Yale Center for Clinical Investigation

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FDA Amendment Act Expands Mandatory Registering of Clinical Trials

On September 27, a new law was enacted that expands the types of clinical trials that must be registered on the government-sponsored website clinicaltrials.gov and increases the information that must be submitted.

The legislative push for registering clinical trials isn't all that new. It actually began with the FDA Modernization Act of 1997, which required HHS to establish a registry so that the public would have access to clinical trials. As a result of this legislation, clinicaltrials.gov was established in 2000. However, only trials testing drugs for serious or life-threatening conditions needed to be registered, and there was virtually no enforcement that this was taking place. Not surprisingly, a 2002 FDA study found that only 48 percent of cancer drug trials were registered and a 2005 study found that 67 percent of companies required to register studies had complied.

In response to a trend for greater public access to research funded by the federal government and in the wake of allegations that adverse events linked to Cox-2 inhibitors were being suppressed, the International Committee of Medical Journal Editors (ICMJE) announced a new policy in 2004: Any trials involving human subjects, medical interventions and health outcomes had to be registered in a public database (clinicaltrials.gov was the only one that met the organization's criteria) in order for the study to be considered for publication in ICMJE journals. This policy included drugs, but unlike the FDA policy it also included devices and procedural interventions. Although it did not at that time include Phase I trials or pharmacokinetics studies, the ICMJE revised its policy in 2007 to include these trials as well.

The ICMJE policy appears to have had a significant impact; at the time it was announced in 2004, about 13,000 trials were registered, but by April 2007, 40,000 trials had been registered. Since the policy's inception, the World Health Organization, the American Medical Association and other groups have supported the registration of clinical trials, and some states have also mandated registration. The FDA Amendment Act of 2007 brings together the various elements involved in this issue:

- It expands registration requirements to most trials of drugs, biologics and devices under FDA jurisdiction (including those approved under 510(k), PMA and HDE)
- It includes pediatric post-marketing device trials
- It preempts all state laws in this area

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Inside This Issue

Next Issue

- YCCI's Educational Programs: An in-depth look at the new programs plus profiles of the trainees and scholars

Terry Degradi

Director's Corner

When YCCI was established, we set out to integrate Yale's clinical and translational research programs and to create an academic home for students, fellows and junior faculty members from the schools of Medicine, Nursing, and Public Health, as well as biomedical engineering, who are committed to careers in clinical and translational research. Our goal was to establish a robust infrastructure that would promote innovative and collaborative research with the long-term goal of improving health.

Now that we've just marked our one-year anniversary, I'm happy to report that we've made a lot of inroads toward achieving the objectives we established for the first year of the program. In addition to major programmatic goals, we have achieved more than 90 percent of the milestones we set out to accomplish in the first year. Here is some of what we've completed since October 2006:

- Opened our new facility at 2 Church Street with administrative offices and the clinical research unit
- Launched the new YCCI Scholars program making 20 awards totaling just over $2.5 million
- Launched the YCCI pilot projects program awarding $740,000 in five areas
- Invested in the expansion of existing and new technologies for Cores to further genomics, proteomics, imaging, and immune biomarkers capabilities.

The first year held many challenges for us, but it has also been an exciting time of growth and progress. As YCCI continues to evolve, we look forward to your continued advice and support in order to realize the vision and mission of the center.

Robert Sherwin, MD
YCCI Director

Announcing our Second Round *Pilot Awards* and Third Round *Scholar* Recipients

See *Funding for Career Development and Research* article on **page 2.**

Events Calendar

FDA Clinical Trial Registries: Issues and Impact

January 24, 10:30 am to noon
Beaumont Room SHM

YCCI presents guest speaker Mark Barnes, executive vice president and chief administrative officer and director of research operations at St. Jude Children's Research Hospital, who will offer an overview of the new legislation requiring the registering of clinical trials. Recognized as one of the nation's top lawyers in the field of research compliance and medical privacy, Barnes will discuss how the new regulations will affect clinical trial research, how they will influence clinical trial agreements, and the potential impacts of reporting study results.

NEW! Joint YCCI/Investigative Medicine Program Scholars Research-In-Progress Meetings

The meetings will feature presentations from individual scholars. Lunch will be provided.

