical education program by reading the issue, using the provided references for further research, and studying the questions at the end of the issue.

Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

The semester ends with this issue. You must complete the evaluation form provided and return it in the reply envelope provided to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you. ■

21. According to experts on human subjects research protection education for clinical trials staff and investigators, which of the following teaching strategy is no longer adequate to effectively train and educate staff?
A. Research regulations seminars
B. Mentoring between principal investigator and junior staff
C. Research credentialing program
D. All of the above are no longer adequate.

22. GeMCRIS, a web-based data system designed to assist researchers and others involved in human gene therapy studies, was launched by which group?
A. The Food and Drug Administration
B. The National Institutes of Health
C. The Office for Human Research Protections
D. Both the FDA and the NIH

23. The primary reason for the Canadian National Placebo Initiative was:
A. To clarify existing Canadian research policy.
B. To develop a response to a U.S.-based research policy.
C. To reconcile two conflicting Canadian research policies.
D. None of the above

24. Some cancer researchers are planning to:
A. Study tumor DNA as a means of targeting patients who are more likely to respond.
B. Study tumor DNA as a means of developing new therapies.
C. Perform longer and larger Phase II studies before moving to Phase III studies.
D. None of the above

Answers: 21-B; 22-D; 23-A; 24-A.