# CLINICAL TRIALS ADMINISTRATOR

*An essential resource for managers of clinical trials*

AHC Media LLC


## IN THIS ISSUE




**Financial Disclosure:**
Editor Melinda Young, Editorial Group Head Lee Landenberger, Managing Editor Leslie Hamlin, and Nurse Planner Elizabeth Hill, DNSc, report no consultant, stockholder, speaker's bureaus, research or other financial relationships with companies having ties to this field of study. Physician Reviewer Stephen Kopecky, MD, is a consultant to GlaxoSmith-Kline and has a research affiliation with Bristol-Myers Squibb.

**FEBRUARY 2007**
**VOL. 5, NO. 2 • (pages 13-24)**


**Special Report: Protecting research participants**

*[Editor's note: In 2007, clinical trial professionals and human subjects protection advocates will mark the 60th year since the Nuremburg Code of International Ethics was created. The Nuremburg Code established the standard of informed consent and the risk versus benefit ratio in assessing research protocols. In honor of the Nuremburg Code's 60th anniversary,* Clinical Trials Administrator *is devoting this issue to how investigators, clinical trial professionals, and others in the human subjects research industry can more efficiently consider the protections of research participants when conducting clinical research.]*

# Component analysis is latest model for IRB review process, particularly with kids

*Model places greater demand on balancing risks and benefits*

A movement slowly gaining ground in North America suggests an alternative way to assess the risks and benefits of human subjects research, particularly when studies involve children.

Called component analysis, the method is different from the more commonly used collective analysis. It sets the IRB review bar a little higher by requiring a more stringent look at various pieces of a proposed study's protocol.

Investigators and clinical trial sites could find the IRB review process more rigorous than it is currently if greater numbers of IRBs begin to use component analysis.

The idea of component analysis was formed in the early 1990's in the Clinical Trials Research Group (CTRG) of McGill University's Biomedical Ethics Unit of Montreal, Quebec, Canada, says **Charles Weijer**, MD, PhD, an associate professor of philosophy and medicine and the Canada research chair in bioethics at the University of Western Ontario in London, Ontario, Canada.

"Some of the earliest parts of component analysis were formed in that group led by Benjamin Freedman, a well-known philosopher and thinker on ethics," Weijer says.

Freedman was the co-founder and director of the CTRG. He died in 1997.

Other groups have struggled with finding a way to conceptualize research benefits and harms, Weijer notes.

"The National Commission, which wrote the Belmont Report, and their view in the end, and report on IRBs, is quite close to component analysis," Weijer says. "So it's an idea that has strong historical roots in the U.S."

The question germane to the whole issue of component analysis is this one: Can anticipated direct benefit that is associated with one intervention in a protocol be used to justify the risks of another intervention? says **Ernest Prentice**, PhD, an associate vice chancellor for academic affairs at the University of Nebraska Medical Center in Omaha, NE, and chair of the Secretary's Advisory Committee on Human Research Protection (SACHRP) for the U.S. Department of Health and Human Services.

Under collective analysis, an IRB will assess the composite of all of the interventions detailed in a study and assess whether the use of interventions that do not provide a prospect of direct benefit is justified by the sum of anticipated benefits associated with those interventions that do have the prospect of direct benefit, Prentice explains.

"Collective analysis allows you to look at all of the risks in total, and if the potential risks are at least balanced by some of the potential benefits then you say the risk-benefit relationship of the research is acceptable," Prentice says.

Under component analysis, IRBs assess the potential harms and benefits of each intervention or procedure, he adds.

"The potential benefits of one component of the research should not be held to offset or justify the risks presented by another," Prentice says.

In the United States, component analysis is something that has been highly recommended for application to pediatric research, but not generally to research applied to adults, Prentice says.

Ideally, it would be applied to all human subjects research, Weijer says.

"It provides a comprehensive approach for competent adults, incompetent adults, and children," Weijer says. "It's such an important idea because until now IRBs have not had a structured approach to thinking through whether benefits or harms in a particular research study are acceptable."

Component analysis provides a clear, structured approach that can be applied to any protocol reviewed by an IRB, he adds.

"IRBs struggle with how to think through whether there are acceptable benefits or harms in studies," Weijer says. "A major challenge in IRBs has been in achieving consistency in review across IRBs."

Component analysis provides precisely the structure IRBs need, he adds.

Weijer's component analysis framework is discussed in an August, 2001, report by the National Bioethics Advisory Commission (NBAC), titled, "Ethical and Policy Issues in Research Involving Human Participants."

NBAC recommended in this report that an analysis of the risks and potential benefits of study

**Clinical Trials Administrator** (ISSN# 1544-8460) is published monthly by AHC Media LLC, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodicals postage paid at Atlanta, GA 30304. POSTMASTER: Send address changes to **Clinical Trials Administrator**, P.O. Box 740059, Atlanta, GA 30374.

