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January 9, 2013

The Honorable Kathleen Sebelius
Secretary
Department of Health and Human Services
200 Independence Ave. SW
Washington, DC 20201

Dear Secretary Sebelius:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, wishes to express its serious concern with the recent dangerously lax compliance oversight determinations made by the Office for Human Research Protections (OHRP) — a program office within the Office of the Secretary of Health and Human Services — that, unless overturned, will seriously undermine the special regulatory protections for children provided under the Department of Health and Human Services (HHS) human-subjects protection regulations, at 45 C.F.R. Part 46, Subpart D ("Additional Protections for Children Involved as Subjects in Research;" hereafter "Subpart D").

In letters to OHRP dated July 19, 2011,[1] and February 28, 2012,[2] we asked the agency to promptly conduct a compliance oversight investigation of the following HHS-funded research study involving children for all institutions engaged in the research:

> Title: *Type 1 Diabetes TrialNet Protocol TN-14: Effects of Canakinumab on the Progression of Type 1 Diabetes in New Onset Subjects*[3]
> Sponsor: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
> Award number: U01 DK061034

In our letters, we alleged the following:

(1) The above-referenced study was unethical and failed to satisfy the requirements of the HHS human-subjects protection regulations at 45 C.F.R. Part 46, Subpart D ("Additional Protections for Children Involved as Subjects in Research," hereafter "Subpart D"). We noted in particular that the study, which proposed to enroll subjects with type 1 diabetes mellitus as young as age six years and involved much greater than minimal risk, (a) did

[1] Carome MA, Wolfe SM. Letter from Public Citizen to OHRP. July 19, 2011. http://www.citizen.org/documents/1956.pdf. Accessed January 3, 2013.
[2] Carome MA, Wolfe SM. Letter from Public Citizen to OHRP. February 28, 2012. http://www.citizen.org/documents/2005.pdf. Accessed January 3, 2013.
[3] ClinicalTrials.gov. Canakinumab study in individuals with newly diagnosed type 1 diabetes (anti IL-1). (ClinicalTrials.gov identifier: NCT00947427). http://clinicaltrials.gov/ct2/show/NCT00947427. Accessed January 3, 2013.

not satisfy the requirements of the HHS regulations at 45 C.F.R. §§ 46.404, 46.405, or 46.406; and (b) was not approved in accordance with the requirements of 45 C.F.R. § 46.407.

(2) Unless the proposed sample consent/parental permission form for this study was substantially modified by the investigators and reviewing institutional review boards (IRBs) that approved the study at each study site, the description of the risks and benefits of the research provided to subjects or their parents failed to satisfy the requirements of HHS regulations at 45 C.F.R. §§ 46.116(a)(2) and (3), respectively.

On November 28, 2012, OHRP issued a compliance oversight determination letter to the University of Minnesota and the University of South Florida regarding the above-referenced research,[4] which we surmise relates to our July 19, 2011, and February 28, 2012, letters to OHRP.

After reviewing OHRP's letter, we are alarmed by the agency's determinations that (a) the research study was approvable under HHS regulations at 45 C.F.R. § 46.405 ("Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects") and (b) the University of Minnesota's IRB had made the findings required under this subsection of Subpart D. The evidence and rationale cited in OHRP's letter to support the agency's determinations are clearly flimsy and insufficient. More disturbing, OHRP's explanation for its determinations reflects a stunning disregard for, and an apparent lack of understanding of, the very regulations that agency is charged with enforcing. Unless these determinations are reversed, OHRP has effectively eviscerated the special HHS regulatory protections intended for children — a population of vulnerable subjects who are unable to consent to participation in research on their own behalf.

More broadly, this OHRP decision reflects a continuing trend spanning several years during which the leadership of OHRP has failed to effectively implement the regulations for the protection of human subjects and has taken stances that place greater priority on protecting the interests of the HHS agencies, research institutions, and investigators than protecting the rights and welfare of human subjects.

