Report on
RESEARCH COMPLIANCE

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News and Analysis for Colleges, Universities and Teaching Hospitals

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With Just One Investigation in 2013, OHRP Seems 'Invisible' After SUPPORT Dust-Up

Perhaps chastened by its public battle with NIH over a study of oxygen levels in premature infants, the HHS Office for Human Research Protections (OHRP) opened just one investigation into allegations of violations of human subject protections in all of 2013, *RRC* has learned. OHRP also closed out the year with a record low number of unique "determination letters" that identify non-compliance and required corrective actions — just five. And as of mid-April, OHRP had not opened any investigations so far this year.

But the controversy over the NIH-funded Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) may simply have accelerated a trend that has marked OHRP in recent years. The number of compliance actions has been skidding downward since the arrival of OHRP Director Jerry Menikoff in October 2008 *(RRC 3/11, p. 1)*. In 2011, OHRP opened five cases, the lowest number up until 2013; prior to 2009 it typically had 20 open cases per year.

The recent near-halt to the activities has caught the attention of Sen. Charles Grassley (R-Iowa), who told *RRC* these developments, and the possibility of a threat to OHRP's "autonomy," were "worrisome."

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Group to Request Rehearing in U.Va. Case, Expand Pursuit of Researchers' Emails

Although the University of Virginia (U.Va.) recently won a case protecting a climate scientist's emails, the ruling is binding only in the commonwealth, and the organization that filed suit plans to keep peppering universities around the country with similar requests under state open records laws.

The Supreme Court of Virginia's April 12 ruling upheld a trial court finding that the emails of climatologist Michael Mann, who was with U.Va. from 1998 to 2005, were excluded from release because they qualified as "proprietary" under the Virginia Freedom of Information Act (FOIA). Mann is currently a professor of meteorology and director of the Earth System Science Center at Penn State.

"In the context of the higher education research exclusion, competitive disadvantage implicates not only financial injury, but also harm to university-wide research efforts, damage to faculty recruitment and retention, undermining of faculty expectations of privacy and confidentiality, and impairment of free thought and expression. This broader notion of competitive disadvantage is the overarching principle guiding application of the exemption," Justice Donald Lemons wrote.

The American Tradition Institute (ATI), now called the Energy and Environment Legal Institute, has been filing federal and state FOIA requests to obtain records, documents, emails and other information since 2009 when hackers released emails from the University of East Anglia's Climate Research Unit, an incident later known as

"Climategate" *(RRC 7/10, p. 1)*. Mann's were among them, and climate change skeptics accused him of manipulating data in a graph known as the "hockey stick." Research misconduct investigations by the National Science Foundation, Penn State and others found no wrongdoing by Mann.

David Schnare, the lead attorney for the legal institute, told *RRC* he was "disappointed but not surprised" by the Virginia Supreme Court decision, which he says is "a complete pass" for universities in the state.

He plans to seek a rehearing before Virginia's top court, although he acknowledged that such requests are rarely granted, and less likely to be successful, especially when, as in this case, a decision is unanimous.

Should his request for a rehearing fail, Schnare said his advice to universities in that state would be "Don't give up anything ever." Others say the ruling is not as broad as that, but does bring needed clarity to the law.

But Share's attention is not focused just on Virginia. The institute is currently in Arizona Superior Court in Pima County in a case it filed against the University of Arizona seeking emails from two climate scientists. It also plans to file new requests for similar information from the University of Maryland (UMD) and a university in Illinois, Schnare told *RRC*.

"All [the requests] are related to faculty working on climate change but the FOIAs do not seek climate change data. Rather, we are looking at [how] these government employees are coordinating with political operatives, something entirely unrelated to science. In the case of the Maryland faculty member, the FOIA will go to the federal agency where he has a joint appointment. In Illinois it will go to the university," Schnare said.

Regarding the Maryland complaint, Schnare said this request "will deal with [the researcher's] contacts with the Union of Concerned Scientists" (UCS).

In 2012, the union issued "Science in an Age of Scrutiny: How Scientists Can Respond to Criticism and Personal Attacks," its guide to help "scientists deal with harassment and other unwarranted attacks on their integrity and their work" *(RRC 12/12, p. 1)*.

Be Aware of Rights, Responsibilities

Michael Halpern, program manager for the organization's Center for Science and Democracy, said he was not aware of Schnare's plans nor who the Maryland scientist at issue might be.

UCS "works regularly with scientists to help them develop public communications skills and to effectively share their expertise with policymakers and elected officials who are charged with making complex decisions on scientific topics, Halpern said. "At times, UCS staff also collaborate with peers who work for private and public universities and for government agencies on scientific research; this is common practice among many non-profit organizations."

But he agreed with Schnare that this case clearly isn't the end of the discussion over public records and climate science. Each state FOIA law is different, Halpern pointed out, and with the exception of Virginia's, no state FOIA laws have been interpreted in court.

While this area of law remains unsettled, attorneys and associations representing research universities "should devote time and resources to determining and publicly disclosing how they will respond to open records requests," Halpern wrote on the union's blog after the Virginia court decision. "Those who work for public institutions should be made aware of their rights and responsibilities for responsibly using email systems."

Halpern also suggested that the National Academy of Sciences and similar entities "should provide guidance to legislators and universities on what kinds of

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materials should be disclosed and what kinds should be protected."

In addition, "proactive disclosure could avoid costly and time-consuming lawsuits. Because really, Freedom of Information Act requests should be considered the option of last resort for those who want to understand the public's business," he said.

What's needed, Halpern said, is a "shared understanding of what should be disclosed, and a system created to proactively disclose certain records" to avoid impending research.

