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Big Drop in OHRP Letters, Open Cases Raise Questions of Agency Commitment

In 2010, the Office for Human Research Protections issued and posted 16 determination letters, the lowest number in its 11-year history and less than half the number issued in each of the previous five years. Since 2007, the office has averaged 35 letters a year, down from a peak of 146 in 2002 and another high of 86 in 2006.

The number of determination letters is tied to the number of cases OHRP opens, and during the recent past, that number has also declined, *RRC* has learned, tumbling to an all-time low of six in 2009. Some tie the decline in activity to the arrival of Jerry Menikoff, whose tenure as OHRP director began in the late fall of 2008.

Agency observers and others expressed concern about the steep drops in letters and open cases, telling *RRC* they raise questions about the agency's current commitment to serious oversight of human subjects research and investigations into possible wrongdoing. One called for the Office of Inspector General in the Department of Health and Human Services, of which OHRP is part, to conduct a review of the agency's oversight activities.

"The protection of subjects in federally sponsored research must be foremost in OHRP's activities," said Art Caplan, director of the Center for Bioethics at the University of Pennsylvania, who called the decline in letters "worrisome."

Aside from conferences, the letters are the most visible evidence of the work that OHRP does in safeguarding people in trials and ensuring that federal regulations on consent, enrollment, continuing review and others are met. The determination letters are an important source of compliance information and are eagerly anticipated and analyzed by many.

For their part, agency officials described the 2009–2010 drop as "in the realm of ordinary variation" and reflective of "small deviations in results from a steady level of oversight activity," according to information Ann Bradley, a spokeswoman for the office, supplied in response to queries by *RRC*.

Asked if the number of letters might go back up, Bradley responded that "OHRP cannot predict whether the number of determination letters issued this year will rise to the recent average."

As of press time, the office had only posted one letter this year on its website, which was in January. In 2010, no letters were issued and posted for the months of October, November or December.

OHRP officials attribute the decline in letters and open cases to several long-term trends, including the shrinking number of institutions over which OHRP has jurisdiction, Bradley said.

None of the reasons cited began or occurred solely in 2010. The possibility that compliance is increasing at institutions was not among the reasons OHRP cited for the drop, and funding is not a problem, Bradley said. "It is not the case that budgetary or staff shortages have influenced OHRP oversight capability," Bradley said. (For more information on funding, staffing and other data, see the box on p. 10.)

OHRP has jurisdiction over all Public Health Service-funded human subjects research and other studies without federal funding if institutions indicate on their federalwide assurance that they voluntarily apply federal regulations regardless of funding source. OHRP has oversight responsibilities for 10,000 institutions that have a federalwide assurance and some 6,000 institutional review boards that have registered with the agency.

A case can typically take a year to resolve from when it is opened, and all open cases result in a determination letter that either confirms that the institution is in compliance or identifies areas of noncompliance and requests a compliance plan to address those deficiencies.

Some PHS-funded research may be for drugs or devices that will be submitted to the Food and Drug Administration for approval, and complaints regarding that research are referred to the FDA for investigation, Bradley said.

"OHRP has altered its policy of routinely evaluating allegations when there is no HHS support for the research study in question but the study is regulated by the FDA and the institution has extended its FWA to all nonexempt human research at that institution," she said. "Since about 2004, such cases typically are referred to the FDA."

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Throughout its 11-year history, the number of cases OHRP has opened per year has varied, with a high of 91 in 2000; from 2004 to 2008, the number of opened cases never dropped below 15 per year.

However, it would appear that the number of allegations of noncompliance has not dropped substantially. OHRP said it did not track this indicator prior to 2005; in that year, OHRP logged 153 allegations. In 2009, the number was 134. Complainants are permitted one year to file information on an allegation, so Bradley termed the 2010 number of 61 allegations of noncompliance an "incomplete" total.

A decline in the number of institutions that extend their FWA to research not supported by HHS is also a factor, according to Bradley.

OHRP officials have previously reported that, in the past, "greater than 90%" extended federal protections to all their human subjects. According to an OHRP paper published last year, that number had dropped to 74% by 2007 *(RRC 4/10, p. 6)*.

The March 2010 paper was one of two analyses of determination letters OHRP has conducted throughout its history.

The first, published in September 2003, was completed by Michael Carome, who retired in January after serving as OHRP director of regulatory affairs since 2002 and director of compliance oversight from 1998–2002. Carome looked at 269 letters OHRP sent to 155 institutions from 1998–2002.

Last year's paper reviewed data that were already three years old by the time it was published, reflecting 253 letters sent to 146 institutions during the five-year period from 2002 to 2007. It showed a decline in letters from the previous period, which appears to have accelerated since that time.

The authors, OHRP staff, noted, however, that letters issued during their analysis period had found more serious deficiencies. "Almost two-thirds of the citations pertained to IRB failure to approve research protocols in accordance with HHS regulations at 45 CFR 46.111, a regulatory provision requiring IRBs to determine, among other things, that 1) risks to subjects are minimized and are reasonable in relation to anticipated benefits; 2) selection of subjects is equitable; 3) when appropriate, privacy of subjects and confidentiality of data is protected; and 4) appropriate safeguards are in place to protect vulnerable subjects," they wrote. "This represents substantially more violations in this category than we found in our last review, which showed about one-third of the citations in this category (153 citations in the 2004 study vs. 277 citations in the current one)."