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of 18 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

AHC Media LLC is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity has been approved for 15 nursing contact hours using a 60-minute contact hour.

Provider approved by the California Board of Registered Nursing, Provider # 14749, for 15 Contact Hours.

This activity is intended for research nurses and physicians. It is in effect for 36 months from publication.

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

**Subscriber Information**

**Customer Service: (800) 688-2421 or fax (800) 284-3291, (customerservice@ahcmedia.com). Hours of operation: 8:30 a.m. -6 p.m. Monday-Thursday; 8:30 a.m.- 4:30 p.m. Friday.**

**Subscription rates:** U.S.A., one year (12 issues), $299. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for multiple subscriptions. For pricing information, call Steve Vance at (404) 262-5511. **Back issues**, when available, are $50 each. (GST registration number R128870672.)

Editor: **Melinda Young**.
Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@ahcmedia.com).
Editorial Group Head: **Lee Landenberger**, (404) 262-5483 lee.landenberger@ahcmedia.com).
Managing Editor: **Leslie Hamlin**, (404) 262-5416 (leslie.hamlin@ahcmedia.com).



AHC Media LLC

**Editorial Questions**

Questions or comments?
Call **Leslie Hamlin** at
(404) 262-5416.

components should be applied to all types of covered research and that each component of a study should be evaluated separately, and the risks should be both reasonable and justified by the potential benefits to society or the participants.[1]

Prentice says that SACHRP looked at component analysis and made this recommendation: "Each research procedure in a study must be evaluated independently in terms of potential benefits and risks to subjects. Different procedures in a single trial may be approved or disapproved under different subpart D categories."

Subpart D is the additional protections for children involved in research, Prentice says.

"If we go back in history to the National Commission's work in 1978, in their report of recommendations for additional protections for children involved in research, they also recommended that we utilize component analysis when assessing the risk-benefit analysis of research involving children," Prentice explains.

"It's because of the vulnerability of children," Prentice says. "Why should we ask children to accept a certain element of risk when there's absolutely no benefit associated with that procedure?"

For example, a randomized clinical trial evaluating drug A versus drug B in pediatric subjects, ages four through 12, has a non-therapeutic component of pharmacokinetic (PK) testing, Prentice says.

The PK testing is not going to be used to alter dosing, and it's done purely for scientific purposes with no associated direct benefit to the child, he adds.

The protocol could be divided into two main elements: one is the administration of drug A or drug B, both of which have the prospect of therapeutic benefit; the second part is the PK testing, which has no prospective benefit.

The PK test will involve an indwelling, intravenous catheter, serial blood sampling, and an overnight hospitalization of the children, Prentice adds.

Under collective analysis, an IRB might find that the risk posed by the PK testing is justified by the anticipated direct therapeutic benefits of the drugs studied in the trial, he says.

"It's only that element of the research that has any prospect of direct subject benefit," Prentice notes. "You add up the risks of the drugs and risks of the PK testing and ask whether they are outweighed or at least balanced by the anticipated benefits of the drugs."

If an IRB uses collective analysis and says that the risks in total are outweighed or balanced by the potential benefits of the drugs, then the IRB can approve the study under a category of subpart B involving research with greater than minimal risk but offering the prospect of direct subject benefit, Prentice explains.

On the other hand, if an IRB uses component analysis and breaks the study down into each intervention, then the review might find that the risks of drug A and drug B are justified by the anticipated direct benefits of the drugs, Prentice says.

But the anticipated benefits of the drugs cannot be used to justify or balance the PK testing.

"You have to look at the PK testing separately," he says. "So the first thing you have to say is, 'What are the risks of PK testing?'"

Risks involve the indwelling intravenous catheter, periodic blood sampling, and the overnight hospitalization.

Since the pediatric subjects in this theoretical case are sick enough to need drugs, one could argue that the indwelling IV catheter and serial blood sampling are a minor increase over minimal risk, Prentice says.

"One would have to then judge whether or not whatever data they get from PK testing is of significant importance — how important is it to do this on kids?" Prentice says. "It's an add-on, and in research we have a lot of add-ons, and you're taking advantage of the availability of the subject population, which is undergoing certain procedures."

IRBs typically review a study's add-on with the "sniff" test, Prentice notes.

"They probably are not applying component analysis, but are asking, 'Why does the investigator want to do this, and is it justified?'" he says. "A lot of IRB members have never heard about component analysis."

However, it's increasingly being used in pediatric research, Prentice says.

One of the reasons why component analysis is catching on is because of a fundamental aspect of clinical research: it often contains a mixture of procedures and some of those procedures hold out the possibility of direct benefit for research subjects, and others are done solely for scientific purposes, Weijer says.