I. OHRP's Determination

Regarding our allegation that the above-referenced research was unethical and failed to satisfy the requirements of the HHS regulations under Subpart D, OHRP stated the following in its November 28, 2012, letter:[5]

> [The University of Minnesota] responded that during a September 16, 2010 IRB meeting, the [University of Minnesota] IRB determined that children can be included in this research in accordance with HHS regulations at 45 CFR 46.405;

[4] Rooney LA. Letter from OHRP to the University of Minnesota and the University of South Florida. November 28, 2012. http://www.hhs.gov/ohrp/detrm_letrs/YR12/nov12a.pdf. Accessed January 3, 2013.
[5] *Ibid*.

research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects. In addition, [the University of South Florida] provided us with an October 12, 2010 UM IRB approval letter reflecting that the [University of Minnesota] IRB determined that children can be included in this research in accordance with HHS regulations at 45 CFR 46.405.

[OHRP] believe[s] that reliance on 45 CFR 46.405 was justified based on information contained in the protocol titled Effects of Canakinumab on the Progression of Type 1 Diabetes in New Onset Subjects (version: August 11, 2010). Specifically, [OHRP] believe[s] that the following information provides a reasonable basis upon which an IRB could conclude that the study could present the prospect of direct benefit to individual subjects and thus be approvable under HHS regulations at 45 CFR 46.405:

> (a) Section 2.1 which states "Any intervention that can stop or delay the complete loss of functional residual B-cell mass is significant as it may provide protection against hypoglycemia and provide improved metabolic control resulting in a delay in the micro and macro-vascular complications of diabetes;"
>
> (b) Section 2.1 which states "An intervention that can enable continued endogenous insulin production would significantly improve the day-to-day management for subjects with diabetes and therefore reduce long-term complications." and
>
> (c) Section 2.2.1 which states
>
> > "Thus, the therapeutic rationale for the use of Canakinumab is based on the inhibition IL-1B to result in 1) delay/arrest of B-cell apoptosis, and 2) sustained restoration of B-cell function. Modulation of B-cell function by targeting the inflammatory cytokine IL-1B represents a novel approach, addressing a newly recognized contributor to the pathophysiology of T1DM progression, which could potentially result in a disease-modifying therapy."

Based on the documentation provided in your correspondence, coupled with the information from the approved protocol, which is outlined above, [OHRP has] determined that this allegation of noncompliance is unproven. From the evidence presented to us, it appears that UM evaluated this research as required by 45 CFR 46.405 and determined it to be approvable. [OHRP] concur[s] with this determination.

II. Critique of OHRP's Determination: A Failure to Demonstrate that the Research Study Satisfied the Requirements of 45 C.F.R. § 46.405

a. The regulatory requirements for approving research under 45 C.F.R. § 46.405

For research involving children that presents greater than minimal risk, a finding by the IRB that the research presents the prospect of direct benefit to the subjects is not sufficient, alone, for approval under 45 C.F.R. § 46.405. The IRB also must make the following three findings:

- The risk is justified by the anticipated benefit to the subjects;
- The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and
- Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in 45 C.F.R. § 46.408.

We also note that for clinical investigations, such as the above-referenced research study, that are regulated by the FDA, these findings must be documented by the IRB.[6]

b. Insufficient basis for finding that the research study held out the prospect of direct benefit

Apparently based solely on three excerpts from the background section of research protocol and superficial assurances from the University of Minnesota that its IRB found the above-referenced research study in accordance with the HHS regulations at 45 C.F.R § 46.405, OHRP concluded that the above-referenced research study presented the prospect of direct benefit to individual subjects and thus was approvable under HHS regulations at 45 C.F.R § 46.405.