Links to Virginia court ruling: http://www.courts.state.va.us/opinions/opnscvwp/1130934.pdf

Link to UCS's blog: http://www.ucsusa.org/news/press_release/virginia-supreme-court-document-requests-0409.html ✧

Managing a COI: The Right Answer May Be to Just Say 'No'

Near the close of a 90-minute panel discussion on managing conflicts of interest (COIs) "in the new age of transparency" held at the recent annual meeting of the Association of University Technology Managers (AUTM), an attendee piped up: "Can we talk about management plans, please?" he implored. "Because we're almost at the end of the session and for most of us that's the hardest part."

The four conference speakers, who hailed from Stanford University, Boston University and two from the Massachusetts Institute of Technology (MIT), were happy to oblige, offering a host of strategies they have employed on their campuses. Their comments are especially timely as all agencies will soon have COI regulations in place.

Perhaps the strongest admonition came from Barbara Flynn, director of the Conflict of Interest Review Program for Stanford University School of Medicine.

"The first thing you can do to manage [a COI] is to say 'No…you can't do it. You're too conflicted to do this study,'" said Flynn, forcefully articulating an opinion formed by 30 years of handling such issues.

"An institution that doesn't have the spine to say that is going to end up in big trouble," Flynn told the attendees at the recent meeting. Other topics included at the meeting were policies for start-up companies *(RRC 4/14, p. 5)*.

All institutional recipients of funding from NIH and other agencies within the Public Health Service (PHS) have been operating under a revised financial COI policy that went into effect in August 2012 *(RRC 8/12, p. 1)*.

Those that receive funding from the National Science Foundation are required to notify NSF of any "unmanaged" conflicts via Fastlane. As of Jan. 1, 2013, NSF's Office of General Council "will contact the institution making the report, obtain a copy of that institution's policy, and follow up with the institution regarding what actions the institution will take with respect to the reported COI *(RRC 8/12, p. 5)*.

More Agencies Must Adopt COI Regulations

Recipients of funding from other agencies who have thus far escaped COI regulations won't be able to do so for long. That's because the omnibus circular published in December by the Office of Management and Budget (OMB), in section 200.112, states in its entirety: "The Federal awarding agency must establish conflict of interest policies for Federal awards. The non-Federal entity must disclose in writing any potential conflict of interest [COI] to the Federal awarding agency or pass-through entity in accordance with applicable Federal awarding agency policy *(RRC 2/14, p. 1)*."

Until regulations are issued — drafts for rules to implement the requirements in the new circular are due to OMB in June — there's no telling what agencies that don't now require FCOI reporting will come up with.

It's likely, though, that they will look to NIH as a model. However, the PHS policy deals only with financial conflicts of interest (FCOI); other agencies could broaden (or restrict) their requirements and adopt policies that differ from PHS's in other ways.

The PHS policy, among other requirements, mandates that PHS-supported principal investigators (PIs) and others as specified report to their institution any significant financial interests that meet certain income thresholds.

Institutions, in turn, determine whether an FCOI as defined in the regulation exists, and, "if so, develop and implement a management plan that shall specify the actions that have been, and shall be, taken to manage such financial conflict of interest" *(RRC 10/11, p. 3)*.

Flynn was joined at the conference session by Jodi Edelstein, compliance manager for COI at Boston University and Boston Medical Center; Rupinder Grewal, the COI officer at MIT; and Catherine Ives, MIT's technology licensing officer. Much of the session was devoted to a discussion of how universities have complied with the PHS COI regulations. The speakers also addressed COI issues specific to start-up firms launched by faculty *(RRC 4/14, p. 5)*.

If institutions can eliminate the FCOI, no management plan is necessary. Saying "no" to conducting the research at all is sometimes necessary, Flynn said,

because the machinations required to manage the conflict can be too costly.

Institutions that develop complicated management plans may find "there's no money" to take the steps required, such as hiring outside, independent data analysis experts, said Flynn.

In these cases, "You're going to have to say, 'No, let somebody else do it.' And usually you can find somebody else to do it," said Flynn, who also counseled being "honest" with investigators.

When talking to the investigator, Flynn may say, "That's going to be really bad for you. And it is going to be really bad for Stanford. But Stanford's going to survive. But I have to ask myself, 'Will the investigator?'"

Edelstein also recommended encouraging investigators to discuss COI issues "really, really, early on and then [the research] budget will account for that. Otherwise, at BU we rely on volunteers" who are already stretched thin to perform functions outlined in the COI management plan.

She and the other speakers stressed that the PIs need to be involved in FCOI discussions to determine ways to manage the FCOI if possible and to help develop those strategies. Each also stressed that steps must be taken to ensure that any students who may be involved are protected from any negative effects of the FCOI.

In offering her thoughts on management plans, Edelstein said these typically address three concerns that might "bias the research" when an FCOI is identified. These are patient recruitment, data analysis and drafting of a manuscript about the research for publication.

"You don't want someone who is highly conflicted, highly personally invested in it to be recruiting patients," Edelstein said. "You don't want them doing data analysis….[You] want to have someone independent doing that kind of heavy work, and you also don't want them doing the manuscript."

A person who is "highly conflicted" might be permitted to "write about the technical aspects of the treatment, the technical aspects of the technology, but when it comes to writing out the conclusion, pulling apart the analysis, you want that high risk person out," Edelstein said.

Her organizations may "also ask the principal investigator to recuse himself from different areas of the project, like the three areas I just said, or we'll have an independent party step into certain areas of the research," Edelstein said.

COI management plans can mandate disclosures to the colleagues and students who are involved in the research.