"Allowing therapeutic benefit in a study to compensate for large amounts of nontherapeutic risk would be a very significant problem in a study where the possibility of excellent treatment allows you to do a lot of things to people for nontherapeutic purposes," Weijer says. "By separating these components out, it allows the IRB to separate their analysis of these two kinds of procedures."

Component analysis allows IRBs to focus on the incremental risk associated with study participation, Weijer adds. ■

Reference:
1. Ethical and Policy Issues in Research Involving Human Participants. National Bioethics Advisory Commission. Vol. 1 Report and Recommendations by NBAC. August, 2001:77.

**Special Report: Protecting research participants**

# WHO network and standards for existing trial registries

*Registries may help research participants*

Fifty-two health ministers met in Mexico in May, 2005, at the 58th World Health Assembly and decided to establish a network of clinical trial registries and a single search portal.

Known as the Mexican Statement, the result was recommendations for registration and a voluntary platform that links clinical trial registries across the globe, says **Davina Ghersi**, MPH, coordinator of the World Health Organization's International Clinical Trials Registry Platform in Geneva, Switzerland.

One of the chief purposes behind clinical trial registries is to provide accountability and greater transparency to the research process, giving potential research participants and the public access to some basic information about trials from a study's beginning to its end.

"The key thing about WHO's effort is that we're not creating a trials registry, but creating a network of existing trials registries," Ghersi says. "And we're developing norms and standards for registries so they can all share information in a uniform way."

The registry platform is in an early stage, and WHO still doesn't know how many registries exist, although the key registries are in the United States (www.clinicaltrials.gov), the United Kingdom, and Australia, Ghersi says.

Also, the platform has created a list of 20 dataset items that should be included for every study on a registry. **(See WHO's 20-item dataset, p. 17.)**

Clinical trial registries are a small response to publication bias.

"Publication bias is when you select whether or not to publish your trial, and you select which information to publish in the study," Ghersi says. "We've known for a long time that you're more likely to publish your trial if it has significant, positive results."

But now with more of a focus on evidence-based medicine and the increased activism of consumer groups, the public wants better information with which to make informed decisions, Ghersi says.

"It's difficult to make a decision when you're only told one part of the story," Ghersi says. "And from the journals' perspective, there is limited space and they can't publish everything."

With the Internet and electronic publishing, there is the potential to make a great deal more information available to the public, and this is where open access, online journals, such as those published by the Public Library of Science come in handy, Ghersi notes. **(See article about open access journals, below.)**

Clinical trial registries are the second part to the solution because they let scientists and the public know about studies that were initiated but, perhaps, never reported at conclusion. Also, online journals that publish such registered studies can provide links to these initial registries and people can draw conclusions based on differences between what was initially presented versus what was finally reported.

"There are studies that would never be reported because they may not be significant, or they may be small," Ghersi says. "They're the ones we need to know about, and that's where registries can be useful."

In the long run, it will be consumers who dictate how much information will be made available with regard to research, Ghersi says.

"I think there will be pressure to register and make the results available," Ghersi says. "We're almost there -- people are accepting that we need to register clinical trials, and we have an obligation to people who take part in research." ■

**Special Report: Protecting research participants**

# On-line journal provides industry with open access

*Journal wants all results — positive and negative*

A relative newcomer to the world of journal publishing is working on improving human subjects and other research

(. . . *continued on page 18*)

# WHO's international clinical trials registration data set

*20 items are needed*

The World Health Organization's International Clinical Trial Registry Platform has created a list of 20 items necessary for the registration of a clinical trial. These items are as follows:

**1. Primary Register and Trial ID#:** Name of Primary Register and the unique ID number assigned by the Primary Register to this trial.

**2. Date of Registration in Primary Register:** Date when trial was officially registered in the Primary Register YYYY/MM/DD.

**3. Secondary ID#s:** Other identifying numbers and issuing authorities besides the Primary Register, if any. Include the sponsor name and sponsor-issued trial number (e.g., protocol number) if available. Also include other trial registers that have issued an ID number to this trial. There is no limit on the number of Secondary ID numbers that can be provided.

**4. Source(s) of Monetary or Material Support:** Major source(s) of monetary or material support for the trial (e.g., funding agency, foundation, company).

**5. Primary Sponsor:** The individual, organization, group or other legal person taking responsibility for securing the arrangements to initiate and/or manage a study (including arrangements to ensure that the study design meets appropriate standards and to ensure appropriate conduct and reporting). In commercial trials, the primary sponsor is normally the main applicant for regulatory authorization to begin the study. It may or may not be the main funder.

**6. Secondary Sponsor(s):** Additional individuals, organizations or other legal persons, if any, that have agreed with the primary sponsor to take on responsibilities of sponsorship.

A secondary sponsor may have agreed to these items:

- to take on all the responsibilities of sponsorship jointly with the primary sponsor; or
- to form a group with the primary sponsor in which the responsibilities of sponsorship are allocated among the members of the group; or
- to act as the sponsor's legal representative in relation to some or all of the trial sites; or to take responsibility for the accuracy of trial registration information submitted.