- *January 28, noon to 1:30 pm*
  Brady Auditorium, 310 Cedar Street
  Topic to be announced
- *February 12, Location to be announced*
  Mechanisms of AMPK Regulation in the Heart, presented by Agnes Kim
- *February 25 (tentative), noon to 1:30 pm*
  Brady Auditorium, 310 Cedar Street,
  Topic to be announced
- *March 4, Location to be announced*
  Genetic Studies of Major Depressive Disorder, presented by Arthur Simen
- *March 31, noon to 1:30 pm*
  Brady Auditorium, 310 Cedar Street
  Topic to be announced

For updates and more information on scholar events, visit http://ycci.yale.edu.

Conducting Research in Community Settings: Issues for Researchers, Community Providers and the IRB

January 30, 5:00 to 7:00 pm
Cohen Auditorium, Yale Child Study Center

For further information and to RSVP to this panel presentation and discussion, please contact the Human Investigation Committee, YSMHIC@yale.edu, 785-4688.

for more events, please see page 4

Funding for Career Development and Research

YCCI is pleased to announce funding for the third round of Scholar Awards and the second round of pilot grant awards.

The YCCI Scholar Awards provide salary and/or research funds to junior faculty members who are strongly committed to careers in clinical and translational research. Individuals must be nominated by a department chair, division head or center/program director and must propose a research project in patient-oriented research, clinical research, translational research or outreach. Funds can be requested for up to 75 percent salary support and/or a maximum of $30,000 per year for research support. Nominations are due by February 13 and awards will be for two years, from July 1, 2008, to June 30, 2010.

In addition, the YCCI pilot program invites proposals in the following areas:

- Pilot projects in translational and interdisciplinary research that combine Yale investigators from diverse disciplines. Approximately three grants of up to $75,000 per year for a two-year period will be awarded.
- Development of novel clinical and translational methodologies that will enhance clinical research studies. Approximately three grants of up to $25,000 for a one-year period will be awarded.
- Pilot projects using cutting-edge Core Technologies. Several grants of up to $15,000 for one year will be awarded.

Applications are due by March 6 for projects that will begin by July 1. Additional information, application forms and budget templates for both programs can be downloaded from the YCCI website at http://www.ycci.yale.edu/.

How New Amendment Will Affect Clinical Research

With the first deadline for adhering to the new clinical trials registration guidelines now passed (see main story on page 1), it's becoming apparent that this legislation could profoundly affect how clinical research is conducted and interpreted. This is especially true because the new amendment also calls for a database of study results and adverse events (see story on page 3). Some worry that the new law could influence pharmaceutical companies to either avoid conducting risky trials or to design trials in such a way that potential effects are minimized, for example by using small sample sizes, selecting earlier endpoints or limiting eligible patient populations to the most healthy individuals.

"What starts out here as an attempt to increase information available to the scientific community and to the public may well have the unintended consequence of reducing the useful information that's available to all of us," said Mark Barnes, vice president and chief administrative officer of St. Jude Children's Research Hospital, in an FDA-sponsored teleconference on the new law. The emphasis on the reporting of adverse events could also deflect interpretation of the meaning of those events or distort the regulatory process by bringing undue pressure on the FDA to approve or disprove drugs.

Another concern is that the new guidelines could create unwarranted public and health provider confidence in results that have not undergone the peer-review process. The idea of posting results that have not been filtered is particularly troublesome if directly provided by sponsors with vested interests, pointed out Deborah Zarin, MD, director of clinicaltrials.gov, and her coauthors in a commentary in the May 16 Journal of the American Medical Association.

"The desire for complete public reporting of results must be tempered with acknowledgment of the problems associated with bypassing independent scientific review and with attempting to convey complex results using simple, summary data," they stated. Meanwhile, the pharmaceutical industry, while insisting it supports "transparency," also urges caution. In a September 17 press release, Ken Johnson, senior vice president of Pharmaceutical Research and Manufacturers of America (PhRMA), said that "it is important not to reach hasty conclusions until all studies and data have been evaluated."