Although we agree that the general statements quoted above from section 2.1 of the research protocol may be true, such statements provide no evidence or support for the claim that a one-year regimen of monthly injections of the potent immunosuppressant canakinumab is an intervention that will significantly improve the clinical course of new onset type 1 diabetes mellitus in children or adults. In addition, prior studies of other immunosuppressive and immunomodulatory drugs for preventing the progression of type 1 diabetes have yet to show that such drugs provide any meaningful, long-term clinical benefit.[7]

The statements quoted above from section 2.1.1 of the research protocol provide a *theoretical* basis for why canakinumab might be beneficial in new onset type 1 diabetes mellitus. However, such hypothetical claims alone fail to provide sufficient evidence to reasonably conclude that the experimental intervention holds out the prospect of *actual* direct benefit to the individual child subjects. Evidence from appropriate pre-clinical animal studies or clinical trials testing

[6] 21 C.F.R. § 50.52.
[7] McCulloch DK, Pietropaolo M. Prevention of type 1 diabetes mellitus. UpToDate. Last updated September 13, 2012.

canakinumab in adults with type 1 diabetes should have been presented. No such evidence is provided in the research protocol or cited by OHRP as being considered by the University of Minnesota IRB, and we are not aware of any such evidence.

Finally, nearly all clinical trials enrolling subjects with a particular disease or disorder are based on some underlying hypothetical framework supporting the assertion that the experimental intervention(s) being tested may offer the prospect of direct benefit to the subjects. If investigators only need to concoct some theoretical framework explaining why an experimental intervention *might* hold out the prospect of direct benefit — regardless of the evidence to support that framework — to meet the threshold for approval under the requirements of 45 C.F.R. § 46.405, none of the needed additional substantive protections would be provided to children under this subsection of Subpart D.

c. OHRP's determination completely disregards the findings required under 45 C.F.R. §§ 46.405(a) and (b)

Even if one were to assume that the administration of canakinumab to subjects enrolled in the above-referenced study did present the prospect of direct benefit to the individual subjects, this determination alone is not sufficient to approve the research study under 45 C.F.R. § 46.405. The IRB also must still make the three findings specified under 45 C.F.R. § 46.405. Of particular importance are the findings that (a) the risk of the research is justified by the anticipated benefit to the subjects and (b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.

To our dismay, in making its determination, OHRP failed to even reference, let alone substantively discuss, these critically important findings. Furthermore, the research protocol offers no discussion of — or evidence to support — these findings, and OHRP makes no mention as to whether the University of Minnesota IRB specifically addressed them or cited evidence to support them.

In particular, there is no comparative, evidence-based analysis by the investigators or OHRP (or presumably by the University of Minnesota IRB) describing (a) why the known risks of receiving monthly canakinumab injections for one year are justified by the speculative, unknown benefits to the subjects, and (b) why the relation of this speculative, unknown benefit to the known risks is at least as favorable to the subjects as that presented by alternative approaches (i.e., standard diabetes management, including treatment with insulin and no immunosuppression).

As discussed in our July 19, 2011, letter to OHRP,[8] given the known serious risks of even a single dose of canakinumab, including the documented risk of life-threatening infections and the possible risk of malignancies because of the marked immunosuppression, and given the absence of any preliminary data suggesting canakinumab presents the prospect of direct benefits to adults or children with type 1 diabetes mellitus, there was no reasonable basis for the investigators to assert, or OHRP or the University of Minnesota IRB to conclude, that (a) the risks of

[8] Carome MA, Wolfe SM. Letter from Public Citizen to OHRP. July 19, 2011. http://www.citizen.org/documents/1956.pdf. Accessed January 3, 2013.

canakinumab injections monthly for one year are justified by the anticipated benefit to the subjects, or (b) the relation of the anticipated benefit to the risks of such intervention with canakinumab is at least as favorable to the subjects as that presented by available alternative approaches.

OHRP's complete failure to address the requirements of 45 C.F.R. §§ 46.405(a) and (b) in making its determination demonstrates a complete disregard for these critically important regulatory requirements for protecting children involved as subjects in research, which is unacceptable.

III. Additional Unresolved Concerns

a. Allegations of inadequate informed consent/parental permission

In our February 28, 2012, letter to OHRP,[9] we raised numerous concerns about inadequacies in the proposed sample consent/parental permission form for the above-referenced research. For example, we noted that the form[10] failed to accurately describe the reasonably foreseeable risks of the intervention with canakinumab, as required by HHS regulations at 45 C.F.R. § 46.116(a)(2), and in fact inappropriately downplayed the risks of this intervention. In particular, we noted the following:

(1) The discussion of the risk of infections failed to disclose that canakinumab, even with a single dose, might cause infections that are serious and potentially life-threatening, and that this risk is likely to progressively increase with repeated dosing. Indeed, as we noted in our July 19, 2011, letter to OHRP,[11] clinical trials of canakinumab in patients with gout had an increased risk of serious infections after only a single dose.