**7. Contact for Public Queries:** E-mail address, telephone number, or postal address of the contact who will respond to general queries, including information about current recruitment status.

**8. Contact for Scientific Queries:** E-mail address, telephone number, or postal address, and affiliation of the person to contact for scientific queries about the trial (e.g., principal investigator, medical director employed by the sponsor). For a multi-center study, enter the contact information for the lead Principal Investigator or overall scientific director.

**9. Public Title:** Title intended for the lay public in easily understood language.

**10. Scientific Title:** Scientific title of the study as it appears in the protocol submitted for funding and ethical review. Include trial acronym if available.

**11. Countries of Recruitment:** The countries from which participants will be, are intended to be, or have been recruited.

**12. Health Condition(s) or Problem(s) Studied:** Primary health condition(s) or problem(s) studied (e.g., depression, breast cancer, medication error). If the study is conducted in healthy human volunteers belonging to the target population of the intervention (e.g., preventative or screening interventions), enter the particular health condition(s) or problem(s) being prevented. If the study is conducted in healthy human volunteers not belonging to the target population (e.g., a preliminary safety study), an appropriate keyword will be defined for users to select.

**13. Intervention(s):** Enter the specific name of the intervention(s) and the comparator/control(s) being studied. Use the International Non-Proprietary Name if possible (not brand/trade names). For an unregistered drug, the generic name, chemical name, or company serial number is acceptable. If the intervention consists of several separate treatments, list them all in one line separated by commas (e.g., "low-fat diet, exercise").

The control intervention(s) is/are the interventions against which the study intervention is evaluated (e.g., placebo, no treatment, active control). If an active control is used, be sure to enter in the name(s) of that intervention, or enter "placebo" or "no treatment" as applicable.

For each intervention, describe other intervention details as applicable (dose, duration, mode of administration, etc.).

**14. Key Inclusion and Exclusion Criteria:** Inclusion and exclusion criteria for participant selection, including age and sex.

**15. Study Type:** A single-arm study is one in which participants are assigned to receive one of two or more interventions are NOT single arm studies. Crossover trials are NOT single arm studies.

A trial is "randomized" if participants are assigned to intervention groups using a method based on chance (e.g., random number table, random computer-generated sequence, minimization, adaptive randomization).

**16. Date of First Enrollment:** Anticipated or actual date of enrollment of the first participant (YYYY/MM).

**17. Target Sample Size:** Number of participants that this trial plans to enroll.

**18. Recruitment Status:** Recruitment status of this trial.

- Pending: participants are not yet being recruited or enrolled at any site
- Active: participants are currently being recruited and enrolled
- Temporary halt: there is a temporary halt in recruitment and enrollment
- Closed: participants are no longer being recruited or enrolled.

**19. Primary Outcome(s):** Outcomes are events, variables, or experiences that are measured because it is believed that they may be influenced by the intervention. The Primary Outcome should be the outcome used in sample size calculations, or the main outcome(s) used to determine the effects of the intervention(s).

Enter the names of all primary outcomes in the trial as well as the pre-specified timepoint(s) of primary interest. Be as specific as possible with the metric used (e.g., "% with Beck Depression Score > 10 "rather than just "depression").

Examples: Outcome Name: all-cause mortality, Timepoints: 5 years; or Outcome Name: Mean Beck Depression Score, Timepoint: 18 weeks.

**20. Key Secondary Outcomes:** Secondary outcomes are events, variables, or experiences that are of secondary interest or that are measured at timepoints of secondary interest. A secondary outcome may involve the same event, variable, or experience as the primary outcome, but measured at timepoints other than those of primary interest (e.g., Primary outcome: all-cause mortality at 5 years; Secondary outcome: all-cause mortality at 1 year, 3 years), or may involve a different event, variable, or experience altogether (e.g., Primary outcome: all-cause mortality at 5 years; Secondary outcome: hospitalization rate at 5 years).

Enter the name and timepoint(s) for all secondary outcomes of clinical and/or scientific importance. Be as specific as possible with the metric used (e.g., "% with Beck Depression Score > 10" rather than just "depression"). Examples: Outcome Name: all-cause mortality, Timepoint: 6 months, 1 year; or Outcome Name: Mean glycosylated hemoglobin A1C, Timepoint: 4 and 8 weeks. ■

through greater transparency and easier access to results — both the positive and the negative.

The Public Library of Science (PLoS) in Cambridge, United Kingdom, was established in 2000 primarily for the purpose of providing the public access to research papers.

The founders were concerned about the problem of access to scientific literature as a whole since most journals seven years ago were subscription based, says **Emma Veitch**, PhD, publications manager of PLoS Clinical Trials.

"You could only read them if you subscribed to the journal or were in a research institution that had a library," Veitch notes. "So the public could not see the results of research that was paid for with tax dollars."