"We have something called a safe haven monitor, which would usually be me," Edelstein said. "I speak with the students, or any other trainees involved just to ensure that they're not experiencing any kind of duress or anything that looks like it might be harm to the research due to financial interest."

Organizations want to ensure that "students that are being supervised by the faculty member who has a significant COI...have the experience that every graduate student should have, which is to do independent research not skirting into the interests of the faculty member's company," MIT's Ives said.

Stanford Requires Disclosure to Lab Members

In a previous position at a different university, Ives said, "if we had to put together a management plan, if we couldn't divest or eliminate the conflict," the investigator had to "disclose, in writing, to every single graduate student that they have this conflict," and spell out what it is. Further, she said, "They have to, with the student, identify another co-advisor" that the student could see.

"One of the things that we do at Stanford is, I actually go in and do lab training in a conflicted lab," Flynn said. "Everybody knows what the conflict is. Everybody knows what the positive values [of these relationships are], what the risks are. Everybody knows where they can go to, either confidentially or not confidentially, say 'I feel like my academic freedoms are being compromised.' Believe me, that goes a long way toward leveling the playing field."

Grewal pointed out that all management plans are different and address the unique issues in the situation. "But I do want to state that the investigator is involved in all of those decisions. Because at the end of the day we can hand down a decision, we can put together a plan, we can hand it to them, but if they can't comply with it then it's all kind of over. So they are a huge part of what we as an institute can do to fulfill our obligations. It's a fairly big process."

A detailed management plan, particularly for a start-up company, may work best at institutions where

"you've got relatively few," Ives added. "These conflict management plans, not just developing them, but monitoring them, is an administrative burden."

Flynn agreed that handling COIs requires buy-in from the entire organization.

"I've said this for years, and I'm going to keep saying it: It takes a village to manage a conflict of interest," she said, meaning that "each and every person involved in that actually knows about it" and is willing to act appropriately.

Even when organizations set up committees to assist with COI management, their effectiveness may be limited.

"I'll tell you something I learned a long time ago. It's real easy to appoint an oversight committee. It's impossible to get that committee to meet. And it's way more impossible to get them to give you a report," Flynn said. "So you stop relying on the techniques to manage something that, in fact, don't work."

Link to conference session (archive available for purchase): http://softconference.com/autm/sessionDetail.asp?SID=350086

Link to PHS FCOI regulation: http://tinyurl.com/kh278cm ✧

Psychological Well-Being of Primates Is New Focus for HSUS

Still in the throes of its battle to see that all captive chimpanzees are retired to sanctuaries, the Humane Society of the United States (HSUS) is also pursuing a campaign to verify that protections for other non-human primates (NHP), including the estimated 70,000 monkeys currently used in research, comply with the law.

The 300 chimpanzees owned by NIH have been the subject of HSUS's efforts over the past three years *(RRC 8/13, p. 6)*. After NIH said it would retire "most" of the chimpanzees, HSUS expressed concern over the far larger number of other NHPs used in research *(RRC 2/12, p. 1)*.

NIH recently announced it would require lab housing for chimpanzees permitted in research to be that of just one-quarter of the footage recommended by NIH's Council of Councils and issued a request for information on retirement options (*RRC 4/10/14*).

RRC has learned that HSUS is now reviewing all available plans for "environment enhancement" of captive NHPs to see if they meet regulations in the Animal Welfare Act (AWA), which applies regardless of who owns the animals, the source of funding for their support, or research in which they may be involved. Public Health Service policy also requires compliance with applicable AWA requirements.

Under the AWA's Specifications for the Humane Handling, Care, Treatment, and Transportation of Nonhuman Primates, Section 3.81, Environmental enhancement to promote psychological well-being, all "dealers, exhibitors, and research facilities must develop, document, and follow an appropriate plan for environment enhancement adequate to promote the psychological well-being of nonhuman primates."

At a "minimum," the plans have to address social grouping, environmental enrichment and the use of restraints. Plans must also address the "special attention" provided to great apes weighing more than 110 pounds and for "(1) Infants and young juveniles; (2) Those that show signs of being in psychological distress through behavior or appearance; (3) Those used in research for which the Committee-approved protocol requires restricted activity; [and] (4) Individually housed nonhuman primates that are unable to see and hear nonhuman primates of their own or compatible species."

"I am doing the portion about the enhancement plans at universities," Kathleen Conlee, vice president for animal research issues, told *RRC*. Other staff are reviewing plans created by dealers and exhibitors. "We are looking at all the plans that are available through state open records law," she added. Thus far HSUS has obtained 40 such plans from research universities, although it believes more than 200 universities have non-human primates.

Conlee plans to share her findings with the U.S. Department of Agriculture (USDA), which enforces the AWA, and the universities. Based on her review thus far, "It appears that many of them are failing to meet the minimum" requirements, she said. For example, some have failed to address the required categories or have not updated their plans, according to Conlee. At this point, HSUS is not intending to visit the research sites to see how the universities' environmental enrichment plans are being applied in practice. But it has in the past.

Single Housing Cited at GRU

In December, USDA cited Georgia Regents University in Augusta (GRU) for violations of the AWA, stating that its NHPs "were identified as being singly housed. There was no indication that there were exemptions from social housing for these NHPs," which the inspection report noted may be granted by institutional animal care and use committees for "scientific reasons set forth in the research protocol."

USDA told GRU to "correct" the issue by June 19. The report does not state how many NHPs were singly housed, but HSUS said its undercover investigation

revealed there were at least 50 among two GRU research facilities. HSUS said some primates were engaging in behaviors that showed their distress. But in February, also responding to HSUS's allegations, the NIH Office of Laboratory Animal Welfare concluded that there were appropriate justifications for the NHPs that were singly housed. Officials did not visit the facilities.