(2) The description of risks failed to include the following additional risks, which have been seen in other studies of canakinumab use for other types of disorders:

- Leukopenia/neutropenia (decreased number of white cells) and thrombocytopenia (decreased number of platelets)
- Declines in renal function
- Elevations in serum triglycerides and total cholesterol
- Liver dysfunction

(3) The description of the risk of cancer due to immunosuppression minimized this risk by merely including the statement that it "had not been seen in previous studies [of this drug]." Given the number of subjects enrolled and duration of follow up in prior studies of canakinumab, it is not surprising that cancers induced by this drug have not been

[9] Carome MA, Wolfe SM. Letter from Public Citizen to OHRP. February 28, 2012. http://www.citizen.org/documents/2005.pdf. Accessed January 3, 2013.
[10] Type 1 Diabetes Trial Net. Model intervention informed consent: Type 1 Diabetes TrialNet protocol TN-14: *Effects of canakinumab on the progression of type 1 diabetes in new onset subjects*. September 28, 2010 version.
[11] Carome MA, Wolfe SM. Letter from Public Citizen to OHRP. July 19, 2011. http://www.citizen.org/documents/1956.pdf. Accessed January 3, 2013.

identified. This does not mean the risk does not exist. Such cancer events are unlikely to be detected until there has been long-term follow up of sufficient numbers of people who receive this drug. The sample consent/parental permission form therefore should have stated that the previous studies that had failed to detect increased risk of cancer were not designed to detect such risk.

We also expressed concern that, compounding the minimization of risks of canakinumab, the sample consent/parental permission form falsely exaggerated the potential benefits of this research to the subjects, given the total lack of any evidence that the drug offers benefits to patients with new onset type 1 diabetes mellitus. Given that this was the first study of canakinumab in subjects with new onset type 1 diabetes mellitus and the fact that prior studies of other immunosuppressive and immunomodulatory drugs for preventing the progression of type 1 diabetes have failed to show any meaningful, long-term clinical benefit, it would have been fairer and more appropriate to state that it is highly unlikely that the subjects would benefit from participation in the research. In fact, given the known risks of serious harm from the canakinumab, subjects were more likely to experience harm than benefit.

Finally, we noted that for subjects or their parents to fully understand the nature of this research and put it into an appropriate context, the consent/parental permission form should have emphasized that (a) this was the first time canakinumab had been studied in subjects with type 1 diabetes mellitus, and (b) prior research testing of other immunosuppressing drugs for this disease had generally yielded results that show little clinically significant long-term benefit. The sample consent/parental permission form provided to us by the National Institutes of Health (NIH) failed to include any such statements.

While the final consent/parental permission forms ultimately approved by the University of Minnesota IRB (and other IRBs) may have adequately addressed the deficiencies observed in the sample form, OHRP's November 28, 2012, determination letter is silent regarding these deficiencies. It is imperative that OHRP directly address these deficiencies before closing its compliance oversight evaluation of the research.

b. The need to evaluate the IRB review at all institutions engaged in the research

The registration entry for the above-referenced research study on ClinicalTrials.gov lists the following institutions as study locations in addition to the University of Minnesota:[12]

- University of California-San Francisco
- Stanford University
- Yale Medical School
- University of Florida
- University of Miami School of Medicine
- Indiana University-Riley Hospital for Children

[12] ClinicalTrials.gov. Canakinumab study in individuals with newly diagnosed type 1 diabetes (anti IL-1). (ClinicalTrials.gov identifier: NCT00947427). http://clinicaltrials.gov/ct2/show/NCT00947427. Accessed January 3, 2013.

