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IRB ADVISOR

Your Practical Guide To Institutional Review Board Management

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Public says no such thing as too much regulation, especially after a fatality

High-profile mistakes linger in people's minds

The suspension last month and subsequent reactivation of human research programs at Johns Hopkins University in Baltimore dealt a heavy blow to an already bruised industry in the public's eye.

The death of 24-year-old Ellen Roche this past June from an experiment at Johns Hopkins Bayview Medical Center was indeed the proverbial straw that broke a weak camel's back. The experiment on how healthy lungs respond to asthma triggers led investigators with the Office of Human Research Protections (OHRP) on July 19 to suspend all human studies at Johns Hopkins except for those where interruptions would harm the participants. OHRP later reinstated its multiple project assurance for research at Johns Hopkins on July 21.

A total of 31 findings were reported by the OHRP regarding the research at Johns Hopkins Bayview Medical Center. **(For more on what to learn from the incident, see p. 15.)**

The death of the patient no doubt further cements attitudes in the public perception of the dangers of medical research. Unfortunately, there are further instances where mishaps taint the public's confidence in medical research. Consider this partial listing of recent actions from OHRP:

• **November 2000:** OHRP suspends research at the National Institute of Child Health and Human Development for involving children in an experiment involving greater-than-minimal risk. The experiment measured insulin sensitivity, energy output, and body composition in obese children and average-weight children of obese parents. OHRP investigators concluded that while intravenous lines of glucose and insulin caused no lasting harm, it did not "represent the category of research involving children that is permissible."

• **December 2000:** OHRP investigators conclude that the National Institute of Mental Health was experimenting on four pediatric participants with the antipsychotic olanzapine — without IRB approval or

Victim's father speaks out on current system

It should be pretty obvious to everyone by now that not enough resources are being spent on the review and oversight of clinical research. This applies to all parties: government agencies, academia, and industry. What needs to be happening simply is not. ***Art Caplan****, director of the center for bioethics at the University of Pennsylvania in Philadelphia, summed up the problem well in a letter he recently published when he stated:*

"But, the suspension of clinical research at Hopkins is a symptom of a much deeper disease — the collapse of adequate protections for those involved in research at every American medical center, clinic, testing facility, and hospital. And if a culprit is to be singled out, it is that disease, not one institution."

I agree with his assessment but don't think he went far enough in his diagnosis. I would encourage everyone involved in clinical research to take a step back and look at everything with a clear eye. In my effort, this one thing is very glaring, and is the source of that disease. The money end of the medical research enterprise has become so huge that is has become increasingly difficult for anyone to remain unbiased in evaluating research findings. For those of you with a spiritual side, a better way of defining it would be literally a damned money machine, the fodder for which is human beings. Take control of that instead of letting it control government and research. The current system is not fair to anyone: not the investors of the new technologies, not to the researchers — who for the most part want to find the answers we all desire — and most certainly not to those willing to put their lives on the line.

— Paul Gelsinger, Tucson, AZ. ■

parental informed consent.

• **June 2001:** OHRP completes its investigation of the death of 3-year-old Tyler Shelton at the University of Arkansas and Arkansas Children's Hospital. The patient was enrolled in the National Wilms' Tumor Study in 1997, but was placed in a stage I tumor category when he should have been placed in the stage II tumor category. The participant died in May 1999 from advanced spread of Wilms' tumor. OHRP concluded that the therapy "may have contributed to [his] premature death."

Did OHRP need a scapegoat?

Some critics argue that the current oversight system is overburdened and OHRP used the Johns Hopkins incident to establish its existence. Others, however, contend that the death is just one warning of an overburdened system failing to keep pace with mounting pressures.

In the meantime, public awareness about problems and potential ones within medical research is mounting. "I think when you combine a death at a prestigious institution with a government shutdown, it does make a deep impression in the particular city at least," says **Michael A. Susko**, president of Citizens for Responsible Care in Psychiatry and Research (CIRCARE), a New York-based group lobbying for oversight for patients in research programs, especially those with mental illness.

"At present, there is sustained national attention on the issue of human research subjects and their safety, so I think the issue is coming to the national consciousness," he adds.

In fact, the *Washington Post* published an editorial in its Aug. 2, 2001 edition defending the actions of OHRP and went further by calling for additional staffing at research institutions. "For research to be properly monitored, most universities need at least to double the number of review board personnel," the paper states.

