

# RESEARCH COMPLIANCE

News and Analysis for Colleges, Universities and Teaching Hospitals

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

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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."

### OHRP Is 'Invisible' After SUPPORT

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 wrong-doing; 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 ap-

pear 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

### **‘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

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

### **‘SUPPORT’ Finding Led to Rare Public Feud With NIH (continued)**

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*).

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> ⇨

#### **Also in the May 2014 issue of *Report on Research Compliance*:**

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