Welcome to Clinical Device Group’s Web Publications series. A lot is happening on the clinical research front in the US. I have a file about 18 inches thick consisting of various reports that have been issued by federal agencies and commissions outside the FDA. In this presentation, we’ll take a broad and shallow look at these reports and use them to predict the future.
Clinical trials sponsored by the federal government consist mostly of basic research initiated by the National Institutes of Health. Other agencies within the federal government, such as the Department of Energy and Department of Transportation, also sponsor clinical research. Altogether, the 15 federal agencies outside of the FDA sponsor 45% of the clinical research in the United States: ~ $3500M in 1995; pharmaceutical companies sponsor about 36% of clinical research, with grants totaling ~ $2700M in 1999; biotechnology and medical devices are tied at $670M in 1999 and $730M in 2000, respectively.

History shows us that when the federal government adopts new ethical or procedural guidelines for clinical research, FDA follows within a few years. This is even more likely to happen in coming years as President Bush, with his background in business, presses for "one Department of Health and Human Services." By examining the reports issued by federal agencies outside of FDA, we can predict the regulations FDA will impose on the device industry in the future.
The chart gives us an idea of how busy the federal government has been. Since 1994, there have been at least 28 new reports, opinions, or initiatives pertaining to clinical research. Many of them indirectly affect research sponsored by device and pharmaceutical companies.
Advisory Committee on Human Radiation Experiments

- Most comprehensive history available of human research in the United States.

To set the historical stage, President Clinton established the Advisory Committee on Human Radiation Experiments early in his administration. The Committee was charged with documenting the history of human experimentation in the United States from 1944-1974. This 300-page report was the culmination of hundreds of interviews and searches of archived documents in library stacks. It is the most comprehensive history of federally-funded human research in the United States that is available. Although most research was conducted ethically and responsibly, the report identified a disturbing thread of improper conduct in our past.

By the way, all of the reports mentioned in this presentation are available on the web.
The National Bioethics Advisory Committee, appointed by President Clinton in 1995, issued five important reports before its decommissioning in 2001. We can tell from the titles of their reports—listed in the slide—that they were very concerned about human protection.
Office of Inspector General

- IRBs: Their Role in Reviewing Approved Research, 1998.

Even the Office of the Inspector General has gotten involved. Typically this office is concerned with financial, legal, and administrative matters within HHS (Health and Human Services). But in 1996 they turned their attention to clinical research, and specifically to the conduct of IRBs.
To date, the OIG has published twelve separate reports on clinical research, most of them dealing with inadequacies in the IRB system, under-training of clinical investigators, and new challenges in tissue donation and research in developing countries.
Partly as a result of the OIG reports and recommendations, the Office of Human Research Protection was created within HHS. Its job is to provide guidance to IRBs and to administer the Federal-Wide Assurance program.

Now—in order for a hospital, clinic, or other institution to obtain federal grant money for human research—the institution must take steps to assure protection of research subjects. One of these steps—hugely significant—is that the investigators must be formally trained in good clinical practices. For the first time in the legislative history of any country, investigators must be formally trained in GCPs before they are considered qualified.

The implications for device and pharma research is obvious—before we reach the decade’s midpoint, investigators for our clinical trials will have to demonstrate formal training, too. As an industry, are we prepared to help facilitate this massive training effort?

One last important draft guidance issued by OHRP: disclosure (to IRBs and subjects) of grant money being paid by sponsors to investigators or investigative sites. Think about it, would your mother be less likely to participate as a subject if she knew her doctor was being paid by the sponsor?
This new committee within HHS—the National Human Research Protections Advisory Committee—provides expert advice to HHS and OHRP. They have issued formal opinions on the safeguards for children in clinical research and the disclosure of financial relationships in clinical research.
Committee on Assessing the System for Protecting Human Research Subjects

CASPHRS.

Created by Nat’l Institute Medicine.


CASPHRS, the Committee on Assessing the System for Protecting Human Research Subjects, was created by NIH’s National Institute of Medicine. They issued a report calling for the accreditation of human research protection programs in 2001.

Just as JCAHO (Joint Commission of Accreditation of Healthcare Organizations) accredits health-care delivery, the CASPHRS report calls for accreditation of human research programs.
Let’s look closer at what CASPHRS means by a human research participant protection program. The figure shows that they include the research organization (hospital, clinic, other investigative site), the IRB, the investigators themselves, and the participants. The idea is to accredit the system of clinical research within an organization. In the CASPHRS model, the sponsor sits outside the HRPPP.

There is an advantage of HRPPP accreditation to device manufacturers. It could help develop a larger pool of qualified investigational sites, and an easier method for assessing qualification.

Step back a minute. Westerners are used to thinking of investigators as human beings, and this has always put us a bit at odds with Japan, where investigators are legal beings. With the accreditation of HRPPPs, the US will be moving a little closer to our Asian friends.
CASPHERS isn’t the only group looking at accrediting human research programs. A new, independent, non-profit organization called Association for the Accreditation of Human Research Protection Programs (AAHRPP), was recently sponsored by five research organizations:

- Public Responsibility in Medicine & Research (PRIM&R), representing IRBs,
- Federation of American Societies for Experimental Biology, representing the basic biological sciences,
- Association of American Medical Colleges,
- Association of American Universities, and
- Consortium of Social Science Associations.