Paul Gelsinger, the father of Jesse Gelsinger, who died in a gene therapy clinical trial at the

COMING IN FUTURE MONTHS

- How to put your IRB in cyberspace
- Dust off those policies and procedures
- Is stem cell research headed to Capitol Hill?
- Your meetings and the HIPAA privacy rule
- How do administrators rate the quality of your IRB's work

University of Pennsylvania in 1999, responded to the Johns Hopkins incident by saying that the current system is not fair to anyone. **(To see his response, see p. 14.)**

How long will they remember?

There likely will be some short-term negative impact on clinical trials, says Susko. Not only in terms of public perception, but in a wariness to participate in a trial "particularly when an ordinary healthy volunteer dies, because the potential participant sees the victim as someone like themselves," he says.

The greater long-term impact, however, would be to continue as is and not provide meaningful informed consent and lose the trust of the general public, explains Susko. "The research institutions should take the medicine now and, after genuine reform, will not have to worry about obtaining subjects. Yet it may be that with genuine informed consent that certain types of challenge studies would not be conducted. But that's the risk the researchers have to take, just as they are asking their subjects to take risks," he contends.

But others suggest that the OHRP actions toward Johns Hopkins will do nothing to help human research subjects. "Suspensions like the Johns Hopkins case will simply shift research subjects to other sites, many of which will have IRBs less qualified than the existing IRB," says **Steven Belknap**, MD, assistant professor of clinical pharmacology and medicine at the University of Illinois College of Medicine at Peoria.

Rather than continuing to focus on punishing the institutions, the OHRP should instead focus on investigator competence, suggests Belknap.

In addition, FDA guidance over whether the use of hexamethonium required an IND is unclear, says Belknap. Had its guidance been clearer, the investigator — and peers at other medical centers — would likely have submitted investigational new drugs (INDs), he notes.

"If the FDA then denied the Johns Hopkins' hexamethonium IND, then Ellen Roche would still be alive, but if the FDA had permitted the IND, the outcome would still be the same despite the IND," explains Belknap. ■

Focus of findings lost in media spotlight

Real lessons learned from others' mistakes

There are lessons to be learned from the Office of Human Research Protections' (OHRP) recent temporary suspension of human research at Johns Hopkins Bayview Medical Center.

In fact, there are three lessons taken from the OHRP report, says **Robert M. Nelson**, MD, PhD, associate professor of anesthesia and pediatrics at The Children's Hospital of Philadelphia.

Johns Hopkins University Medical Institutions was suspended from human research on July 19, after a 24-year-old research participant received a lethal inhalation of hexamethonium bromide solution. Investigators reinstated the multiple project assurance on July 21.

The OHRP multiple project assurance suspension and subsequent reinstatement affected the following Johns Hopkins institutions:

- Johns Hopkins University School of Medicine;
- Johns Hopkins University School of Nursing;
- Johns Hopkins Hospital;
- Johns Hopkins Bayview Medical Center;
- Gerontology Research Center of the National Institute of Aging — Bayview campus;
- Kennedy Krieger Institute;
- Applied Physics Laboratory.

The most surprising allegation in the OHRP report, however, is not the use of the hexamethonium bromide solution that the mainstream media focused on, notes Nelson. It is that the IRB failed to conduct an initial review of new protocols.

"Of note, the minutes and audiotapes of IRB meetings and our discussions with IRB members and administrators indicate that no review takes place at convened meetings for most protocols undergoing initial review. Most protocols are neither individually presented nor discussed at a convened meeting of any IRB," the OHRP report states.

Learn from others' mistakes

So what can IRBs learn from the investigation? "I take at least three lessons from the report," says Nelson. Here are the important lessons to learn from the OHRP report:

1. Conduct independent reviews.

"An IRB needs to be diligent in conducting an

How Johns Hopkins University Medical Institutions responded

Johns Hopkins Medical Institutions' response to the U.S. Food and Drug Administration's observations concerning the death of a research volunteer:

1. Failure by the sponsor / clinical investigator to submit an investigational new drug (IND) to the U.S. Food and Drug Administration (FDA) prior to conducting this clinical investigation, which involved the administration of hexamethonium bromide by inhalation to three human subjects.

Both the investigator and the IRB believed an IND was not needed for two reasons: a) the study was not meant to test the therapeutic value of hexamethonium, but was a basic physiological study; b) hexamethonium was long used as an approved drug and was taken off the FDA registry in 1997 at the request of the manufacturer, presumably not because of adverse effects, but because other, better agents were available for treatment of high blood pressure.