"We were very encouraged when the *Guide for the Care and Use of Laboratory Animals*…was renewed a couple of years ago to strengthen guidelines regarding the social housing of nonhuman primates and housing density of mice — but it's clear that those can be easily skirted," Conlee told *RRC*. Institutions that receive HHS funding for animal research are required to follow the *Guide*.

Link: http://www.nal.usda.gov/awic/pubs/Primates2009/primates.shtml#contents ✧

OHRP Is 'Invisible' After SUPPORT

continued from p. 1

Concern is being voiced by medical ethicists and advocates for clinical trial participants, including those who thought OHRP over-reached last February in its actions in the SUPPORT situation (see story, p. 11).

Among them is Art Caplan, director of the Division of Medical Ethics at New York University's Langone Medical Center, who signed a letter published in the *New England Journal of Medicine (NEJM)* backing NIH over OHRP in the SUPPORT dispute. "The drop in investigations is deeply disturbing since there is no reason to presume any shift in the research ethics climate," he told *RRC*. The decline "merits both an explanation and public concern," he added.

"Very disturbing" was how Michael Carome, director of the Health Research Group at Public Citizen, put it. "The only thing that would be more disturbing is if the number [of new investigations] was zero."

OHRP's activities are "spiraling down" to a level that makes the office "seem invisible," Carome said. OHRP "is doing an insufficient job in its compliance oversight role. They are either too reluctant to open cases or to go looking for indications of possible non-compliance."

The fact that OHRP opened only one investigation last year was among the information *RRC* requested of OHRP, which was provided by the HHS public affairs office assigned to OHRP.

OHRP does not post any specific or summary data about its investigations, such as the volume and nature of the complaints and their disposition. The only public evidence of investigations is determination letters that OHRP posts either during or at the conclusion of an investigation.

HHS responded to all of *RRC*'s questions and requests for data about OHRP and did not require the filing of a Freedom of Information Act request.

Regarding the single case opened in 2013, the agency said it "cannot discuss" any details of that investigation, and said it opens cases when appropriate.

RRC also asked whether NIH had exerted any influence on OHRP to not issue determinations. OHRP did not answer this question but referred it to NIH.

"To our knowledge, NIH has not asked OHRP for the opportunity to review determinations/actions OHRP is considering or planning," NIH said in a statement. "OHRP routinely advises agencies about the status of its compliance evaluations. NIH is also copied on OHRP correspondence to institutions."

From 91 Cases to Just One

OHRP has oversight of the largest portion of human subjects research funded by the federal government; its fiscal year (FY) 2015 budget calls OHRP "the lead federal office assuring the integrity of the clinical research enterprise." By its own count, OHRP is charged with safeguarding the well-being of "millions" enrolled in HHS-funded "biomedical and social-behavioral research." It has jurisdiction over some 10,000 institutions that, by virtue of filing a federalwide assurance, pledged they will comply with 45 CFR Part 46, also known as the Common Rule; FWAs are a prerequisite for applicable HHS research funding and are routinely required of subawardees as well.

The Division of Compliance Oversight within OHRP is responsible for investigating allegations of wrongdoing; it calls such investigations "for-cause compliance oversight evaluations." It also conducts "not-for-cause surveillance evaluations" that review an institution's overall oversight of human subjects research; these may or may not include a site visit. OHRP may post determination letters it sends to the institutions being investigated for non-compliance or without cause, which describe the issues and any corrective actions needed or already taken.

OHRP also annually reviews 600 or more "incident reports" from institutions, which cover "unanticipated problems involving risks to subjects or others; serious or continuing noncompliance" with the Common Rule "or the requirements or determinations of the institutional review board (IRB); and suspension or termination of IRB approval." OHRP does not appear to publish any information about these incident reports, even in summary or deidentified formats.

Currently, OHRP is more than halfway into FY 2014, which ends Sept. 30. It is not clear that OHRP will complete the activities described in that year's budget, which

included plans to "open six new compliance oversight investigations" and "close three" such investigations, and open four not-for-cause investigations. In contrast, the FY 2015 budget does not include any predictions of these activities.

OHRP opened 91 cases in 2000, its first year in operation. During the following decade, the number opened per year has fluctuated, dropping to 18 in 2004 before jumping back up to 43 the very next year. In 2006 and 2007, OHRP opened 15 and 16 cases, respectively. But by 2008, however, the number of cases OHRP was opening was in the single digits. In 2008, it opened eight investigations, six in 2009 and eight in 2010.

From 2011 to 2013, OHRP opened a total of 16 investigations. Specifically, OHRP opened five investigations and closed six in 2011; it opened 10 and closed eight in 2012. Five of the 10 investigations opened in 2012 have already been closed. Complicated investigations often take several years to resolve.

As of mid-April, OHRP had not "opened any cases so far this year, but is likely to open two within the next few weeks," the agency said.

OHRP Prefers 'Informal' Resolutions

Complaints that can lead to investigations may come from research subjects, investigators, institutions and elsewhere. Incident reports could also give rise to an investigation, but rarely have, according to OHRP.

The HHS official told *RRC* that OHRP does not get many complaints that are appropriate for it to investigate. "We receive about 100 complaints each year, the vast majority from individuals who call themselves 'targeted individuals' or from individuals who have been involved in FDA-regulated, non-government-funded research. In the latter case, we refer those cases to the FDA," the agency said.

The number of complaints OHRP cited is about 25% fewer than what the agency said it received before 2011. In comparison, OHRP recorded 153 allegations received in 2006, 97 in 2008, and 134 in 2009, OHRP told *RRC* at the time.