'Discretion' Behind the Drop?

Bradley said the number of opened cases is a better, although "still imprecise," gauge of OHRP activity than the letters are. However, as noted earlier, that number is also dropping. Bradley said OHRP is resolving some allegations informally. "OHRP, at its discretion, evaluates allegations in research covered by an FWA," she said.

"In recent years, OHRP has attempted, when possible, to address relatively straightforward allegations (for example, a complaint from an uncompensated research subject) informally — for example, by conversation with the delinquent payer institution. In cases so resolved,

Office for Human Research Protections, 2000–2010

Year	Determination Letters	Total Budget	Total Full-Time Equivalents	Division of Compliance, FTEs	Allegations Received	Opened Cases	Not-for-Cause Evaluations
2000	78*	na	na	na	na	91	na
2001	126	$5,800,000	28	na	na	42	1
2002	146	$7,002,370	35	na	na	30	4
2003	93	$7,505,000	39	5.5	na	32	4
2004	73	$7,274,748	39	5.5	na	18	3
2005	39	$7,341,500	39	5.5	153	43	4
2006	86	$6,921,000	33	4.5	120	15	4
2007	37	$6,893,500	33	5.5	129	16	4
2008	34	$6,663,000	26	4.5	97	8	3
2009	35	$6,875,000	31	4.5	134	6	4
2010	16	$6,949,000	29	4.5	61**	8	4

* Six months only

** This number is incomplete; if OHRP originally receives inadequate information, it gives complainants a year to provide additional information. So far, OHRP says it "knows of at least 61 allegations."

Source: Office for Human Research Protections, www.hhs.gov/ohrp

a determination letter is usually unnecessary," Bradley added.

Carome told *RRC* he had observed such discretion first hand, noting, "In the past couple of years, OHRP has more frequently than ever, under its discretion, chosen not to open a compliance oversight evaluation in response to complaints of noncompliance." Carome is now the deputy director of Public Citizen Health Research Group in Washington, D.C.

Bradley told *RRC* that the decision about whether to open a case is made by the director of the compliance oversight division, in consultation with Menikoff. The division operates with just 4.5 full-time staff members.

Bradley declined to address whether this was a change under Menikoff, saying, "consistent with departmental practice, we prefer to discuss operations rather than individuals…."

'Letters Are Important'

Caplan told *RRC* OHRP needs to explain what is happening. "The precipitous drop in letters is of concern," he said. "While the office has cut back its oversight of non-HHS-funded research, a huge fall in letters is worrisome. Since OHRP itself does not think the drop is due to increased compliance, it is important that the reasons for the sudden lack of letters receive more explanation."

The diminishing number of letters also caught the attention of Greg Koski, the first-ever OHRP director. Koski said the office faced a "huge" backlog of allegations when he took over in September 2000 that accounted for the large number of letters in the beginning of the office's history. Koski served in his post until October 2002. He said he did not know why the letters had dropped off so dramatically in one year but hoped OHRP would continue issuing them.

"The research community has looked to those letters to reflect on their own programs, to look at areas that might need improvement," Koski said. "They are extremely valuable. I think it is important that OHRP continue to investigate the cases that come before them and to report back to the institutions and the community and the public."

A research official at a university in the central part of the United States agreed the letters are useful for educational and compliance purposes.

"Our IRB manager and support personnel are familiar with the OHRP website and the posting of determination letters. The letters allow us to better understand how OHRP's Division of Compliance Oversight addresses noncompliance," said the official, who wished to remain anonymous. "We sometimes select particular letters to use as guidance documents, finding the corrective action information particularly useful. We also use the letters as educational tools."

Call for OIG Investigation

An observer of OHRP who asked to remain anonymous called for OIG to undertake a thorough review of the agency. "The question that needs to be asked of the agency is, 'What kind of real oversight do you do?'" he said.

"I think an oversight system should have some degree of accountability," he added, noting that the last such review of human subject protections oversight was in 1998.

OIG should look at how many site visits OHRP conducts, as well as the number of allegations received versus opened cases and the volume of not-for-cause evaluations it begins, he said. OIG should also explore whether the number of institutions not extending their FWAs is creating an unsafe environment for research subjects, he added.

Congress showed some interest in assessing whether OHRP was doing its job when it was caught in a "sting" in 2009, orchestrated by the Government Accountability Office (*RRC* 4/09, p. 1).

But attention focused less on whether subject protections were being adequately enforced and more on arcane procedural issues and the questionable actions of a private IRB overseeing non-PHS-funded research, over which OHRP would have had no jurisdiction. That IRB quickly went out of business, and congressional interest in OHRP seemed to have disappeared along with it.

Link: www.hhs.gov/ohrp/index.html. ✧