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February 1, 2018

The Honorable Charles E. Grassley
Chairman
Committee on the Judiciary
U.S. Senate
224 Dirksen Senate Office Building
Washington, D.C. 20510-6050

Dear Chairman Grassley:

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, applauds your interest in the adequacy of federal oversight of human subjects research, as reflected in your January 4 inquiry letter to the Department of Health and Human Services (HHS) regarding an unethical clinical trial that involved testing an experimental vaccine in humans without the proper human subjects protections that are required by U.S. law.

We would like to call your attention to a July 2017 report issued by the HHS Office of Inspector General (OIG),[1] which revealed that the Office for Human Research Protections' (OHRP's) enforcement of regulations for the protection of human subjects has literally become moribund. Of particular concern, the OIG report documented a precipitous drop over the past several years in the number of formal compliance oversight evaluations initiated by OHRP in response to written allegations of noncompliance. This decline — and the unsatisfactory explanations that OHRP staff have offered for it — indicate that OHRP now routinely bypasses its own formal procedures for investigating allegations of misconduct and can no longer be trusted to meaningfully enforce the federal human subjects protection regulations.

We therefore respectfully urge you to expand you inquiry to include a broad examination of the adequacy of OHRP's compliance oversight activities.

OHRP's compliance oversight procedures

OHRP has long-standing written procedures, last updated in 2009, for its compliance oversight evaluations.[2] The procedures for for-cause compliance oversight evaluations — which historically have made up the largest proportion of OHRP's compliance oversight activities — begin by stating that "For-cause evaluations occur, *at OHRP's discretion*, in response to OHRP's receipt of substantive written allegations or indications of non-compliance with the HHS regulations" [emphasis added]. They further note that the agency "may choose to use other

[1] Department of Health and Human Services Office of Inspector General. OHRP Generally Conducted Its Compliance Activities Independently, but Changes Would Strengthen Its Independence. July 2017. https://oig.hhs.gov/oei/reports/oei-01-15-00350.pdf. Accessed January 26, 2018.
[2] Office for Human Research Protections. Compliance oversight procedures for evaluating institutions (2009). October 14, 2009. https://www.hhs.gov/ohrp/compliance-and-reporting/evaluating-institutions/index.html. Accessed January 26, 2018.

mechanisms to address allegations or indications of noncompliance rather than conducting a for-cause evaluation."

The public reasonably expects that OHRP will exercise such enforcement discretion judiciously and that the use of other mechanisms to address substantive allegations or indications of noncompliance will be the exception, not the rule.

According to written procedures, if OHRP determines that it has jurisdiction to evaluate allegations of noncompliance and chooses to conduct a formal for-cause evaluation, the agency sends an initial inquiry letter to the institution(s) involved in the relevant research. The letter describes the allegations and potential regulatory violations and asks the institution to conduct an investigation of the potential noncompliance, provide a written response to the allegations along with supporting documentation, and submit a corrective action plan if noncompliance is found. OHRP eventually issues one or more letters to the institution documenting OHRP's determinations regarding whether it finds that noncompliance occurred and, if so, whether adequate corrective actions have been taken by the institution. In some cases, OHRP requires additional corrective actions.

Importantly, OHRP's written procedures for conducting for-cause compliance evaluations contain provisions to ensure the transparency of the agency's enforcement activities for complainants and the public, including the following:

- Notifying complainants as to whether OHRP will open a compliance evaluation of the allegations raised
- Upon completion of an evaluation, informing the complainant in writing of OHRP's determinations and any corrective actions taken by the institution
- Posting on the agency's website each determination letter no later than 10 business days after the letter is issued to the institution
- Once a compliance oversight evaluation is closed, making available upon request under the Freedom of Information Act all documents related to the evaluation

OHRP's written compliance procedures also stipulate an appeals mechanism under which a complainant (or institution) may request that the OHRP Director reconsider any determinations from a for-cause compliance oversight evaluation.

The OIG report's findings

For its July 2017 report, the HHS OIG analyzed data on OHRP's compliance activities for 2000 through 2015 as part of a congressionally requested assessment of OHRP's independence.

The most striking observation presented in the report was the steep decline in the rate at which OHRP has initiated formal for-cause compliance evaluations in response to allegations of noncompliance since 2000. For the four-year period from 2000 to 2003, the agency received a total of 487 allegations and initiated for-cause compliance evaluations for 195 (40 percent) of these. In contrast, for the four-year period from 2012 to 2015, OHRP received 456 allegations but initiated for-cause compliance evaluations for only 22 (5 percent) of these — a nearly 90 percent drop in the rate of initiating such evaluations.

Although some of this dramatic falloff is due to an erosion of resources as well as an increase in the proportion of allegations that are related to research deemed to be outside of OHRP's jurisdiction, much of the decline clearly reflects a fundamental — and troubling — change in how OHRP approaches its enforcement of the HHS human subjects protection regulations.

