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Dear Dr. Menikoff and Dr. Borror:

We are writing in follow-up to our July 19, 2011 letter[1] in which we asked the Office for Human Research Protections (OHRP) to promptly conduct a compliance oversight investigation of the following research study, which is entirely supported by the Department of Health and Human Services (HHS), 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*[2]
> Sponsor: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
> Award number: U01 DK061034

In our first letter, we alleged that 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"). We noted in particular that the study, which enrolled subjects with type 1 diabetes mellitus as young as age six years 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.

Since submitting our first letter, we have obtained from NIDDK under the Freedom of Information Act copies of the research protocol (October 19, 2011 version) and the sample informed consent/parental permission form (Model Intervention Informed Consent: Type 1 Diabetes TrialNet Protocol TN-14, version 9-28-2010) for the above-referenced study.

A review of the research protocol reaffirms and provides evidence for our initial allegation. Furthermore, our review of the sample informed consent/parental permission form for this study reveals that, unless this sample form was substantially modified by the reviewing institutional review boards (IRBs) that approved the study, 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.

Failure to satisfy the requirements of 45 C.F.R. Part 46, Subpart D

In discussing the risks and benefits of the research (see section 9.5 of the research protocol), the investigators acknowledged that the research involves greater than minimal risk, and sought to justify approval of the study 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"). In particular, they noted the following:[3]

> There is the prospect of direct benefit to the individual subjects for their participation in the study. These potential benefits include the recognized benefits of being in a clinical study, including close monitoring and additional resources available to maintain tight glycemic control offered to all subjects, regardless of study group assignment. Further, the intervention has the prospect of direct benefit to a given subject and is likely to yield general knowledge about [type 1 diabetes mellitus (T1DM)] that is of importance for the understanding and amelioration of T1DM in children.
>
> The study procedures, while possibly slightly greater than minimal risk, offer the possibility of benefit in the close monitoring of all children. Assent of children along with consent of the parents will be obtained prior to any study procedures. This research proposal in children is therefore consistent with United States Department of Health and Human Services, Protection of Human Subjects, subpart D, section 46.405 (research involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects)…

The investigators' justification for approval of this research under 45 C.F.R. § 46.405 is seriously flawed for several reasons, including the following:

(1) In discussing the prospect of direct benefit to the individual subjects, the investigators focused on the "recognized benefits of being in a clinical study, including close monitoring and additional resources available to maintain tight glucose control."

Reliance on the argument that participation in a clinical trial itself, with close monitoring, provides the prospect of direct benefit – regardless of the risks and benefits of the primary experimental intervention being tested in a study – essentially eviscerates the protections for children intended under the provisions of 45 C.F.R. Part 46, Subpart D. Indeed, such an argument, if accepted by IRBs, could be used to justify any clinical study in children, regardless the level of risk or the degree of evidence (or lack thereof) for benefit with respect to the primary intervention being tested.

(2) A finding that a study is found to hold out the prospect of benefit for individual subjects is not sufficient to approve research under 45 C.F.R. § 46.405. The IRB must also find that (a) the risk of the research is justified by the anticipated benefit to the subjects, and (b) the relation of anticipated benefit to risk is at least as favorable to the subjects as that presented by available alternative approaches. The justification offered by the investigators in this case fails to address these critically important findings. In particular, there is no comparative analysis by the investigators describing why the relation of anticipated benefit to risk of monthly canakinumab injections for one year is a least as favorable to the subjects as that presented by alternative approaches (i.e., standard diabetes management, including treatment with insulin and no immunosuppression).

Moreover, as discussed in our first letter, 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 basis for the investigators to assert, or the IRBs to find, that (a) the risk of canakinumab injections monthly for one year is justified by the anticipated benefit to the subjects, or (b) the relation of the anticipated benefit to risk of such intervention with canakinumab is at least as favorable to the subjects as that presented by available alternative approaches.

Finally, prior studies of immunosuppressive and immunomodulatory drugs for preventing the progression of type 1 diabetes have failed to show any meaningful, long-term clinical benefit from such drugs.[4]

(3) The investigators' statement that the study procedures involve "possibly slightly greater than minimal risk" inappropriately minimized the risk of monthly injections with canakinumab in the experimental group subjects and misled the IRBs.