The conventional process also slows down research, Veitch says.

"You can stimulate the process of scientific discovery by widening access to scientific materials, and with the Internet, you don't need to use a subscription," she adds.

While it costs money to review research and publish it, this can be covered by a one-time cost, Veitch says.

"The business model behind PLoS is having grants from foundations established for initial funding, and then there are charges for funders who sponsor research," she explains. "It's a one-time fee for studies that are good enough to be published in a PLoS journal."

The one-time fee is $1,250 to $2,500. For those who cannot find funds for the publication fee, then they can specify this when they submit their study, and if the study is accepted for publication the fee will be waived, Veitch says.

What's most unique about PLoS journals, including PLoS Clinical Trials, which was launched in May 2006, is that researchers agree to PLoS' copyright stipulations that anyone can access the content, reproduce it, use it in derivative publications, use it in slide shows, use it in teaching materials, or put it to any creative use, so long as they acknowledge the original citation and publication, Veitch says.

One of the goals of PLoS Clinical Trials is to

encourage researchers to send in their unpublished results, particularly if the results are negative, Veitch notes.

"We're trying to motivate people by saying, editorially, that we will not be prejudiced against those studies," she says. "The methodological rigor and quality of reporting of the trial are the only things that matter in our editorial evaluation of the paper."

As long as the trial is done properly, the journal will make an effort to publish it, without concern about the results, she adds.

The reason for this approach is to address the problem of publication bias in trial literature," Veitch says. "As a lot of people are aware, you have the problem of negative results are less likely to be published."

Therefore, the evidence-based rule is skewed by what's publicly available, and these typically are positive results, Veitch says.

"You can get a mistaken estimate of efficacy and safety of drugs and other types of therapeutic interventions, and clearly that can have a damaging impact on patient care," Veitch says. "So we're trying to encourage reporting of negative results and encourage reporting outcomes of clinical trials."

The open access agenda of PLoS and the recent push for clinical trial registries have a natural link, Veitch notes.

"In my mind they fulfill a very distinct and not-overlapping function," Veitch says. "Registries provide the core dataset of each trial."

These include 20 or so data elements that tell the following:

- what condition is being studied;
- what the sample size is;
- how many people enrolled;
- who is running the trial;
- what the main outcomes are;
- what the drug intervention is, and;
- what the basic elements of the study are.

The purpose of registries is to promote transparency by allowing a trial to be tracked throughout the course of the design of the trial, including recruiting, patient enrollment, conducting the study, and closing the study, Veitch explains.

"You make sure you can track those results," she adds.

"At the moment, registries are not providing a way for presenting results from trials," Veitch adds. "What PLoS Clinical Trials does is provide a way to report the results effectively and show what is happening in the trial."

The online journal will provide links, when available, to the original registry so there is a connection between them, she says.

"I think in that way there is a very close link, and someone can go back and look at the original trial registry to see if outcomes were reported as originally stated," Veitch explains.

"Someone can say, 'This paper shows XYZ, but we can see from the registry the investigator planned to show this outcome that is not presented in the paper,'" Veitch says. "It helps you pinpoint possible selective bias or reporting."

PLoS has eight peer-reviewed, open access scientific and medical journals, including these:

- PLoS Biology;
- PLoS Medicine;
- PLoS Computational Biology;
- PLoS Genetics;
- PLoS Pathogens;
- PLoS Clinical Trials;
- PLoS ONE; and
- PLoS Neglected Tropical Diseases, which will be launched this year.

For PLoS Clinical Trials there are three peer reviewers, typically, including a statistician and an academic/clinician expert in the appropriate subject, Veitch says.

Peer reviewers, who are community members and are unpaid for their work in evaluating studies, normally are specialists in a particular study's field.

Peer reviewers assess whether the study was done properly, methodologically sound, properly reported, and whether all statistics and results were reported properly.

"These are the main things we're trying to bring out — a set of more detailed guidelines based on the Consolidated Requirements for Reporting Clinical Trials guidelines," Veitch explains. "We want readers to get the most out of what our findings are in a study and what it means in the larger context of what other research is available."

So far, PLoS Clinical Trials has published about 50 trials.

One recent published study involved the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), which was stopped early.

"Efficacy information isn't yet available, but safety data are available from the study, and this is important in contributing to the debates about safety of COX inhibitors," Veitch says.

"We're trying to say that we're very happy to publish results of studies that are stopped early," she adds.

"We're publishing across a broad range of specialty areas, but our main focus is to have enough

## Reporting Results from Clinical Trials

*What's the problem?*

• Clinical trial results are scattered and often difficult to access.

• Non-publication of unfavorable trials or negative results causes systematic publication bias.

• Standard journal articles often omit important details.

• Traditional peer-review and journal publishing delays the publication of findings.

