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'Nothing Short of Appalling:' Inaction by HHS Oversight Agencies Sets off Alarms

So far this year, the HHS Office of Research Integrity (ORI) has not issued any findings of research misconduct, marking nearly 12 months since the last finding was issued.

ORI, which has been beset by staff turmoil and turnover since the arrival in December 2015 of Director Kathryn Partin, historically has made 12-15 findings of fabrication, falsification and plagiarism per year *(RRC 1/17, p. 1)*.

But it's not the only federal research watchdog agency that has outwardly slowed down or ceased its enforcement efforts. The HHS Office for Human Research Protections (OHRP), which safeguards the millions of people enrolled in hundreds of thousands of clinical trials, has not posted a determination letter in eight months; these letters are the vehicle for holding institutions responsible for following 42 CRF Part 46, also known as the Common Rule.

Sen. Chuck Grassley, R-Iowa, and leaders in the ethical conduct of research contacted by *RRC* are expressing alarm at the lack of enforcement and other actions by these unique, key oversight agencies. The new incoming HHS assistant secretary for health must focus on these offices and correct problems, they say, arguing that to do nothing may result in lasting damage.

"It is nothing short of appalling that the activities of two leading oversight agencies for research conducted with U.S. federal funds have ground to a halt," medical ethicist Ruth Macklin told *RRC*.

Macklin and others point out that the declines in activity by both agencies are not accompanied by a corresponding decline in lack of problems for them to tackle—quite the opposite.

"The paucity or absence of responses from these agencies is in direct opposition to what we have learned about an increase in cases of scientific misconduct—to which ORI responds—and a series of failures to obtain informed consent, as required by the federal regulations, [which is] the job of OHRP," Macklin said.

Macklin maintained there are "numerous cases that should be addressed by these two federal oversight agencies."

RRC has previously documented problems at both OHRP and ORI, but they have intensified in recent months, particularly at ORI (for details on ORI, see box, p. 3). Money doesn't seem to be at the root of any problems. Both agencies have received stable levels of funding over the years—approximately $8.5 million for ORI and $6.5 million for OHRP. The President's FY 2018 budget, released May 23, calls for the same amount for both agencies.

According to the reporting structure at HHS, both ORI and OHRP are under the Office of the Assistant Secretary for Health (ASH). Donald Wright is currently the acting ASH, a position he has held during the various vacancies and since the resignation of Karen DeSalvo, the prevision OASH. The position is a political one that requires Senate confirmation. DeSalvo was never confirmed but served in an acting capacity as she was already a federal employee.

continued

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President Trump announced his intention to nominate Brett Giroir, former CEO of the Texas A&M Health Science Center, to be the new ASH (*RRC 5/14/17*). As of *RRC*'s deadline, the nomination had not been posted on the Senate's website as formally submitted.

Determination letters issued by OHRP are the main vehicle the federal government has for communicating the appropriate conduct of human research trials, both to the public and the regulated institutions and investigators. In years past, OHRP occasionally published correspondence it had with institutions.

Last year OHRP issued 15 determination letters, a number that had set a record low in 2010. In 2015, however, OHRP only issued five letters. From 2007-2009, OHRP issued an average of 35 letters, down from a high of 86 in 2006 and a peak of 146 in 2002. The decline coincided with the arrival in 2008 with Director Jerry Menikoff; the agency told *RRC* he prefers informal means of resolving noncompliance allegations *(RRC 3/11, p. 1)*.

The letters are the product of investigations that began years earlier. Fewer investigations lead to fewer letters and vise-versa. The letters reflect OHRP findings from investigations that result from complaints, called "for cause," and those stemming from an oversight review that may or may not include a site visit, called "not-for-cause."

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Asked why OHRP hasn't published any letters so far this year, and none since October, an agency spokeswoman said simply, "There have been no determination letters to publish since October 2016."

RRC asked whether the lack of letters could be seen as a sign that enforcement and compliance is not a priority for the agency. "OHRP staff has been very busy, particularly with the revised Common Rule," she said. The revised Common Rule was published in January, following a process that began in 2011. It is now under review by the Trump Administration (see story, p. 5).

In response to a request from *RRC*, OHRP provided the following data on its investigations for the last three years:

◆ 2014: Opened seven for-cause, closed four. Opened four not-for-cause, closed four.

◆ 2015: Opened five for-cause; closed three. Opened three not-for-cause, closed two.

◆ 2016: Opened four for-cause, closed nine. Opened five not-for-cause, closed six.

◆ 2017 to date: Opened four for-cause, closed none. Opened one not-for-cause, closed none.