Asked how OHRP decides when it opens a case, the HHS statement said OHRP "takes many factors into consideration when determining whether or not to open a case, such as: is the research funded or supported by HHS? Is the research ongoing? How risky is the research? How serious are the allegations? How straightforward would it be to address the allegations informally? Etc."

In its statement, OHRP said that the agency "in recent years…has attempted, when possible, to address relatively straightforward allegations (for example, a complaint from an uncompensated research subject) informally (for example, by having a conversation with the delinquent payer institution). These allegations used to be handled by opening a case and issuing a determination letter, but more recently, the allegations have been resolved informally, making determination letters unnecessary."

In 2011, OHRP also cited a preference for "informal" means of addressing allegations of non-compliance as among the reasons for the decline in investigations and letters. As a result of fewer investigations, OHRP has issued fewer determination letters. In 2012 OHRP issued 13 unique letters, of which five were from not-for-cause evaluations. The number of determination letters had fallen from a high of 146 (in 2002) to a low of 16 (in 2010).

In 2013, as previously noted, OHRP issued five unique for-cause determination letters; it also issued two not-for-cause determination letters, setting a new record low. No letters were issued in August, September, October or November. Its final letter of 2013 was issued to the University of Washington in St. Louis, closing out a not-for-cause, onsite evaluation that found no non-compliance. So far this year, OHRP has issued three letters, all of which close out not-for-cause evaluations. Two of the letters, issued Jan. 6 and April 21, close out evaluations that were begun in 2012 and 2013, respectively. The third, dated April 23, closes out an evaluation that was conducted from March 18-20, 2014, of this year.

In the past, OHRP's determinations have identified serious issues. OHRP's own analysis of 253 determination letters issued to 146 institutions from August 2002 to August 2007 found that the two "most common areas of noncompliance and deficiency involved informed consent documents and procedures (34%) and the process for IRB initial review of research protocols (20%)."

These were followed by written IRB policies and procedures (15%) and IRB review of protocol changes (5%). It has not issued an analysis of letters since this report was published in the March-April 2010 issue of the journal *IRB Ethics and Human Review,* published by The Hastings Center.

OHRP said it does not plan to handle all complaints informally. It "believes that the [determination] letters offer value for educational purposes and does *not* plan to cease issuing them as a matter of practice," the agency said in its written responses to *RRC*.

If ORI Is Up, Why Is OHRP Down?

OHRP is just one of two HHS agencies concerned with "integrity" in HHS-funded research — the other is the Office of Research Integrity (ORI), which investigates cases of fabrication, falsification and plagiarism.

And in contrast to OHRP, ORI's case load has exploded in recent years. In 2012 and 2013 alone, ORI received approximately 420 complaints, according to

testimony then-ORI Director David Wright gave to the Presidential Commission for the Study of Bioethical Issues *(RRC 3/14, p. 1)*.

ORI is also more transparent about its operations than OHRP. It has published a quarterly newsletter and an annual report since 1994; these can be downloaded from its website, although the most recent annual report is from 2011. Data provided include the number of allegations received and the number of cases opened, closed and carried forward into the next year. In 2011, for example, ORI received 240 allegations and opened 44 cases. It makes 12 to 15 findings of misconduct per year, of which 30% involve clinical research. It is not clear whether OHRP and ORI share cases to see if Common Rule regulations may have been violated in misconduct cases, and vice versa.

Wright was the director of ORI for two years before he resigned in February. In his pointed resignation letter, Wright said that both ORI and OHRP should be moved out of the HHS office to which they report to escape the untenable political motives of higher-ups *(RRC 4/14, p. 1)*.

Sen. Grassley, who initially began investigating ORI's handling of a misconduct case at a university in his home state, has broadened his inquiries based on Wright's allegations of the dysfunction and micromanagement at HHS that caused him to leave. *RRC* shared OHRP's recent statistics with Grassley's office.

"Based on what I've learned from my investigation so far, I'm concerned that the Office of Research Integrity might not be allowed enough responsibility or autonomy from HHS and NIH to do its job." Grassley said in the statement to *RRC*. "It's worrisome to hear that the same conditions could apply to the Office for Human Research Protections. These offices have important functions."

A Call for Answers

The problems with OHRP are not new to Public Citizen. Carome was the one who brought SUPPORT into the limelight, believing OHRP had not gone far enough in its corrective actions.

Before the SUPPORT trial, Carome criticized OHRP for what he termed "lax oversight" of clinical trials, particularly those involving children *(RRC 2/13, p. 6)*. Public Citizen urged HHS Secretary Kathleen Sebelius to stop all NIH-funded pediatric research and began a petition drive asking her to apologize to the parents of infants enrolled in the study and to take other actions (*RRC 5/9/13*). Before Carome joined Public Citizen in 2011 he was the director of regulatory affairs at OHRP; from 1998 to 2002 he was OHRP's director of oversight compliance.

If the caseload has fallen this low, OHRP should be redeploying staff to conduct not-for-cause investigations, Carome said, and described OHRP as "under-funded and under-staffed." However, OHRP's not-for-cause activity did not increase in 2013.

The lack of investigations, the paucity of determination letters and the failure of OHRP to make any "significant findings" send messages both to the regulated community that they don't need to worry about enforcement actions by OHRP, and to whistleblowers and any research subjects who "feel they were wronged and were not treated appropriately" that their concerns will not be addressed, Carome said.

John Lantos, director of pediatric bioethics at Children's Mercy Hospital and the University of Missouri-Kansas City School of Medicine, suggested that OHRP may be immobilized by an "antiquated and dysfunctional" system of regulations. He called the problem "deeper than a lack of determination letters from OHRP." Like Caplan, Lantos signed the *NEJM* letter supporting NIH's view in the SUPPORT situation.