• Enforcing commitments to publish all results are hampered by a lack of a clear definition of publication.

What are the opportunities?

• Trial registers/linking protocols with publications.

• Online publication on websites with minimal running costs.

• Data banks are a possibility for the future.

What's the solution?

• If all trials were registered at inception, redundant publication would be easy to spot and non-publication could be challenged.

• Links between trial protocols (or registers) and results would highlight selective reporting and ad hoc analyses.

• Electronic templates for results reporting should raise standards and improve searchability.

• Results could be posted on publicly accessible websites at minimal cost.

• Peer-reviewed journals should concentrate on interpretation, synthesis, commentary, and discussion. ■

Source: Elizabeth Wager. Publishing clinical trial results: The future beacons. PLoS Clinical Trials. October, 2006:e31:1-4. Web: www.plosclinicaltrials.org.

information for everyone to get something out of the findings because it's published under open access," Veitch says. " PLoS is a very young organization, but the feedback we get is it has very quickly acquired a degree of respect amongst the scientific and clinical trials communities."

In the October, 2006, edition of PLoS Clinical Trials, author Elizabeth Wager wrote about why clinical trial results are published, including medical research motivations of improving clinical practice, informing patients, influencing future research, and preventing duplication of effort.

Other motivations are personal, including enhancing reputations and career prospects, and measuring a department's productivity, and financial, such as increasing a drug's sales.[1]

Wager's essay also offers examples of problems with reporting clinical trials and some possible solutions, including one solution that PLoS Clinical Trials has affected: posting results on accessible Web sites at minimal (or no) cost.1 (See table regarding reporting results, above.)

PLoS Clinical Trials focuses primarily on the results of randomized trials because these are the most carefully controlled studies, Veitch says.

"We only publish the most rigorous sorts of results," Veitch says. "We're looking at broadening our focus in the future, but we specifically look for randomized trial results from across all specialties."

PLoS ONE is a new concept at PLoS. It's an open access journal that aims to provide a place for publication of original research across all biology and medicine, and it's not restricted to any research area, Veitch says.

"We intend to break down the boundaries between disciplines," she says. "And what's new and special about PLoS ONE is that after peer review and the paper is published, the PLoS ONE platform provides a way for the scientific community to engage with the paper and have an open discussion post-publication on the accepted paper."

People can see on the Web site how to directly discuss the paper through a comment that's posted as an open comment on the article, and people can add their comments to the comments, as well, she explains.

"So it becomes a living object, as it were," Veitch says. "It's really moving to a more Wikipedia-like model for publication, but you obviously have the process of vetting very much like peer review."

The PLoS ONE content is similar to PLoS Clinical Trials, she notes

"It's focused on the methodological rigor of the study," Veitch says. "As long as it provides a novel advance in its field, and the study has been properly done and the methodological quality is good, it will be published."

PLoS ONE launched with 103 papers ranging from ecology to genetics to psychiatry. ■

Reference:
1. Wager E. Publishing clinical trial results: The future beacons. PLoS Clinical Trials. October, 2006:e31:1-4. Web: www.plosclinicaltrials.org.

**Special Report: Protecting research participants**

# Improve communication using these techniques

*Role playing and actor/patient are used*

Clinical trial sites could improve staff's informed consent communication skills through the use of role playing and using trained actors or others skilled in this type of exercise to portray potential research participants, an expert suggests.

While the clinical trial industry focuses intently on the informed consent document, less attention is paid to the process of consent and determining a potential participant's comprehension of the consent information, says **Susan Dorr Goold**, MD, MHSA, MA, director of the bioethics program and an associate professor of internal medicine and health management and policy at the University of Michigan in Ann Arbor, MI.

"There is an understanding that this is an issue," Goold says. "But the regulations and the industry's focus are on what you have to cover in informed consent and much less on how to do it."

So the University of Michigan's curriculum focuses on skills rather than knowledge among research staff and trainees, with the goal of improving the informed consent process, Goold says.

This is done through a mini-lecture, distribution of communication strategies, and role playing exercises that involve a trained actor who portrays a potential participant. The trainee has to obtain informed consent from the actor in a role playing exercise, she says.

"They have to discuss research with the simulated participant, and this improves their skills and the process of consent," Goold adds.

The University of Michigan has established a reputation as a leader in using simulated patient instructors to teach communication skills for both medical training and clinical trial research training.

"We've used simulated patient instructors (SPIs) for medical training for many years," Goold says. "We have a parallel clinical consent process we adopted first, and then we adapted it to the research context."

Actors are hired and trained to portray potential research subjects and to evaluate researchers and research staff, Goold says.

The evaluation includes videotaping the role playing process and an assessment of consistency in how informed consent is obtained, as well as a 30-item checklist of other indicators of success in learning the most effective communication skills, she says.

