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February 27, 2013

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Dear Dr. Menikoff and Dr. Borror:

Public Citizen, a consumer advocacy organization with more than 300,000 members and supporters nationwide, is writing in follow-up to our July 19, 2011,[1] and February 28, 2012, letters[2] in which we asked the Office for Human Research Protections (OHRP) to conduct a compliance oversight investigation of all institutions engaged in the following research study involving children, funded by the National Institutes of Health (NIH):

> 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

Our July 19, 2011, letter alleged that the above-referenced study was unethical and failed to satisfy the requirements of the Department of Health and Human Services (HHS) human-subjects protection regulations at 45 C.F.R. part 46, subpart D ("Additional Protections for

[1] Carome MA, Wolfe SM. Letter from Public Citizen to OHRP. July 19, 2011. http://www.citizen.org/documents/1956.pdf. Accessed February 20, 2013.
[2] Carome MA, Wolfe SM. Letter from Public Citizen to OHRP. February 28, 2012. http://www.citizen.org/documents/2005.pdf. Accessed February 20, 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 February 20, 2013.

Children Involved as Subjects in Research"). We noted in particular that the study, which proposed to enroll subjects with type 1 diabetes mellitus as young as age six and involved much greater than minimal risk, (a) did 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. As you are aware, on January 9, 2013, we wrote to Secretary of Health and Human Services Kathleen Sebelius expressing serious concern with the recent dangerously lax compliance oversight determinations made by OHRP regarding the protection of children involved in this research.

Our February 28, 2012, letter to OHRP raised numerous concerns about inadequacies in the proposed sample consent/parental permission form for the above-referenced research.[4] For example, we noted that the sample form 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 that it in fact inappropriately downplayed the risks of this intervention. We also expressed concern that in addition to minimizing the risks of canakinumab, the sample consent/parental permission form falsely exaggerated the potential benefits of this research to the subjects, given the lack of any evidence that the drug offers benefits to patients with new onset type 1 diabetes mellitus. Finally, we noted that for subjects or their parents to fully understand the nature of this research and put it into appropriate context, the consent/parental permission forms 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 showing little clinically significant long-term benefit. Thus, subjects were far more likely to experience clinically significant harm than any clinically significant benefit.

Because at the time of our previous letters we did not have access to any final versions of the consent/parental permission form approved by the institutional review boards (IRBs) from the institutions engaged in the research, we acknowledged the possibility that the final consent/parental permission forms ultimately approved by the IRBs may have adequately addressed the deficiencies we identified in the sample form.

However, we now have obtained final versions of the consent/parental permission forms for two institutions engaged in this research study: Stanford University[5] and the Benaroya Research Institute.[6] Our review of these IRB-approved consent/parental permission forms reveals that they are essentially identical to the seriously deficient sample consent/parental permission form with respect to the description of the study's risks and benefits. Therefore, at least two IRBs that

[4] Type 1 Diabetes TrialNet. 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.
[5] Stanford University. Intervention consent form for Type 1 Diabetes TrialNet Protocol TN-14: *Effects of canakinumab on the progression of type 1 diabetes in new onset subjects*. IRB approval date: October 21, 2010. http://dped.stanford.edu/Consents%202010/Canakinumab/Anti-Il-1Beta_Intervention_Consent.pdf. Accessed February 20, 2013.
[6] Benaroya Research Institute. Intervention consent form for Type 1 Diabetes TrialNet Protocol TN-14: *Effects of canakinumab on the progression of type 1 diabetes in new onset subjects*. IRB approval date: September 27, 2010. http://www.benaroyaresearch.org/files/webfm/diabetes/canakinumab-intervention-assent.pdf. Accessed February 20, 2013.

reviewed and approved the study failed to recognize and correct the serious deficiencies that we identified in the sample form.

Finally, we also have obtained an IRB-approved consent form for another study testing multiple doses of canakinumab over a prolonged period of time.[7] The study, sponsored by Novartis Pharmaceuticals Corporation, is entitled *A randomized, double-blind, placebo-controlled, event-driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP*.

Our February 28, 2012, letter noted that the consent/parental permission form for the NIH-funded study in diabetic children downplayed the risk of infection by failing to disclose, among other things, that canakinumab exposure could cause serious, life-threatening infections. In contrast, the consent form for the Novartis-sponsored trial provides a much more accurate portrayal of the risks of serious infections due to canakinumab:

> **ARE THERE RISKS TO ME IF I AM IN THIS STUDY?**
>
> What can happen if I receive canakinumab?
>
> All drugs carry a risk of side effects.… As with any new drug, there is a risk that a rare or previously unknown side effect could occur and the researchers cannot rule out the possibility that an unknown side effect may be life-threatening.
>
> **Serious Infections**
>
> Canakinumab is a study drug which may affect your immune system and has been associated with an increased risk of serious infections.… There have been serious adverse events with the study drug. "A serious adverse event" is defined as a side effect that is fatal, life-threatening or requires a study participant to be hospitalized for a time; it may or may not be related to a study drug … in other canakinumab research studies three participants, one with lung infection, one with intestinal infection and one with blood infection, have died.
>
> Drugs that affect the immune system have been associated with an increased risk of tuberculosis. It is possible that taking canakinumab may increase the risk of tuberculosis.... One patient dosed with canakinumab outside of research studies experienced a serious fatal tuberculosis infection.

Unlike the consent form for the Novartis-sponsored trial, the sample form and at least some final, IRB-approved consent/parental permission forms for the NIH-funded study in diabetic children fail to state that canakinumab "has been associated with an increased risk of serious infections,"

[7] Novartis Pharmaceuticals Corporation. *A randomized, double-blind, placebo-controlled, event-driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP: Information and consent form.* Version 1, February 23, 2011. Approved by Quorum Review March 23, 2011. http://www.neimef-research.org/webres/File/HeartAttackInformedConsent.pdf. Accessed February 20, 2013.

that at least three patients exposed to canakinumab in other trials have died with serious infections, and that the drug is associated with an increased risk of tuberculosis.

In conclusion, the failure of at least two IRBs at major academic medical centers to recognize and correct the serious deficiencies in the sample consent/parental permission form for the Type 1 Diabetes TrialNet Protocol TN-14 is very troubling. We therefore again urge OHRP to carefully assess the adequacy of the IRB review and the final IRB-approved consent/parental permission form for each institution engaged in the study. In addition, OHRP should require that the study investigators promptly contact all subjects and parents of child subjects who signed a deficient consent/parental permission form; inform them of the deficiencies; and provide more appropriate information regarding the nature, risks, and benefits of the research.

Please contact us if you have any questions or need additional information.

Sincerely,

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Public Citizen's Health Research Group

Sidney M. Wolfe, M.D.
Director
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cc: The Honorable Kathleen Sebelius, Secretary of Health and Human Services
The Honorable William B. Schultz, Acting General Counsel, HHS