While the IRB reached its conclusion in a thoughtful manner, since the event, the IRB placed a hold on investigations involving agents for which there is not an IND number until it consults with the FDA on the IND issue.

2. Failure to report a unanticipated adverse event to the IRB (a persistent cough in the first subject, from April 25 to May 3, 2001).

Dr. Alkis Togias informed the FDA inspectors that it was his opinion that the cough was due to an upper respiratory ailment going around the campus at that time. We are reiterating to faculty that all unanticipated adverse events must be reported to the IRB.

3. and 4. Failure to follow protocol and to report changes to the protocol, specifically by adding sodium bicarbonate to the hexamethonium to be administered by inhalation to the second and third subjects, thus altering the saline solution listed in the protocol.

As previously reported, for the comfort of the volunteers the investigator made alterations in the administered substance in accordance with preparations previously used and reported in the literature. Nonetheless, these should have been reported to the IRB. We have reminded faculty of the necessity to obtain approval for all changes to approved protocols.

5. Failure to obtain effective informed consents from subjects by failing to disclose that inhalation administration of hexamethonium was an experimental use of the drug.

After review and consideration, our IRB believed the lengthy consent form was adequate in addressing known risks. This issue is being addressed by the internal review committee, and we are awaiting its findings.

These preliminary observations may have had nothing to do with the death of the research volunteer, but we agree that they raise issues that we are addressing. We will do whatever it takes to protect those people who generously volunteer to help advance medical knowledge and care.

Source: Johns Hopkins Medical Institutions, Baltimore. ■

independent review of the safety of the interventions in any protocol," notes Nelson. Johns Hopkins officials stated that they will develop a policy about how independent reviews will take place at their facilities, including database searches, adds Nelson.

"My practice is to search the medical databases when I review a new protocol and a continuing review," explains Nelson. As a result of the OHRP report, however, Nelson plans to develop a formal policy and put it into place as soon as possible.

2. Review the use of off-label drugs.

All uses of off-label or unapproved drugs should be reviewed, including chemicals, says Nelson. Also consider whether or not an investigational new drug (IND) application should be required, he adds. "My preferred approach is to assume an IND will be required and put the burden of proof on the investigators."

3. Review informed consent documents.

Consent documents should undergo more rigorous reviews to clearly identify risks to the participant, says Nelson. "The standard information for a research study should include all risks rather than a clinical consent. The assumption that the intervention is in the participant's best interest may not — and likely will not — hold up in the research setting," explains Nelson.

What someone would want to know in order to enroll in a research study, or the "reasonable volunteer," is more than what someone would want to know to accept a recommended treatment, or the "reasonable patient," says Nelson.

Consent review assessments should include a comprehensive list of risk information, he adds.

"Being able to turn right on red is a good idea at most corners, but deciding to do this on our own in the absence of legislation to that effect produces chaos," says Nelson. Institutions need to be held accountable to meeting the current standards of IRB review, he adds. ■

Stress safety to ease fears

Tips on educating volunteers

Do patient recruits ever ask the question, "Are clinical trials safe?" Chances are, they do.

Naturally, patients are hesitant to participate when questions are left unanswered or risks aren't adequately explained. The best method to ease fears and answer questions is to educate patients beforehand, says **Christopher P. Steidle**, MD, a researcher for AmericasDoctor and medical director of Northeast Indiana Research in Fort Wayne. AmericasDoctor is a Chicago-based clinical research company with more than 213 investigative sites and over 550 studies ongoing in urology, rheumatology, pulmonology, women's health, and endocrinology, to name just a few.

"While the Food and Drug Administration closely monitors the majority of clinical research, it's important for prospective volunteers to learn everything they can about the study, including whether it is sanctioned by the FDA," says Steidle.

Steidle, a urologist and researcher on male and female sexual dysfunction, offers several tips on helping patient participants make an informed choice before entering a clinical trial. Here are ways to help participants determine if a trial is right for them:

• **Do your homework.** Find information on clinical trials by visiting local health fairs, checking with a local teaching hospital or medical school, or browsing sites on the Internet. Always verify the credibility of the site you are visiting to gather information. Steidle recommends AmericasDoctor.com, which has a series of educational articles about the clinical trial process, from an overview to a detailed discussion of such issues as institutional review boards and the informed consent process. Other good resources include CenterWatch.com and clinicaltrials.gov, which offer both trial listings and information about the entire research process.