Beyond ensuring compliance by individual institutions, OHRP's letters provide insights and best practices that can prove educational for others. For example, in February 2016, OHRP sent a letter to University of Texas at San Antonio (UTSA) describing two instances of non-compliance. OHRP said the IRB had violated federal human subjects regulations by giving the go-ahead for NIH-funded studies about which it had requested but not yet received "substantive information or information necessary to make the required determinations for approval" *(RRC 4/16, p. 1)*.

UTSA told *RRC* that correspondence with OHRP on this issue had begun in 2012.

The agency has not availed itself of the other options to provide specific direction and guidance to institutions and investigators beyond determination letters. For example, the agency does not act on the recommendations and proposed guidance documents developed by its hard-working advisory panel, the Secretary's Advisory Committee on Human Research Protections (SACHRP).

Instead, Menikoff has suggested that SACHRP members publish their work on their own, stating that guidance has little value because it doesn't carry the legal authority that regulations do *(RRC 8/14, p. 1)*.

Data on OHRP's activities leads to many questions, said Macklin.

"Short staffing and other personnel difficulties at these oversight agencies may be part of the explanation," Macklin said. "But in an era when the highest

levels of government are seeking to weaken, undercut or eliminate a wide variety of federal regulations, I fear that the system designed to protect the human subjects of biomedical research is at risk of collapse."

OHRP's inaction was highlighted in two books published in 2015, which both concluded that, as a result, the IRB system nationally was beset by inconsistencies and labored with little accountability *(RRC 5/15, p. 1)*.

One of OHRP's harshest critics is a former member of its staff—Michael Carome, MD, who now heads the Health Research Group of Public Citizen, which he joined in 2011. Carome was OHRP's director of regulatory affairs upon his retirement from the agency, having served as its director of oversight compliance among other positons during several decades with the federal government.

Carome expressed outrage that OHRP has released no letters since October.

"From Public Citizen's vantage point, it is clear that OHRP has repeatedly abused the agency's discretion under its existing compliance oversight policies by refusing to open formal compliance oversight investigations into multiple substantive complaints of material violations of federal regulations and ethical principles related to the protection of human subjects," Carome said. "The agency's leadership seems to look for excuses to avoid opening investigations and to be more interested in protecting research institutions rather than protecting human subjects."

In the last four years alone, Public Citizen has asked OHRP to investigate four clinical trials on the basis that they are unethical, and to take action against the University of Minnesota, whose human subjects protections program was the subject of enhanced state oversight *(RRC 7/15, p. 6)*. In each case, OHRP has not done so, Carome said.

Lois Shepherd, professor of biomedical ethics, law and public health sciences at the University of Virginia, also expressed concern and wondered whether OHRP would ever regain the enforcement muscle it seemed to have lost in recent years.

"This is an alarming trend, and we need to be asking what it is going to take to reverse it," said Shepherd. "Does OHRP need more funding and staffing? Better leadership? More independence? Certainly questions remain about OHRP's independence from NIH after the fallout over the SUPPORT study. OHRP was bludgeoned during that conflict."

SUPPORT stands for the Surfactant, Positive Pressure, and Oxygenation Randomized Trial, which OHRP in 2013 determined was conducted without appropriate disclosure to the parents of premature infants of all foreseeable risks, including death.

But NIH, which funded the multicenter trial, opposed the finding, leading to an unpreceded debate in the academic literature with dueling essays written by NIH Director Francis Collins himself (and coauthors, along with signatories) and by Macklin and Shepherd (and their signatories).

This study was termed "standard of care research," a loose concept closely aligned, if not identical, to comparative effectiveness research.

OHRP ultimately backed off, holding instead a meeting on standard of care research, followed by the publication of proposed guidance on the topic *(RRC 12/14, p. 1)*.

But OHRP has never issued final guidance, and the final Common Rule purposely does not address comparative effectiveness research. The preamble to the rule notes that draft guidance was issued (but doesn't mention that final guidance hasn't been).

The public scuffle left an impact on OHRP: In 2014 it opened only one investigation.

Guidance on Consent Called Lacking

OHRP's lack of direction on comparative effectiveness studies is a significant source of worry, Shepherd added.

"I'm especially concerned about the lack of enforcement actions—and guidance—coming out of OHRP on informed consent in comparative effectiveness studies," Shepherd told *RRC*. "Studies are being conducted and results published without the required consent of subjects, and even though results are published in top journals and the lack of consent is freely acknowledged, nothing appears to be happening at the top level to issue corrections."

The value of OHRP's determination letters, when they are issued, is that they communicate the "visible and public corrections" that OHRP asks institutions to make, said Shepherd. Along with guidance, these "are necessary to clarify the standards for IRBs to follow, especially on what the regulations require in terms of consent for new forms of research."

Shepherd also spoke of how OHRP actions are needed to support IRBs, given they are "generally internal organs and are overwhelmed" and argued that the "case law on research injury is undeveloped and therefore little help."