Indeed, OHRP explained to the OIG that "it decided over the years to initiate fewer [for-cause] compliance evaluations both to better leverage its limited resources and to focus the evaluations on broad policy issues in protections for human subjects." This explanation is disturbing for two reasons. First, deciding whether to open a formal for-cause compliance evaluation based on whether a particular allegation raises "broad policy issues" enshrines an approach to enforcement that by its very nature is arbitrary and capricious. In particular, the public, complainants, and other stakeholders do not know when or on what basis OHRP has decided which policy issues are broad enough and of sufficient interest to use as a litmus test for deciding whether a particular substantive allegation warrants a for-cause compliance evaluation. Nor do they know which broad policy issues OHRP is using to make these decisions at any particular time or whether the agency is applying them consistently and fairly.

Second, many substantive allegations of noncompliance do not raise broad policy issues but nevertheless often constitute the most serious types of noncompliance with the HHS human subjects protection regulations — such as conducting human subjects research without appropriate review and approval by an institutional review board or without the informed consent of the human subjects. In such cases where the potential for harm to the rights and welfare of human subjects is greatest, there is no sound basis for bypassing OHRP's written procedures for conducting formal for-cause compliance evaluations.

The agency also told the OIG that "it increased its use of other mechanisms — for example, contacting the research institution directly — to address allegations of noncompliance." But this explanation is nonsensical because, as noted above, under OHRP's written procedures for formal for-cause compliance evaluations, contacting research institutions directly in writing has always been one of the first steps in addressing substantive allegations.

The OIG report thus clearly reveals that OHRP is abusing its discretion when deciding whether to initiate formal for-cause compliance evaluations of substantive written allegations. Use of "other mechanisms" has become the rule rather than the exception for OHRP's approach to addressing substantive allegations of noncompliance, effectively eclipsing the agency's procedures for conducting formal for-cause compliance evaluations. As a result, OHRP has undermined the integrity of its enforcement activities.

By routinely using "other mechanisms" to address substantive allegations, the agency and institutions that conduct research in violation of regulations are more likely to escape public scrutiny. Complainants are kept in the dark about the outcome of the agency's review, and determination letters describing regulatory violations and any corrective actions taken by institutions are not written by OHRP or made publicly available on the OHRP website, even in circumstances where serious allegations of noncompliance are confirmed. Complainants also apparently are deprived of the right to appeal the agency's determinations in most compliance matters.

Furthermore, OHRP has, with this lax approach, signaled to the research community that there is little chance that the agency will formally investigate allegations of even serious regulatory violations. Indeed, since October 2016, OHRP has issued only a single compliance oversight determination letter, and that letter appears to have resulted from a not-for-cause compliance oversight evaluation.[3] This dearth of compliance oversight activity demonstrates that OHRP has become a paper tiger when it comes to addressing allegations of noncompliance and properly enforcing the HHS regulations for the protection of human subjects.

Public Citizen's Health Research Group itself has directly experienced OHRP's abuse of its discretion when responding to formal allegations of noncompliance. Over the past three years, our group has submitted detailed formal written complaints to OHRP regarding serious allegations of noncompliance with the HHS regulations for the protection of human subjects with respect to five clinical trials.[4] In each case, OHRP refused to open a formal compliance oversight evaluation.

Conclusions

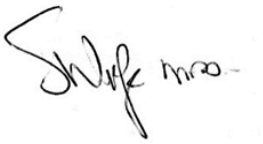
Researchers who violate HHS regulations for the protection of human subjects undoubtedly are delighted to see an OHRP that is unwilling to aggressively enforce the human subjects protection regulations. Unfortunately, human research subjects can no longer depend on OHRP to meet its obligation to protect their rights and welfare by consistently and transparently enforcing the regulations.

In closing, we respectfully urge you to (1) broadly examine the adequacy of OHRP's compliance oversight activities and (2) demand that the agency cease abusing its discretion when deciding whether to initiate formal for-cause evaluations in response to substantive written allegations or indications of noncompliance with the HHS regulations for the protection of human subjects. We would be happy to meet with your staff to provide additional information.

Thank you for your interest in this important matter.

Sincerely,

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group



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[3] Office for Human Research Protections. Letter to the Fred Hutchinson Cancer Research Center. December 1, 2017. https://www.hhs.gov/ohrp/december-1-2017-fred-hutchinson-cancer-research-center.html. Accessed January 26, 2018.

[4] See Public Citizen letters to OHRP at https://www.citizen.org/sites/default/files/2382_0.pdf, https://www.citizen.org/system/files/case_documents/170614_complaint_letter_to_ohrp-support_final-signed-with_enclosures.pdf, https://www.citizen.org/sites/default/files/2315.pdf, https://www.citizen.org/sites/default/files/2283.pdf, and https://www.citizen.org/sites/default/files/2284.pdf.