• **Seek expert knowledge.** Talk with your doctor or health care provider before reaching any final decisions. Ask your doctor if he or she or a physician they know and trust has done any research, and what other concerns should be addressed, given your medical history.

• **Get all the information available.** Leave nothing to chance, and don't be afraid to ask as many questions as you need to feel comfortable. Find out all you can, including benefits, dangers, duration, and location, for each research study. Make sure you get the particulars up front so you can make an informed decision. Many trials have a new drug brochure to help you cover all the bases.

• **Network:** Check with trusted family and/or friends who may have been in a research study about their feelings and experiences. But be warned: What might be right for one person may not be right for another.

• **Pay constant and careful attention:** Read consent forms through to the end before signing on the dotted line. These all-important documents lay out your rights and responsibilities, as well as every intricate detail, including any known risks and benefits associated with the clinical trial. Again, ask as many questions as you need.

• **No matter what, you have the option to drop out of a trial at any time, for any reason.** Don't worry that once you've made the commitment, you're stuck in something that doesn't work for you. Naturally it is the goal of researchers to complete a trial in order to benefit as many patients as possible. But your chief concern is your own safety. The laws are there to protect your rights. Know the process and everyone wins. ■

OK job, but more work to do

FDA goes under congressional microscope

Women and men have different metabolic reactions to medications.

While it may be obvious news to administrators and investigators, the government agency responsible for ensuring the differences are

documented isn't doing its job. That's the mixed assessment from a new report released by the congressional watchdog agency, the General Accounting Office (GAO).

FDA needs more monitoring

The good news is that the GAO found that clinical trials adequately include women in new drug testing. The bad news is that the U.S. Food and Drug Administration (FDA) doesn't adequately oversee the testing through outcomes data related to the differences in sex.

The report, titled *Women's Health: Women Sufficiently Represented in New Drug Testing, but FDA Oversight Needs Improvement* (GAO-01-754), found three areas of concern regarding regulations from the U.S. Food and Drug Administration (FDA). First, there is a small number of women enrolled in early, small-scale safety studies. Second, GAO investigators doubt that new drug application sponsors and FDA reviewers took advantage of available data to learn more about the effects of drugs in women and to explore potential sex differences in dosing. Third, the FDA does not have adequate management systems in place to monitor the number of women enrolled in clinical trials, or to ensure sponsors and reports comply with regulations for presenting outcome data by sex and that sex-related issues are adequately addressed in reviews.

Three attempts since 1992

Prior to publishing the report, GAO staff investigated the FDA's progress in including women in clinical drug trials since 1992. Specifically, the GAO report addresses:

- FDA guidance documents and regulations that govern the inclusion of women in clinical drug trials;
- whether the regulations are being followed;
- whether the appropriate number of women are included in clinical drug trials to ensure the safety and efficacy of drugs for women;
- how the FDA oversees the collection, presentation, and analysis of data related to differences in gender.

The FDA published three documents since 1992 in an attempt to address the inclusion of women in clinical drug trials. The first, a set of guidelines, was published in 1993. Subsequently, new regulations were announced in 1998 and 2000.

GAO investigators acknowledge that the 1993 guidelines lacked the force of law, but the legally binding regulations from 1998 and 2000 provide fewer specifics on complying with the regulation. Investigators also note that the regulations enacted in 2000 allow the FDA to suspend research programs where eligible men and women are excluded from participation based solely on their reproductive potential. The regulation does not, however, specify a particular number of men or women to be enrolled. **(For GAO estimates on participation by sex, see charts, pp. 19-20.)**

No management system

GAO investigators conclude that the FDA is ineffective in overseeing the presentation and analysis of data related to sex differences in drug development based on the following:

- There is no management system in place to record and track the inclusion of women in clinical drug trials or to monitor compliance with relevant regulations.
- The FDA is unaware that many new drug application submissions failed to meet standards.
- The FDA does not routinely review required tabulations of demographic data by sex in annual reports for drug development.
- FDA management lacks procedures to determine whether written reviews of new drug applications prepared by its medical officers adequately discuss sex differences.