"We really have to have a strong, independent federal agency looking out for human subjects," Shepherd said. "We have to have a system of checks and balances." ✧

ORI Inaction a Worry 'For All Scientists'

RRC first reported on the recent turmoil within the HHS Office of Research Integrity (ORI) in 2016, but has documented upheaval at the agency for years. However, the situation has reached a new low.

ORI is likely to go close to an entire year without any findings, compared to the typical number of a dozen or more per year. The other research oversight agency in HHS, the Office for Human Research Protections, is also showing evidence of an enforcement slowdown (see story, p. 1).

Determinations by ORI that fabrication, falsification or plagiarism in Public Health Service-funded research have occurred can result in debarment of investigators, as well as the imposition of supervisory plans. ORI can also require sanctioned investigators, whose names and misdeeds are published in the *Federal Register*, to retract papers containing errors.

ORI has been roiled by vacancies and lack of leadership for nearly a decade. When the current director, Kathryn Partin, was hired in December 2015, the job had been open since David Wright resigned in March 2014, after just two years. When he quit, Wright publicly lambasted HHS for causing "dysfunction" at ORI *(RRC 4/14, p. 1)*.

During these periods ORI continued to churn out misconduct findings, anchored by John Dahlberg. He retired from the No. 2 slot at ORI two years ago after being with the agency since its founding in 1992.

Under Partin's reign, however, ORI's investigative division has seen departures of many workers, and ORI's director of the Division of Education also left *(RRC 2/17, p. 1)*.

Distraught ORI staff have shared their concerns with *RRC* anonymously because they fear for their jobs and have been unable to secure others. The entire federal government is essentially under a job freeze. Investigative staff have written letters and emails to HHS leaders about Partin and met with both agency leaders and with members of Grassley's staff. To date they have received no help, ORI staff say.

ORI's policy is not to discuss personnel matters, and officials have not commented on staff complaints about Partin. After *RRC* reported that ORI had ended 2016 with a record low of six findings, Partin explained to the website Retraction Watch that several of ORI's current cases are "extremely large and complicated." She said ORI was bringing on new investigators, but staff have told *RRC* that these individuals are unqualified and are adding to their inability to close cases.

Today ORI is "critically short of scientist-investigators to pursue findings," due to "poor management and support for ORI by [HHS leadership] in the past, current internal divisions at ORI and subsequent staff departures" Wright said.

Given the continued lack of findings since August, fears of lasting detrimental impact are growing, Wright told *RRC*.

Published findings "have a deterrent effect on future misconduct, I believe," Wright said. "Institutions also look to ORI findings to validate and support their own investigations and institutional findings. The failure of ORI to move forward expeditiously with warranted findings may encourage [accused investigators] and their counsel to delay settling cases or to decline to communicate at all with ORI in hopes that the problem will go away."

Sen. Charles Grassley, R-Iowa, gave a speech on the Senate floor asking HHS to get to the bottom of Wright's complaints after he resigned, a call he repeated in an email to *RRC*.

Proper functioning of ORI is essential, Grassley said. "This office has to function well for the integrity of tax dollars and patient benefit. The new secretary of the Department of Health and Human Services should make sure the office is looking for waste, fraud and abuse at its fullest capacity," he said in an email.

In addition to his long-term interest in research integrity, Grassley became more involved when a researcher in Iowa fabricated results in an HIV vaccine trial, leading to his criminal prosecution and the return of NIH funds *(RRC 8/15, p. 1)*.

Before his resignation, Wright testified before the Presidential Commission on the Study of Bioethical Issues that ORI had begun receiving more than 400 complaints a year of possible misconduct, a doubling from the past.

This increase makes ORI's mission all the more critical, said Ferric Fang, director of the Harborview Medical Center Clinical Microbiology Laboratory at the University of Washington School of Medicine, who also researches misconduct in science.

ORI's lack of findings "is certainly concerning, as there has been a steady rise in allegations, inquiries and investigations reported to the ORI over the past decade," Fang told *RRC*. He noted that

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ORI Inaction a Worry 'For All Scientists', continued

the recent National Academy of Science report on research integrity stressed that ORI, along with the Office of Inspector General at the National Science Foundation, "play an essential role in addressing research misconduct" *(RRC 5/17, p. 1)*.

It is "reasonable" to fear that "a weakened ORI could encourage institutional inaction with regard to research misconduct," Fang said.

"The problems you describe are very disconcerting," agreed Arturo Casadevall, MD, chair of molecular microbiology and immunology at Johns Hopkins Bloomberg School of Public Health, in an email to *RRC*. Casadevall is also the founding editor of *MBio*, an open access journal, and frequently an author and researcher with Fang on misconduct, reproducibility and related issues.

"The ORI is a critically important institution for the integrity of science and any dysfunction involving that office should be of great concern to all scientists," he said.

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