Some of these checklist questions include the following:

- Did the person obtaining informed consent assess the patient's comprehension of the research protocol?
- Did the person obtaining informed consent treat the patient with respect?
- Did the person obtaining informed consent pick up on nonverbal cues?

The informed consent students also do a self-assessment which is compared with the SPI's assessment during a debriefing process, Goold says.

Role-playing with a facilitator and practice protocol is conducted separately from the SPI sessions.

"We give them their parts to play, saying, 'This is the research project that you're discussing,'" Goold says. "For role-playing we have a lot more flexibility to target different groups, so if we have a group of pediatric researchers, we'll focus on role-play that works with family members."

If the group being trained involves social science research, then the role-playing will involve social-science research.

"So the role-playing exercise is a small group exercise that we lead and they practice obtaining informed consent on each other, and they give feedback to each other," Goold says. "The role-playing comes before the SPI, so they have practice before meeting with the SPI."

"Most learners had favorable reports of their experience with both role-playing and the simulated patient instructor," Goold says.

SPIs, which are also called simulated potential participant instructors, portray the common participant, but there are a few added twists in the role-playing sessions, Goold notes.

"There will be children, people who don't speak English, or someone who is only in the research

for the money or who really believes the research will benefit his or her health," Goold says.

One goal of role-playing is for the person being trained to develop skills in determining a potential participant's true motives for becoming involved in research.

For example, the person being trained needs to be aware of cues that the person may be participating due entirely to an incentive, rather than for altruistic or other purposes.

"The goal overall is that the learners will first uncover that the potential patient is involved solely for the money," Goold says. "They would realize that the potential participant doesn't realize how much risk is involved and how many interventions will happen to him or her."

In the case of therapeutic misconception, the role-playing student needs to uncover the fact that the role-playing potential participant is doing the study with a belief his or her health will improve and a cure will be found, Goold adds.

"We want them to uncover these motives, but you can only uncover that if you can communicate skillfully with the participant," she adds.

The three different scenarios include the socio-behavioral research scenario, an intervention study that is a drug trial for heart disease, and a basic science protocol that involves collection of a sample, Goold says.

"That is also because we have a huge variety of learners who take this training program," Goold says. "We have some in epidemiology, some in behavioral, and some in clinical research."

The consent communication curriculum includes 2.5 hours in lecture and role-playing and 1.5 hour one-on-one sessions with the SPIs, Goold says.

"We don't have a way to evaluate the impact of the SPI, but we use the SPI to assess the outcomes of other portions of the curriculum, Goold says.

"What we've found so far, and this is preliminary, is that people's confidence in their abilities to communicate about research participation are improved," Goold says. "And, also, their attitudes about communications strategies are improved."

The trainees' knowledge of informed consent had not improved significantly, but that was probably because their knowledge was high to begin with, Goold says.

"We focus on skills, not knowledge," Goold says. "People also have more of a commitment to using these techniques and more competence in their ability to do so." ■



# Avoid common mistakes when dealing with the IRB

*Volunteer for IRB service, if possible*

Investigators often fail to see the connection between their research and the human subjects review process.

"Investigators need to understand this human subjects review process is part of the research and part of the intent to see things they didn't see when they were going to the protocol," says **Brad Noren**, MA, CIP, research and contracts administrator for the Oregon Health and Science University, department of ophthalmology in Portland, OR. Noren also has worked in an IRB office and helps investigators understand the regulatory requirements.

"The overall goal of all parties is to protect human subjects, and if that can be with collaboration, an almost peer review of the research, it can strengthen the research," Noren says.

"Too often the investigator comes into an IRB review with an us-versus-them attitude," Noren says. "They have an 'I'm a scientist and you're a bureaucrat' attitude."

Rather, they should see the IRB as a group of mostly research experienced people who want to facilitate research and make sure a trial is conducted effectively with as significant results as can be obtained, Noren says.

"Many investigators are used to getting critiques and criticisms through peer review from federal grants, and if they could see the IRB review as a similar mechanism of improvement of the science and protections of human subjects, then they could come out with stronger protocols and change their attitude," he adds.

Noren offers these tips on how to improve investigator-IRB relations:

• **Join the local IRB:** "As a former IRB administrator, I would always encourage investigators to join the local IRB and provide service, which is the best way to understand the process," Noren says.

"I've seen cases where investigators who perhaps didn't appreciate the utility of the IRB would join the IRB and become valuable members, providing unique insight into their own practice in the clinic," Noren explains. "And I've seen people do a complete 180 from being very opposed to IRB review to supporting the process."

• **Address all points IRB raises in response to review:** It will improve collaboration between the investigator and IRB if the investigator addresses all of the points an IRB raises in his or her response to the review, Noren suggests.

"When I help investigators write these responses, I take an electronic copy of the IRB review and insert spaces under every question, and that's where we insert our response," Noren says. "I use the IRB's format and put the investigator's response right under the question the IRB raised."