(Continued on page 21)

Recommended Reading

- **Drug Safety:** *Most Drugs Withdrawn in Recent Years had Greater Health Risks for Women* (GAO-01-286R, Jan. 23, 2001).
- **Women's Health:** *NIH has Increased Its Efforts to Include Women in Research* (GAO / HEHS-00-96, May 2, 2000).
- **Women's Health:** *FDA Needs to Ensure More Study of Gender Differences in Prescription Drug Testing* (GAO / HRD-93-17, Oct. 29, 1993).
- **National Institutes of Health:** *Problems in Implementing Policy on Women in Study Populations* (GAO / T-HRD-90-50, July 24, 1990). ■

Estimate of Women and Men in Clinical Drug Trials by Drug Class

	NDA Overall			Small-Scale Safety Trials			Subsequent Safety and Efficacy Trials		
	Total	Percent Women	Percent Men	Total	Percent Women	Percent Men	Total	Percent Women	Percent Men
Analgesics and Anesthetics (3)									
A	28,815	66	34	813	23	77	28,002	67	33
B[a]	10,702	44	17	1,531	14	18	9,171	49	17
C[a]	5,659	24	35	523	24	73	5,136	24	32
Anti-Infectives and Immunosuppressants (9)									
A[a]	5,924	40	59	482	21	74	5,442	42	57
B[a]	6,578	52	44	490	28	72	6,088	54	42
C	1,545	15	79	418	11	68	1,127	17	83
D	6,860	51	49	722	34	66	6,138	53	47
E[a]	4,272	53	45	274	17	83	3,998	55	42
F[a]	9,327	51	49	557	9	79	8,770	54	46
G	2,995	32	68	730	22	78	2,265	35	65
H	1,673	21	79	675	27	73	998	16	84
I[a]	7,544	46	36	1,103	10	78	6,441	52	28
Cancer (5)									
A[a]	1,195	34	53	202	21	32	933	37	57
B	3,527	99	1	123	73	27	3,404	100	0
C[a]	1,472	4	5	40	50	50	1,432	3	4
D[a]	684	31	64	186	38	55	498	28	67
E[a]	927	51	48	184	45	55	743	52	46
Diabetes & Cholesterol (5)									
A[a]	1,543	42	43	240	4	4	1,303	50	50
B	2,455	40	60	155	8	92	2,300	43	57
C[a]	4,689	37	53	529	11	89	4,160	41	48
D[a]	8,084	34	65	528	19	81	7,556	35	64
E	4,465	43	57	720	23	77	3,745	47	53
Neuropharmacological (6)									
A	3,226	50	50	307	20	80	2,919	53	47
B	5,480	83	17	352	31	69	5,128	87	13
C	5,042	84	16	289	43	57	4,753	86	14
D[a]	5,833	52	37	391	31	69	5,442	54	35
E[a]	9,333	56	15	578	15	81	8,755	58	11
F[a]	955	26	39	104	0	100	851	29	32
Ophthalmological (5)									
A	1,557	58	42	82	44	56	1,475	59	41
B[a]	1,084	34	33	40	20	80	1,044	35	32
C	5,238	52	48	22	50	50	5,216	52	48
D[a]	2,438	39	33	34	41	59	2,404	39	33
E[a]	988	46	44	271	39	61	717	48	38
Other (3)									
A	1,855	77	22	220	23	71	1,635	85	15
B	6,895	52	48	207	17	83	6,688	53	47
C[a]	5,847	66	28	1,443	28	72	4,044	85	15
Total[a]	**176,706**	**52**	**39**	**15,565**	**22**	**67**	**160,781**	**55**	**36**

[a]Indicated NDAs where the sex of some or all of the participants was not specified by clinical drug development stage (sum of percent women and percent men does not equal 100).

Source: Estimated from GAO analysis of 36 NDAs and FDA medical Officer Reviews.