Underlying all of these issues is the erosion of intellectual property protection due to the necessity of disclosing what may be proprietary information, which may also discourage drug and device companies from wanting to invest in clinical research. As the requirements of the new legislation continue to be refined, the debate over what, when and how to disclose data from clinical trials will no doubt continue.

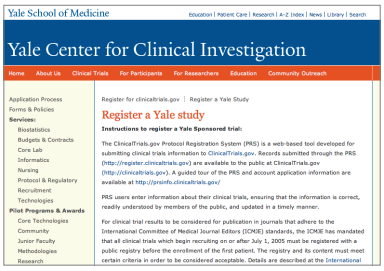
FDA Amendment Act *continued from page 1*

Although the amendment excludes phase I trials, Yale researchers are advised to register these trials as well, since they are covered by the ICMJE guidelines to be considered for publication in peer-reviewed journals.

For clinical trials that were initiated after September 27 or were ongoing as of December 26, the registration deadline was December 26, or 21 days after the first subject was enrolled, whichever is later. Trials that were ongoing as of September 27 that do not involve a serious or life-threatening condition have until September 27 of this year to register, although Yale is encouraging researchers to register their trials as soon as possible. Entries must be updated at least every 12 months and within 30 days of recruitment status changes or completion. HIC recommends that researchers notify study participants via informed consent that trials will be registered. Information and guidance regarding how to include this information in the consent process can be found at http://info.med.yale.edu/hic/.

Registration is the responsibility of the study sponsor or the PI. Failure to register carries stiff penalties that include significant fines ($10,000 per violation plus $10,000 per day if not corrected within 30 days after notice) and the withholding or recovery of grant funds for federally funded trials. The NIH has the task of posting drug trials on the public registry within 30 days of submission, but device trials, which also need to be registered, will not be posted until the device is approved by the FDA.

YCCI is available to help researchers navigate the registration process. Please visit our website or contact us for assistance.



How to Register a Trial

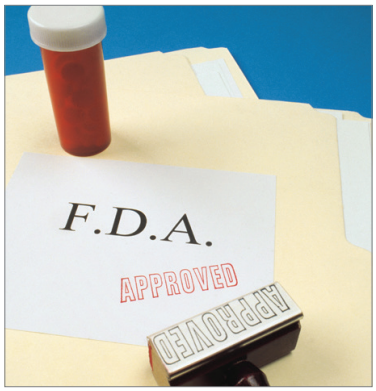
Registration instructions and guidance, including how to request a password, can be found on YCCI's website at: http://ycci.yale.edu/researchers/register_a_trial.html.

If you have additional questions, please call Melody Sacatos at 737-4512.

Additional guidance can also be found on the NIH website at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html and at http://prsinfo.clinicaltrials.gov/fdaaa.html for a detailed explanation of required data elements.

Expanded Trials Database to Include Results and Adverse Events

The FDA Amendment Act of 2007 has a broader scope than the expansion of registration requirements for clinical trials (see main story on page 1); it also calls for a database of study results as well as adverse events associated with them. Unlike registration on clinicaltrials.gov, however, the details of how this will work are much less well-defined. By December 26, the NIH was required to establish a database of results of clinical trials that form the basis of an efficacy claim or are conducted after the drug or device is approved. The new legislation requires the database to include a number of FDA documents, such as advisory committee summary reports and assessments of drug trial results, public health advisories and action packages for drug approval, as well as summaries of new device safety and efficacy. By September 26, 2008, for approved drugs and devices, the database must also include demographic and baseline data on subjects, primary and secondary outcomes and information regarding any agreement between the sponsor and PI that restricts the PI from discussing or publishing results. This means that the NIH will probably be issuing guidelines for collecting this information sometime during the spring and summer of this year.



By September 26, 2010, HHS must issue guidelines for researchers to submit results of clinical trials, which will be posted whether or not the drug or device has been approved by the FDA. The guidelines must include submission of both a lay language and a technical summary of trials and results, as well as either the full protocol or as much of the protocol as is necessary in order for the results to be understood.

"This is a huge deal for all of us in regard to academic privacy, in regard to commercial privacy, and we can look forward to a fight over the next three years over how much has to be disclosed," said Mark Barnes, vice president and chief administrative officer of St. Jude Children's Research Hospital. Results must be reported by the responsible party within one year or earlier of the estimated trial completion date or the actual date of completion. Extensions may be granted in some cases, but specific guidelines for this have not yet been drafted.