This is the most efficient way to make certain that every issue raised is addressed adequately.

Also, investigators should make sure they give a full, direct, and complete response, leaving no room for additional questions, Noren says.

"Don't provide extra information that's going to muddy the waters or distract from what the issue is," he adds.

For example, in one review in which Noren assisted an investigator, there was a question from the IRB about the biological samples. The IRB wanted to know whether blood or tissue samples would be retained and used for future research, Noren explains.

"That was never part of the original protocol, and in reassessing whether we needed those samples, we decided we didn't even need to take those samples," Noren recalls. "So we said, 'There is no intent to store samples for future research, and, beyond that, we've decided those samples are not even central to our real research question, so we're not going to be collecting those.'"

• **Provide literature citations when indicated:** "Another thing you can do is provide citations from the literature if there are questions raised that are medical in nature and related to the standard of care or to what other physicians do in this sort of case," Noren says.

"Do a literature search and provide references from peer review literature that explain that it's consistent with current thought and standard of care from other institutions," Noren says. "This can strengthen the review response and help the IRB understand the physician investigator's position."

For instance, if the IRB had a question about whether a particular drug that the investigator proposes using in children has been used in children before, then the investigator should cite the other studies where this drug has been used in children, Noren says.

"The IRB still has to address a number of regulatory questions, but their minds can be put a little at ease knowing that this drug has been used before and that we now know a little more about associated risks than if this had been the first time it was used in children," Noren adds.

Literature citations is becoming more popular in IRB submissions, Noren notes.

"There's such a stigma and fear built up around the IRB review process, and, often times it is rightly so because the process can be such a black box: mysterious, arbitrary, and unpredictable," Noren says. "The bottom line is to use common sense, provide as much information as you can, provide information in a clear and concise manner, and understand in the best sense that it's a collaborative review process."

• **Request previews judiciously:** It's a great idea to have the IRB office perform a preview of a protocol submission, but IRB staff tend to be overworked, so

## CE/CME Objectives / Instructions

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.

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.

After completing this activity at the end of each semester, you must complete the evaluation form provided and return it in the reply envelope provided to receive a letter of credit. When your evaluation is received, a letter of credit will be mailed to you. ■

## COMING IN FUTURE MONTHS

- ■ Improve training for clinical research coordination
- ■ Mentoring program for investigators, CR professionals
- ■ Effect policies for stopping clinical trials
- ■ Manage problems during phase I and II clinical trials

this request should be reserved for special cases, such as studies that pose significant risk, Noren suggests.

"When you get into a situation where you'll see there will be a difficult review, the IRB administrators that I know will make time in their schedules to sit down with you and talk about it," Noren says. "You wouldn't expect that with every review, but if you are a newer investigator or doing the type of research that might pose significant risks then it would be appropriate to ask for a consultation to talk about some of the issues."

Another option would be for a research department to hire staff who are knowledgeable about the regulations and the IRB process or to have senior investigators or study coordinators help junior investigators or study coordinators with the IRB review process, Noren suggests.

• Respect the IRB office's workflow issues: "The local IRB has an established process, and part of that process is to make sure the regulatory issues are addressed, and the other part is to manage the workflow," Noren says.

"Also, you should remove personality from the process to the degree that you're not having an argument with an individual, but you're discussing a matter of research with a peer of some sort, and you're both trying to get to the same place," Noren adds. ■

## CE/CME *questions*

4. Research ethicists have devised a new model for analyzing risks and benefits of a research study. Which of the following describes the model that is called component analysis?
A. An IRB assesses the composite of all the interventions detailed in a study and assesses whether the use of interventions that do no provide a prospect of direct benefit is justified by the sum of anticipated benefits associated with those interventions that do have the prospect of direct benefit.
B. An IRB assesses each potential risk and benefit of a study and rates these according to a scale of one equals minimal risk and minimal benefit and five equals maximum risk and maximum benefit, and then adds the two columns to see if the sums are equalt.
C. An IRB assesses the potential harms and benefits of each intervention or procedure and does not use one potential benefit to offset or justify the risk posed by a separate intervention or procedure.
D. None of the above

5. Which of the following is not one of the 20 items listed in the WHO's International Clinical Trial Registry Platform for what should be collected in CT registries:
A. Key inclusion and exclusion criteria.
B. Target sample size
C. Recruitment status
D. All of the above are on the list

6. Which of the following is a copyright stipulation for journals published by the Public Library of Science, which is promoting open access to research studies?
A. Researchers and the public can reprint article tables or material only with written permission from the publisher
B. Research institutions may not use the articles in educational materials, unless they pay a nomimal fee for the privilege
C. Anyone can access the content, reproduce it, use it in derivative publications, use it in slide shows, use it in teaching materials, or put it to any creative use, so long as they acknowledge the original citation and publication
D. None of the above

Answers: 4. (c); 5. (d); 6. (c)