"The current system was designed to address a particular type of research ethics problem — the problem of deceptive, non-therapeutic research that was done without any formal oversight. The Tuskegee syphilis study is a good example," he said. "Today, the research problems are very different."

Lantos: 'Confusion' Led to Controversy

In Lantos' view, more studies today take place within "learning healthcare systems" that integrate research and clinical care. "In these situations, low-risk studies are done with informed consent and IRB oversight, but federal regulations do not address the problems raised by such studies. So it is unclear what is permitted and what is not," Lantos said. "The SUPPORT controversy was a result of this confusion. Nobody knows, anymore, what is permitted, forbidden, required, or optional. There is serious debate going on about what should be permitted and what should not. This important debate should lead to an overhaul of the current system of research regulation, and then, I think, OHRP's role will be clearer."

The lack of investigations "could be a sign things are working well," Lantos said, but added that it was not possible to reach a conclusion without reviewing complaints OHRP receives.

Carome has no doubts. "We believe they are not opening investigations when substantive questions and allegations are being raised," Carome told *RRC*. He cited as one example the Transfusion of Prematures (TOP) study that Public Citizen urged OHRP and HHS in August to suspend, saying its design and consent forms shared problems found in SUPPORT.

Eight months later, OHRP is still deliberating whether to open an investigation, Carome said agency officials told him.

Lois Shepherd, professor of bioethics, of law and of health sciences at the University of Virginia, echoed the demands for answers as to whether OHRP is doing its job.

"It seems it's time for both an internal and external review — the agency appears in need of a serious self-examination…and those outside the agency need to be asking some probing questions about why there are so few and increasingly fewer investigations," said Shepherd, who also signed the *NEJM* letter supporting OHRP.

"It would be nice to think the lack of investigations stems from the lack of ethical lapses, but that seems unlikely, given the number of serious reports OHRP apparently receives each year and just given the tremendous amount of human subject research that is taking place and the financial and other pressures to produce research results," Shepherd added.

"And even well-intentioned investigators and IRBs can make ethical missteps. Education and prevention are wonderful tools — but they will never be 100% effective," she said.

Link: http://www.hhs.gov/ohrp/compliance/letters/index.html ✧

Inside NIH

Dates that appear at the end of NIH news briefs indicate the issue of RRC's *weekly emails in which a news item first appeared, where links for documents may be included. Go to "Recent Email Issues" at www.ReportonResearchCompliance.com.*

◆ **Beginning tomorrow, NIH will remind institutions when an annual financial conflict of interest (FCOI) report can be filed, the agency announced April 18.** Since July 1, 2009, NIH has required institutions to submit FCOI reports via the electronic Research Administration Commons FCOI Module. NIH will send an email to the FCOI signing official that the "annual report link" is available. Also as of April 25, the annual report link "will appear closer to when it is due," typically "75 days prior to the next budget period start date, following the submission of an Original Report or Annual Report when there is a future noncompeting year pending within a current competitive segment." *(4/24/14)*

◆ **At the request of NIH, *Age*, the American Aging Association's journal, has retracted a 2012 paper written by a team of NIH researchers.** According to an April 12 retraction notice, NIH "found" that Fei Gao, one of the authors, "engaged in research misconduct by fabricating and/or falsifying data" in seven figures and one table in "Aging decreases rate of docosahexaenoic acid synthesis-secretion from circulating unesterified ?-linolenic acid by rat liver," published in the March 3, 2012, issue. A "retraction note" on the publication's website states, "This article has been retracted by the authors as they were unable to reproduce some of the data and therefore consider them unreliable." It is followed by another note, signed by Stanley Rapoport, chief of the National Institute on Aging's (NIA) Brain Physiology and Metabolism Section, the paper's senior author. Due to the misconduct, "I request a full retraction of this paper. Please note, none of the other authors were implicated in any way," he wrote. *(4/17/14)*

◆ **Responding to concerns that a recent policy change "resulted in many meritorious research applications being deemed ineligible for additional submissions, and many investigators having to propose substantial changes to productive research programs," NIH announced April 17 that, effective immediately, it will "accept a new (A0) application following an unsuccessful resubmission (A1) application.** The subsequent new application need not demonstrate substantial changes in scientific direction compared to previously reviewed submissions, and must not contain an introduction to respond to the critiques from the previous review." This alters a policy in effect since 2009 that permitted only one "resubmission" after an application was rejected." *(4/17/14)*

◆ **NIH has determined that captive chimpanzees used in federally supported research do not need "at least" 1,000 square feet of "ethologically appropriate" space per primate as was recommended by a specially created advisory panel and accepted by its Council of Councils, but, rather, that 250 square feet will do, the agency said in an April 9 notice in the *Federal Register.*** The larger space parameters were among the most significant recommendations proposed in January 2013 by the Working Group on the Use of Chimpanzees in NIH-Supported Research. The working group studied the issues related to chimpanzee research for a year following an Institute of Medicine study that concluded "most" chimpanzee biomedical research was unnecessary and called for the retirement of these primates, estimated at 310, with the exception of a reserve group of 50 that could be used for research (*RRC 5/13, p. 5*). *(4/10/14)*

'SUPPORT' Finding Led to Rare Public Feud With NIH

In recent years, the HHS Office for Human Research Protections (OHRP) has been operating without much fanfare, and scuffles with NIH — if there were any — happened out of the public eye. That changed in February 2013 when the two publicly locked horns over OHRP's determination regarding the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT).

The 23-site study, under the coordination of the University of Alabama at Birmingham (UAB), involved applying varying levels of oxygen saturation to 1,300 "extremely low birth weight infants." SUPPORT was covered in the *New York Times* and other media outlets and was featured in a syndicated hour-long talk show on National Public Radio.