Estimate of Women and Men in Pivotal Drug Trials by Drug Class

	Overall			Comparison Group			Treatment Group		
	Total	Women	Men	Total	Women	Men	Total	Women	Men
Analgesics and Anesthetics (3)									
A[a]	19,082								
B	3,022	2,279	743	1,111	850	261	1,911	1,429	482
C	931	253	678	373	106	267	558	147	411
Anti-Infectives and Immunosuppressants (9)									
A	1,572	649	923	790	337	453	782	312	470
B	5,829	3,258	2,571	2,102	1,201	901	3,727	2,057	1,670
C	736	128	608	366	67	299	370	61	309
D	1,588	808	780	775	419	356	813	389	424
E	1,346	670	676	443	228	215	903	442	461
F	7,246	3,617	3,629	2,967	1,506	1,461	4,279	2,111	2,168
G	1,295	438	857	291	109	182	1,004	329	675
H[a]	998	164	834	386	66	320	385	75	310
I[a]	5,644	3,021	1,556	2,508	1,836	672	2,145	1,302	843
Cancer (5)									
A	387	145	242	113	41	72	274	104	170
B	1,176	1,176	0	597	597	0	579	579	0
C	59	29	30	0	0	0	59	29	30
D[a]	178	58	94	0	0	0	152	58	94
E	287	118	169	103	45	58	184	73	111
Diabetes & Cholesterol (5)									
A[a]	561	283	278	110	56	54	450	227	223
B	2,090	961	1,129	715	324	391	1,375	637	738
C	2,826	1,300	1,526	1,406	642	764	1,420	658	762
D	2,635	932	1,703	753	233	520	1,882	699	1,183
E[a]	2,319	1,047	1,272	789	366	423	1,512	677	835
Neuropharmacological (6)									
A	904	431	473	312	156	156	592	275	317
B[a]	2,319	1,987	332	549	463	86	1,768	1,522	246
C[a]	4,057	3,520	537	319	273	46	1,123	961	162
D	1,289	803	486	428	263	165	861	540	321
E[a]	5,986	5,100	886						
F	366	167	199	126	57	69	240	110	130
Ophthalmological (5)									
A	305	167	138	25	17	8	280	150	130
B	388	194	194	193	94	99	195	100	95
C	2,406	1,237	1,169	923	473	450	1,483	764	719
D	1,127	583	544	470	242	228	657	341	316
E	609	344	265	207	130	77	402	214	188
Other (3)									
A	484	453	31	164	155	9	320	298	22
B	3,177	1,766	1,411	1,597	915	682	1,580	851	729
C	881	731	150	288	240	48	593	491	102
Total[a]	**86,105**	**38,817**	**27,113**	**22,299**	**12,507**	**9,792**	**34,858**	**19,012**	**15,846**

[a]Indicated NDAs in which the sex of some or all of the participants was not specified for some 0-=09 or all of the pivotal studies overall, the comparison group, or the treatment group.

Source: Estimated from GAO analysis of 36 NDAs and FDA medical Officer Reviews.

(Continued from page 18)

• FDA's medical officers are not required to discuss sex differences in their reviews of new drug applications, and GAO found that many of them do not do so **(see chart, below)**.

• Roughly 30% of new drug applications specified that concentrations of the drug in the bloodstream were greater in people who weigh less (such as women), FDA reviewers did not comment in their summaries on the lack of dose adjustments based on sex.

FDA in the hot seat

The FDA's written response to the GAO charges includes its improvements to existing management techniques, says **Theresa M. Mullin**, PhD, acting associate commissioner for planning at the FDA.

Medical office reviewers soon will fill out templates and demographic worksheets to help monitor women in clinical studies, notes Mullin. "In addition, increased electronic submission of new drug applications by sponsors will allow reviewers easy access to demographic information for further analyses," wrote Mullin in the report.

In addition, the FDA's Office of Women's Health is establishing a clinical trials demographic database in conjunction with all FDA medical product centers. The database will help monitor the inclusion of women in clinical trials, and track other demographic variables could affect the evaluation of safety and efficacy, explains Mullin. Factors such as race, age, and geographic information will be collected.

"The database will help determine level of analysis, differences identified, statistical or clinical relevance, and labeling," writes Mullin. The database is intended to start in fiscal year 2002, depending on resources, she adds.

Seminars planned

The Office of Women's Health plans to offer training and educational seminars based on the recent Institute of Medicine report *Exploring the Biological Contributions to Human Health: Does Sex Matter?* Topics covered in the seminar include the biological basis of gender differences and improving the overall consistency in reviews regarding gender differences.

Lastly, Mullin notes that the FDA had all of the stated improvements in planning well before the GAO began its investigation.

(Editor's note: The first copy of each GAO report is available free of charge. Additional copies are $2 each. To order by mail, write: U.S. General Accounting Office, P.O. Box 37050, Washington, DC 20013. Make checks and money orders payable to the Superintendent of Documents. Or order by telephone: (202) 512-6000. Fax: (202) 512-6061.