AAHRPP issued draft guidelines for accreditation of human research protection programs in 2001. As of today, the guidelines are available for public comment.
AAHRPP has a slightly different model for human research protection programs (and a slightly different name). Most importantly, the sponsor is considered to be a part of the system, not sitting outside the system.

If AAHRPP’s model for accreditation is adopted by FDA, medical device and pharmaceutical manufacturers could find themselves seeking independent accreditation of their clinical research programs.
VA Human Research Protection Accreditation Program

- As of 2001, VA medical centers must be accredited before allowed to conduct clinical research.
- Program administered by NCQA: National Committee for Quality Assurance.

Accreditation is already a reality in some settings. Last year the Veteran's Administration began requiring accreditation of VA medical centers before they would be allowed to conduct clinical research. The program is administered by the National Committee for Quality Assurance (NCQA).

As a sponsor, if you are considering initiating a clinical trial in an Veteran's Administration medical center, you should ask to see their NCQA accreditation.
Let’s shift our focus to within FDA. In keeping with President Bush’s business strategy of streamlining the government, a new office called the Office for Good Clinical Practices was created in 2001. This office, formerly the Office of Human Research Trials, provides a focal point within the agency for good clinical practice issues.

In March, OGCP issued a notice regarding proposed new rulemaking. The new regulations—amending 21 CFR Part 56—would require sponsors and investigators to inform IRBs of any prior IRB reviews for a clinical trial.
President’s Council on Bioethics

- Created by President Bush in 2001.
- Purpose is to provide a forum for discussion of important bioethics topics.
- First meeting, 17 Jan 02, focused on human cloning.

In November 2001, President Bush created the President’s Council on Bioethics. Their first meeting in January 2002 focused heavily on human cloning.
Many of the OIG reports identified inadequacies in the IRB system. In response—and possibly as a preemptive strike to prevent additional federal regulation—the Applied Research Ethics National Association (ARENA) developed a certification program for IRB professionals in 2001.

Sponsors should be prepared to take advantage of this new development, and ask IRB chairmen to provide evidence that at least some of their members are certified.
The Health Information Portability and Accountability Act was passed several years ago. What’s new is the security and privacy rules passed in December of 2001—it was one of the last actions in President Clinton’s administration. In February 2002, President Bush announced that he would not challenge the new rules, but rumors still abound that he may rescind them. As of today, the rule becomes effective in April 2003.

The purpose of the rule is to protect the privacy of medical information. It specifically applies to hospitals, physicians, insurance companies, pharmacies, informatics companies, and others who handle or manage personal medical information.
The problem for sponsors will come in planning clinical research. Investigators must have access to medical records in order to design a protocol, estimate enrollment capabilities, or identify patients for recruitment into trials. But to get access, they either need the patient’s authorization or a waiver of authorization from an IRB.

Device and pharmaceutical sponsors should plan on an additional 2-3 months in their timelines to allow for this additional IRB process.
Additions to Informed Consent

- Description of historical medical records needed for study.
- Statement of when authorization expires.
- Statement that neither medical treatment nor insurance coverage are conditioned upon signing.
- Description of information that will not be disclosed.
- If/when/what study results will be available to subject.

Sponsors will need access to a subject’s records during a study in order to carry out monitoring responsibilities. Several additions to the informed consent are advisable.

- The consent should describe how far back in time the sponsor will need to review the subject’s records (five years, beginning of disease occurrence).
- The consent should describe when authorization to review the subject’s records will expire (end of treatment, end of data analysis, marketing approval).
- The consent should state that medical treatment and insurance coverage will not be affected by whether or not the patient signs the consent.
- The consent should describe exactly what medical information will be disclosed to the sponsor.
- The consent should state if, when, and what study results will be available to the subject, e.g., the results of diagnostic tests or treatment outcomes.
While the device industry has been generally opposed to the Security and Privacy rules, there is one positive side. The new rules bring the US into harmony with Europe. Some sponsors have had difficulty importing clinical data into the US from Europe, because the European directive prohibits exporting personal data into countries that do not have a comparable law. Sponsors who meet the requirements of HIPAA Security and Privacy can rightfully claim to comply with EU’s Data Privacy Directive.
Conclusions: Key Events

- Investigator training to GCPs for federal money.
- VA medical centers accredited.
- Draft guidelines for HRPP accreditation.
- IRB professionals may be certified by CCIP.
- Medical information protected.

In summary, the past two years have brought major changes to the way clinical research is conducted in the US:

1. investigators must demonstrate training to good clinical practices in order to receive federal funding,
2. Veteran’s Administration medical centers must be accredited before they can host clinical research,
3. draft guidelines for accreditation of other human research protection programs have been issued,
4. a certification process for IRB professionals is in place, and
5. medical information is protected.

These changes affect device and pharmaceutical research indirectly today, but tomorrow we’re sure to be directly responsible as FDA endorses and adopts these changes.
More Information?

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