In a Feb. 8, 2013, determination letter posted on its website, OHRP said that consent forms used in the SUPPORT study violated federal informed consent requirements "stemming from the failure to describe the reasonably foreseeable risks of blindness, neurological damage and death."

OHRP asked UAB to submit to OHRP a plan that its institutional review board (IRB) "will use to ensure that approved informed consent documents include and adequately address the basic elements of consent" as required by HHS regulations at 45 CFR 46.116(a). The plan was due by March 22. It made no demands of any other study site.

Public Citizen Criticized OHRP

RRC, which reviews every posted OHRP determination letter and reports on most of them, provided a copy of the UAB letter to former OHRP official Michael Carome, director of the Health Research Group at Public Citizen, for comment. Carome, who held oversight and compliance positions for OHRP for 11 years prior to his retirement in January 2011, told *RRC* OHRP should have concluded that the study, because of its lack of a control group of infants receiving the standard of care, violated requirements for IRB approval (*RRC 3/7/13*). Carome had previously called on HHS to investigate OHRP for what he termed "lax oversight," particularly of research involving children *(RRC 2/13, p. 6)*.

Carome said the agency also should have both required all the study sites to submit a plan like that requested of UAB and to contact the parents of infants in the study and explain to them the risks that should have been disclosed prior to enrollment. Public Citizen subsequently launched a public awareness campaign about the study and a petition drive requesting that HHS Secretary Kathleen Sebelius apologize to the families of the infants in the study.

But while Public Citizen was drawing attention to SUPPORT because of what it believed was an insufficient response, its actions appeared to further inflame NIH's objections to OHRP's determination. NIH tried to convince OHRP to back off, and failing that, took the issue higher up the HHS leadership chain. According to an account given by Alan Guttmacher, director of the National Institute of Child Health and Development, at a public meeting of NICHD's advisory council, unidentified HHS officials asked NIH and OHRP to "align" their views on the propriety of the study *(RRC 7/11, p. 4)*.

NIH *NEJM* Articles Were Unprecedented

The two failed to do so, Guttmacher said, and HHS permitted NIH and OHRP to each publicly and separately state their views. For NIH, this took the form of an unprecedented article in the *New England Journal of Medicine* by NIH Director Francis Collins, Guttmacher and one other NIH official. That letter was published along with an accompanying letter to the editor in agreement signed by several dozen ethicists, investigators and others.

They consider the interventions in the SUPPORT trial variations on "standard of care," and the signatories to the letter believe this type of study should be subject to different requirements, particularly regarding consent.

OHRP's response was to withdraw, at least temporarily, from its determination calling for the IRB plan. Although it reaffirmed its findings, OHRP agreed in a June 5 follow-up letter to UAB — posted on its website the same day as the *NEJM* pieces — to "put on hold compliance actions against UAB" and to develop guidance on standard of care research.

Three weeks later, 45 "physicians, bioethicists, and scholars in allied fields who agreed with OHRP's assessment of SUPPORT" published a counter letter favoring OHRP's position. This group also thought it was important to highlight what it believed was inappropriate behavior by NIH toward a sister agency that is supposed to have independent oversight.

HHS held a day-long meeting to solicit public testimony as background for the guidance, which is yet to be released *(RRC 4/14, p. 3)*.

In This Month's E-News

The following are summaries of news transmitted to RRC *subscribers this month in email issues, the date of which is indicated in parentheses following each item. Weekly email and monthly print issues of* RRC *are archived at www.ReportonResearchCompliance.com. Please call 800-521-4323 or email customerserv@aispub.com if you require a password to access* RRC*'s subscriber-only Web site or are not receiving weekly email issues of the newsletter.*

◆ **HHS needs to do a better job of ensuring that awardees of Small Business Innovation Research (SBIR) funds are eligible to receive them, are not receiving duplicative federal awards and are successfully using the funds, according to an April 22 report by the HHS Office of Inspector General (OIG).** "HHS awarded $360 million in SBIR funds to nearly 1,000 awardees in 2011 and had the highest average SBIR award amount of any participating agency," said OIG, which reviewed four HHS operating divisions (OpDivs). To address "vulnerabilities," OIG recommended that HHS "create a central office to oversee the SBIR program. HHS OpDivs should track and assess the commercial success of SBIR projects, ensure compliance with eligibility requirements, and improve procedures to check for duplicative awards." HHS did not comment on each recommendation but agreed "additional coordination and oversight across participating OpDivs is warranted and agreed that HHS must ensure that applicants meet SBIR eligibility requirements." *(4/24/14)*

◆ **Eight working groups have recommended a series of changes and steps the Food and Drug Administration (FDA) should consider that would provide greater public access to FDA's "compliance and enforcement data."** Their report, which FDA issued on April 22, is part of an effort begun in 2011. Among the recommendations is that FDA make more use of social media and mobile technology, as well as consider changes to "enable facilities to submit their compliance and enforcement information electronically" and "using standardized investigator forms to help promote reporting consistency." As far as next steps, the report states that "the recommendations advanced in this report are being referred to [FDA's] Transparency Task Force, which, after assessing their relative priority in the context of one another as well as other Agency priorities, will consult with senior FDA leadership about the feasibility of implementing them to the extent available resources permit." *(4/24/14)*