For information on how to access the GAO report on the Internet, send an e-mail message with "info" in the body to: Info@www.gao.gov, or visit the GAO home page on the web: www.gao.gov.) ■

Medical Officer Reviews Not Discussing Sponsor-Reported Sex-Related Analyses of Differences in Drug Response

(All figures in percent)

	No discussion of analyses of differences in drug response between men and women	No discussion of analyses of differences in drug response between women using the test drug and women in a comparison group
Safety	61	81
Efficacy	58	75
Pharmacokinetics	44	n/a[a]

[a] Pharmacokinetic studies are usually performed using just the test drug.

Source: GAO's review of 36 Medical Officer Reviews.

AIDS research needs more women, physicians say

Historically, women were excluded from clinical drug trials because the majority of AIDS patients were men, but not anymore. Women now make up more than half of the more than 36 million adults infected with human immunovirus (HIV) worldwide.

In fact, women are the fastest growing group of HIV-infected patients in the United States. The percentage of women newly diagnosed with the virus has doubled over the last 10 years. The problem is equally disturbing in European countries, where similar increases are reported. The numbers are likely to rise because the virus increasingly is transmitted through heterosexual contact, says AIDS researcher **James Witek**, from MCP Hahnemann University in Philadelphia.

More women are needed in research because female patients respond differently to the disease and treatment, he adds. One difference is through detection, says **Carlos Arboleda**, treatment director at the National Minority AIDS Council in Washington, DC. "One of the main differences is that women are diagnosed later in the disease than men because they do not perceive themselves as at risk," he notes.

The next step following diagnosis is balancing an effective treatment with minimal side effects, which is an especially tough task for physicians treating female patients, says **Cathy Christeller**, executive director of the Chicago Women's AIDS Project.

"If the doctor's don't know how to fine-tune treatment for gender, it makes it difficult," says Christeller. "We're trying to educate women that there are really good treatments available, but we're kind of handicapped."

Determining an appropriate treatment for women can be difficult due to women generally weighing less and having lower viral loads than men who might be just as sick, adds Christeller.

Researchers are making an effort to recruit more women into studies, says Witek. "There is a push to try and include women in clinical trials. Some of the trials now consider things like providing money for child care and other expenses." ■

Medical journals change policy

Researchers — not the drug companies who fund the studies — will have final editorial control over medical studies published in the world's leading medical journals.

That's the announcement made from the International Committee of Medical Journal Editors at its annual meeting held in May in Philadelphia. The policy changes, along with an editorial explaining them, will be published in the respective journals in September.

Under the changes, authors will have control over the content of reports submitted to journals for publication in addition to having access to all data gathered during the study. At stake are millions of dollars in research funds because the results determine whether the U.S. Food and Drug Administration (FDA) approves the drug or allows additional uses for existing drugs.

The changes were made because editors were concerned that drug companies sometimes wield too much influence over article content and have veto powers over what is submitted for publication.

Journals are overreacting to a few examples of questionable conduct, counters **Jeff Trewhitt**, a spokesman for the Washington, DC-based Pharmaceutical Research and Manufacturers of America. "In the vast majority of cases, these studies are conducted soundly and with scientific credibility," he says.

"If you play fast and loose with the data, it will catch up with you eventually. If you lose credibility with the FDA, doctors and patients, you have a major problem, and companies are very aware of this," explains Trewhitt.

Editors, however, are concerned over instances where study authors do not have access to data and only see what the drug sponsor gives them. In a few cases, drug companies have attempted to block publication of unfavorable results. The drug companies state that contractual agreements allow them final approval of what gets released.

"Nobody knows how often agreements get written that way. The number of egregious examples is small, but the sense is a lot more of that

goes on than anyone is able to document," says **Frank Davidoff**, MD, editor emeritus of the *Annals of Internal Medicine.*

Publications agreeing to the policy change include the *New England Journal of Medicine* (Boston), *The Lancet* (London), the *Journal of the American Medical Association* (Chicago), the *Annals of Internal Medicine* (Philadelphia), and the national medical society journals of Australia, Canada, the Netherlands, New Zealand, and Norway. ▼

Oversight council to monitor stem cell research

President Bush's stipulations supporting limited stem cell research included the creation of an oversight council. The council will be responsible for monitoring research and recommending appropriate guidelines and regulations for stem cell research.