Even before the final issuance of the results database, by March 26, 2009, HHS has the task of determining the best method for including information on serious and frequent adverse events for drugs in the registry and results database (devices were inadvertently omitted but are expected to be added). "It's actually in some ways more stunning to post adverse events

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Events Calendar *continued*

Racial and Ethnic Disparities in Diabetes Care in the United States

February 20, noon to 1:00 pm
Winslow Auditorium, 60 College Street

Presentation by Ronny A. Bell, PhD, MS, professor of epidemiology and prevention, and director of the Maya Angelou Research Center on Minority Health, Wake Forest University Health Sciences. Lunch and a community forum will follow. RSVP for lunch/forum to dana.greene@yale.edu or call 785-2846.

Milestones in Public Health Grand Rounds: Health Disparities – the Challenge of the New Millennium

Throughout 2008 there will be six lectures on this topic, followed by a community forum and lunch. The speaker schedule will be announced shortly and the first lecture will be held in February.

Expanded Trials Database *continued from page 3*

information publicly than to post the results of a clinical trial, because at least the results have been interpreted where the adverse events are a much more complete set of data which need not be interpreted and may be easily misinterpreted," said Barnes. Even more alarming, if HHS fails to formulate guidelines by 2009, Congress has formulated its own detailed set of instructions: clinical trials will have to include a table reporting serious adverse events by organ system and all adverse events that exceed a frequency of five percent within any arm of a trial.

While the legislation is broad in its scope, there are still many issues regarding the reporting of results and adverse events that have yet to be ironed out. YCCI will keep researchers informed of the new guidelines as they develop.

New Billing Policy for Clinical trials

As of November 1, 2007, YMG initiated a new policy for registering clinical research studies involving human subjects. The goal is to register clinical studies and the patients enrolled in them in the GE/IDX Practice Management System.

Because clinical care in research studies receives different levels of funding by sponsors, billing can be complex. Clinical services may be fully funded by a sponsor, partially funded, or billable to the patient or a third party payer. Universal registration is important because it will:

- Enable YMG to correctly bill clinical services and avoid double billing
- Allow YMG to track patients involved in clinical trials in a single database
- Help ensure billing compliance

New study and patient enrollment forms will be required in order to open a clinical trial and for reapproval of current studies. Forms can be found online at http://www.yalemedicalgroup.org/comply/. An online tutorial is also available at http://yalemedicalgroup.org/comply/alert/formtrain/ResearchFormTutorial3.pps.

Questions may be directed to Judy Harris, director of Medical Billing Compliance, at 785-3868.

YMG is a beta partner with GE/IDX to develop a Patient Protocol Manager System that will supplement the current billing system to allow for the tracking of patients in research studies. The new system will be available for testing from February through August and is expected to roll out to clinical departments beginning in the fall.

YCCI Launches Website

YCCI home page

Do you have a question about getting a protocol approved? Or maybe you're wondering what services YCCI offers to help you carry out a clinical trial. You'll find answers to these questions and more on the YCCI website at http://ycci.yale.edu/index.html.

Launched in June, the website was conceived to serve as a portal to aid researchers who are designing and implementing clinical trials, as well as patients who participate in them.

Researchers will find information about protocol development, the application process, study implementation services, inpatient and outpatient facilities, core laboratory services, pilot programs, budgets and contracts, biostatistics, informatics, and registering clinical trials. All of the necessary forms can be conveniently downloaded directly from the website, which is also being developed to serve as a recruitment tool for trials.

Patients can also visit the website to find listings of clinical trials at Yale, learn what's involved in participating in a clinical trial, and how to register.

The education component of the website features information about the YCCI Scholars, Mentors and Investigative Medicine Programs, while the community outreach section highlights the Community Alliance for Research and Engagement (CARE), including instructions on how to apply for funding for community-university pilot projects.

"YCCI is meant to serve as one-stop-shopping for Yale researchers performing clinical trials and the website is a good place for researchers to begin when they need to set up and design trials," said YCCI Chief Operating Officer Tesheia Johnson. "We hope they'll take advantage of all it has to offer."

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