◆ **The Food and Drug Administration (FDA) is seeking comment on draft guidance regarding when sponsors may include "live case presentations" in research conducted under an investigational device exemption (IDE) application or supplement, according to a notice in the April 17 *Federal Register.*** FDA said it has seen an "increase in the number of requests for certain investigations to conduct live case presentations," which it defined as "treatment of a human subject under the auspices of an approved or conditionally approved IDE, conducted and broadcast in real time, or recorded for broadcast at a later time." The guidance is also intended to provide assistance to institutional review boards (IRBs) "on factors to consider when evaluating an investigation that contains a live case presentation." Comments are due by July 16. *(4/17/14)*

◆ **"Animal rights groups have pressured nearly all large commercial air carriers from shipping nonhuman primates (NHP) for research purposes.** As of this writing, Air France is the ONLY airline shipping NHPs for research," reads the April 16 "Action Alert" from the Foundation for Biomedical Research (FBR). Arguing that "it's time for all of us in biomedical research to be heard," FBR has organized a petition to thank Air France. "Even if you don't personally do research involving NHPs, as a member of the research community, you have a stake in the outcome of this campaign. Our collective voices make a difference and will help to bolster Air France's resolve in the face of increased targeting from activist groups," the alert states. *(4/17/14)*

◆ **Sen. Patrick Leahy (D-Vt.) plans to revise S. 1720, the Patent Transparency and Improvements Act, and will issue a new version once the Senate returns from its two-week recess on April 28, he announced April 9.** That was the day the Senate Judiciary Committee, which he chairs, was scheduled to hold a business meeting to mark up the current version of the bill; S. 1720 is being closely followed by research institutions. Consideration has been postponed twice. On April 2, the Association of American Universities (AAU) joined other members of a patent reform coalition that wrote to Leahy and Sen. Charles Grassley (R-Iowa), committee co-chair, to express their concerns "that some of the measures under consideration go far beyond what is necessary

In This Month's E-News continued)

or desirable to combat abusive patent litigation, and, in fact, would do serious damage to the patent system." Congress reformed the patent system in 2011 to one that requires inventors to be the "first to file" for a patent, rather than a first to "invent" (*RRC 10/11, p. 8*). This has led to the rise of so-called patent "trolls," and legislation to combat them. AAU and other organizations previously expressed concerns with this bill and with similar ones in the House. *(4/10/14)*

◆ **A Morgan State University professor was convicted April 1 of multiple charges related to the "theft of government property in connection with a scheme to fraudulently obtain research grants from the National Science Foundation and kickbacks from students' stipends,"** Rod Rosenstein, the U.S. Attorney for the District of Maryland, and NSF Inspector General Allison Lerner announced following the jury trial. Manoj Kumar Jha "faces a maximum sentence of 20 years in prison for each of four counts of wire fraud, and for one count each of mail fraud and falsification of records; and a maximum sentence of 10 years in prison for theft of government property," they announced. Sentencing by U.S. District Judge Ellen Hollander is scheduled for July 11. It was not clear from the announcement or the indictment against Jha what prompted the investigation by NSF's Office of Inspector General, which began in 2011, or how the fraud was discovered. *(3/27/14)*

◆ **In a March 28 letter, the Association of American Universities (AAU) told Reps. Lamar Smith (R-Texas) and Eddie Bernice Johnson (D-Texas), the chair and ranking member of the House Science, Space and Technology Committee, that its members are opposed to H.R. 4186,** the Frontiers in Research, Science and Technology (FIRST) Act, "in its current form." The bill, which reauthorizes NSF among other actions, passed a subcommittee of the Science Committee on March 13. AAU described the bill's five "most problematic" provisions, including new requirements for scientific misconduct "with penalties that far exceed those imposed by other federal research agencies." *(3/27/14)*

◆ **DoD, the General Services Administration (GSA) and NASA are seeking comments on a proposed rule that would amend the federal acquisition regulation (FAR) to "extend the limitations on contractor employee personal conflicts of interest [COIs] to apply to the performance of all functions that are closely associated with inherently governmental functions and contracts for personal services,"** according to a proposed rule published in the April 2 *Federal Register*. Such limitations now apply only to contractor functions related to acquisition; a 2009 defense appropriation law required DoD to consider revising its guidance on contractor COIs, an action that was broadened to include GSA and NASA. Comments are due by June 2. *(3/27/14)*

◆ **On behalf of the research funding agencies that use the Research Performance Progress Report (RPPR) for grants and cooperative agreements, the National Science Foundation (NSF) has published a Federal Register notice revising the report.** Once final, the revised *RPP*R will be used for submitting both interim and final reports. The proposed revised format retains the basic structure of and categories in the existing *RPP*R; however, the addition of one new category is proposed: "Project Outcomes." This category is optional for use by a federal agency and would be used in the final report only. The proposed revised format is available on the NSF website at www.nsf.gov/bfa/dias/policy/rppr/index.jsp. *(3/27/14)*

◆ **Federal science and engineering fiscal 2011 obligations to academic institutions fell 11% from fiscal 2010 levels.** However, this statistic is somewhat misleading, in that if American Recovery and Reinvestment Act (ARRA) funds are excluded from 2010 totals, obligations actually increased 4.1% in fiscal 2011, according to recent statistics from the NSF's National Center for Science and Engineering Statistics. In fiscal 2011, federal agencies obligated $31.4 billion to 1,134 colleges and universities for science and engineering. *(3/27/14)*

◆ **During the last fiscal year, the number of proposals competitively reviewed by NSF increased by almost 400, while the number of new awards decreased by 6%, the lowest level since fiscal 2006.** The result: a funding rate of 22%, down two percentage points from the previous year. In fiscal 2013, 81% of 1,922 NSF awards were to academic institutions, accounting for 24% of all federally funded basic research performed at U.S. colleges and universities. These stats and others are included in NSF's recent *FY 2013 Performance and Financial Highlights,* an annual report issued in the first quarter of the year. *(3/27/14)*

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