The council also will consider medical and ethical ramifications of biomedical innovations from stem cell research. The President named **Leon Kass**, a biomedical ethicist at the University of Chicago, as chair of the council. Members of the council will include scientists, physicians, ethicists, lawyers, and theologians.

The federal funding for stem cell research will apply only to existing stem cell lines derived from embryos that have already been destroyed. The existing stem cell lines can regenerate themselves indefinitely, which will create ongoing opportunities for further research. ▼

FDA may ban researcher

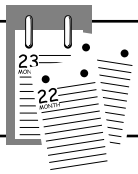
A former researcher at the University of Oklahoma in Tulsa may be banned from further research from the U.S. Food and Drug Administration (FDA).

The FDA alleges that the researcher violated its regulations intended to ensure patient safety in trials involving investigational new melanoma vaccines. Specifically, the researcher failed to abide by safety provisions in the protocol and made changes to the protocol before obtaining approval from the university's IRB, according to the FDA.

The Office for Human Research Protections (OHRP) first discovered violations to patient safety rules last year. OHRP ordered the University of Oklahoma Health Sciences Center at Tulsa to end all government-funded clinical research involving human subjects.

The ban was later lifted after the university disbanded the IRB at the Tulsa campus and instituted additional reforms. ■

CALENDAR



• **Certification Exam for IRB Professionals — Oct. 20, 2001.** Sponsored by Applied Research Ethics National Association (ARENA). Interested candidates should contact Professional Testing

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Vice President/Group Publisher: **Brenda Mooney**, (404) 262-5403, (brenda.mooney@ahcpub.com).
Editorial Group Head: **Leslie Coplin**, (404) 262-5534, (leslie.coplin@ahcpub.com).
Managing Editor: **Kevin New**, (404) 262-5467, (kevin.new@ahcpub.com).
Production Editor: **Nancy McCreary**.

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Editorial Questions

Questions or comments?
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• **IRB 101 — Dec. 1, 2001.** A training program for IRB members, administrators, chairs, and clinical investigators. Sheraton Boston Hotel, Boston. Sponsored by Public Responsibility in Medicine & Research (PRIM&R). For more information, contact PRIM&R, 132 Boylston St., Fourth Floor, Boston, MA 02116. World Wide Web: www.primr.org.

• **RCR 101 — Dec. 1, 2001.** An educational workshop to teach responsible conduct of research. Sheraton Hotel Boston, Boston. Sponsored by Public Responsibility in Medicine & Research (PRIM&R). For more information, contact PRIM&R, 132 Boylston St., Fourth Floor, Boston, MA 02116. World Wide Web: www.primr.org. ■

CME*questions*

The CME objectives for *IRB Advisor* are to help physicians be able to:

- establish clinical trial programs using accepted ethical principles for human subject protection;
- understand the regulatory qualifications regarding human subject research;
- comply with the necessary educational requirements regarding informed consent and human subject research;
- apply the necessary safeguards for patient recruitment, follow-up, and reporting of findings for human subject research;
- have an understanding of the potential for conflict of financial interests involving human subject research;
- understand reporting adverse events during research.

5. The Office of Human Research Protections investigators concluded a total of how many findings against the research program at Johns Hopkins University's medical institutions:
   A. 10
   B. 31
   C 50
   D. more than 100

6. According to Robert M. Nelson, MD, PhD, associate professor of anesthesia and pediatrics at The Children's Hospital of Philadelphia, which of the following lessons can IRBs take from the Office of Human Research Protections report on research at Johns Hopkins?
   A. Conduct independent reviews
   B. Review the use of off-label drugs
   C. Review informed consent documents
   D. All of the above

7. According to Christopher P. Steidle, MD, a researcher for AmericasDoctor and medical director of Northeast Indiana Research, the best method to ease fears for potential patient volunteers in medical research is through:
   A. thorough screening processes
   B. weekly communication
   C. education
   D. all of the above

8. One of the main findings of a recent Government Accounting Office report on women and clinical trials found:
   A. both government regulatory agencies and medical research programs adequately recruit and monitor women's differences in medications and no changes were recommended.
   B. the U.S. Food and Drug Administration doesn't adequately oversee the testing through outcomes data related to the differences in sex.
   C. more women need to be recruited by research investigators into clinical trials so that government agencies can adequately monitor differences.
   D. the Office of Human Research Protections needs to develop an educational awareness program for research investigators on the necessity of more women in clinical trial research.