(4) The investigators provided no evidence to support their assertion that the research study was likely to yield generalizable knowledge about type 1 diabetes mellitus that is of importance for the understanding and amelioration of type 1 diabetes mellitus in children.

Therefore, the investigators for this study failed to provide the IRBs with sufficient justification for approving this study under the HHS regulations at 45 C.F.R. § 46.405, and the IRBs should not have approved it.

Inadequate informed consent/parental permission

The sample informed consent/parental permission form for the above-referenced study provided the following description of the risks of canakinumab:[5]

> Possible side effects from canakinumab include upper respiratory, urinary tract, and other types of infections. We will carefully check you for signs of infection during the study. If we see signs that you developed a new infection[,] we will temporarily discontinue giving your monthly injections until the infection has resolved. You should contact your doctor if you develop any infections, any flu-like symptoms, or are not feeling well at any time. Another uncommon, but possible, side effects [sic] include vertigo (dizziness) which is temporary and subsides. There is also the possibility that you could have an allergic reaction. For your safety the research staff will watch you closely after each injection for any possible effects. As with other medications that alter responses by the immune system there is a theoretical risk that canakinumab can possibly lead to an increased risk of certain types of cancer. However, this has not been seen in previous studies.
>
> Reactions can occur at the injection site, including discomfort, within one day after you are given the study treatment. You may also develop some redness, swelling, or even a scab at the injection site.

This description 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 down played the risks of this intervention.

For example, 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 initial letter to OHRP, clinical trials of canakinumab in patients with gout had an increased risk of serious infections after only a single dose.

The above description also failed to describe the following additional risks which have been seen in other studies of canakinumab use for other types of disorders:

- Leukopenia, neutropenia, and thrombocytopenia
- Declines in renal function
- Elevations in serum triglycerides and total cholesterol
- Liver dysfunction

Finally, the description of the risk of cancer due to immunosuppression minimized this risk by including the statement that this “had not been seen in previous studies.” 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 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 informed 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.

The sample informed consent/parental permission form for the above-referenced study also provided the following description of the potential benefits of participation in the research:[6]

> If you decide to take part in this study, there is no guarantee that your health will improve. It is hoped that the canakinumab will help your body continue to make insulin, but there is no guarantee this will happen. Even if the canakinumab can protect the insulin producing cells that are left, you will still need to take insulin shots. Studies have shown that people who continue to make insulin have less trouble with low blood sugars and few complications from their diabetes than people who no longer make their own insulin. We will follow your health and diabetes closely.

In contrast to the minimization of risks of canakinumab, the informed consent/parental permission form falsely exaggerated the potential benefits of this research to the subjects. Given that this was the first study of canakinumab in subjects with 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, in order for subjects or their parents to fully understand the nature of this research and to put it into an appropriate context, the informed 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 that show little clinically significant long-term benefit.

Conclusions

In closing, we encourage OHRP to consider these additional comments when investigating the adequacy of the IRB review for all sites participating in this study.

We are expanding our original request to ask OHRP to evaluate the serious deficiencies in the informed consent/parental permission form noted above. Unless the IRB-approved forms were revised to address these deficiencies, OHRP should require that all subjects (or the parents of subjects) who have already been enrolled in this study be contacted and provided with more accurate information regarding the nature, risks, and benefits of this research.

Finally, we also ask OHRP 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 informed consent/parental permission forms.

Please note that OHRP may share this letter, with identifiers, with anyone. We will be posting a copy on our website as well.

We look forward to OHRP's thorough and careful investigation of our allegations. 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: Honorable Kathleen Sebelius, Secretary of Health and Human Services

[1] Carome MA, Wolfe SM. Letter to the Office for Human Research Protections requesting a compliance oversight investigation of the study entitled *Effects of canakinumab on the progression of type 1 diabetes in new onset subjects*. July 19, 2011. Available at http://www.citizen.org/documents/1956.pdf. Accessed February 28. 2011.
[2] 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 on February 28, 2011.
[3] Type 1 Diabetes TrialNet. Effects of canakinumab on the progression of type 1 diabetes in new onset subjects (protocol TN-14). Version: October 19, 2011.
[4] McCulloch DK, Pietropaolo M. Prevention of type 1 diabetes mellitus. UpToDate. Last updated October 4, 2011.
[5] 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.
[6] 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.