- Columbia University
- University of Pittsburgh
- University of Texas-Southwestern Medical School
- Benaroya Research Institute
- Toronto Hospital for Sick Children

In our February 28, 2012, letter to OHRP,[13] we asked the agency to evaluate the performance of each IRB that reviewed and approved this research study, since different IRBs may have reached different conclusions regarding the justification for approval of this research and the adequacy of the sample consent/parental permission form.

Since OHRP's November 28, 2012, determination letter is addressed only to the University of Minnesota and the University of South Florida, which apparently is not enrolling any subjects, we are concerned that OHRP has failed to pursue an evaluation of our allegations at the other institutions that may be engaged in this research and enrolling subjects. It is imperative that OHRP fully explore whether multiple institutions failed to ensure that children enrolled in this research study were adequately protected in accordance with all applicable provisions of the HHS human-subjects protection regulations. This is of special concern given the serious deficiencies, discussed above, in the proposed sample consent/parental permission form that presumably was provided to investigators at all of the above institutions.

IV. Conclusions and Requested Actions

In summary, Public Citizen is deeply troubled by OHRP's determinations that (a) the above-referenced research study was approvable under HHS regulations at 45 C.F.R. § 46.405 ("Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects"), and (b) the University of Minnesota's IRB had made the findings required under this subsection of Subpart D. These determinations will seriously undermine the special regulatory protections for children involved in research intended under Subpart D. The evidence and rationale cited in OHRP's letter to support the agency's determinations are clearly flimsy and insufficient. Moreover, OHRP's explanation for its determination reflects a stunning disregard for, and an apparent lack of understanding of, the very regulations that agency is charged with enforcing. Unless these determinations are reversed, OHRP has effectively rendered meaningless the special HHS regulatory protections intended for children involved as subjects in research.

We also have concerns that OHRP appears to have failed to appropriately address potential inadequacies regarding the informed consent/parental permission process of this research and to pursue an evaluation of our allegations at all institutions engaged in the research.

We therefore urge you to take the following actions regarding the above-referenced research study:

[13] Carome MA, Wolfe SM. Letter from Public Citizen to OHRP. February 28, 2012. http://www.citizen.org/documents/2005.pdf. Accessed January 3, 2013.

(1) Direct OHRP to reassess whether the study satisfies the requirements of HHS regulations at 45 C.F.R. § 46.405 and demand that the agency produce a robust, evidence-based rationale to support all findings required under this subsection of Subpart D. If such a rationale cannot be produced, direct OHRP to (a) retract the determinations regarding compliance with the HHS regulations at 45 C.F.R. § 46.405 that were made in its November 28, 2012 letter, (b) suspend the research study, and (c) require compliance with the provisions of HHS regulations at 45 C.F.R. § 46.407 as a condition for allowing the research to resume.

(2) Direct OHRP to (a) fully assess our allegations regarding inadequacies in the sample consent/parental permission form for the study, as outlined above, and (b) issue detailed determinations regarding these allegations.

(3) Direct OHRP or NIH to immediately make publicly available the final IRB-approved version of the consent/parental permission form for the study for each institution engaged in the research so that Public Citizen and other consumer advocates can independently assess the adequacy of these documents *before* OHRP completes its compliance oversight evaluation of this research study.

(4) Direct OHRP to pursue a thorough evaluation of our allegations at each institution engaged in this research.

(5) Direct the Secretary's Advisory Committee on Human Research Protections (SACHRP) to conduct an in-depth evaluation of (a) OHRP's implementation and enforcement of the requirement of the HHS regulations under Subpart D more broadly, and (b) the effectiveness of OHRP's compliance oversight program.

Thank you for your prompt attention to this important human subjects research issue. Please contact us if you have any questions or need additional information.

Sincerely,

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Sidney M. Wolfe, M.D.
Director
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cc: Dr. Jerry Menikoff, Director, OHRP
Dr. Kristina Borror, Director, Division of Compliance Oversight, OHRP
Dr. Griffin P. Rodgers, Director, NIDDK
Dr. Jeffrey Botkin, Chair, SACHRP