DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

Jonathan W. Emord, Esq.
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MAR 16 2007

RE: Patient Advocacy Council, Inc.

Dear Mr. Emord:

This letter responds to your letters dated February 21, February 26, and March 6, 2007 regarding the Food and Drug Administration (FDA) Warning Letter issued February 1, 2007.

We appreciate your clarification that the previous name of the Patient Advocacy Council, Inc. ("PAC") parent institution was "Discovery Alliance International" and not "Discovery Alliance."

This letter also clarifies that the Warning Letter was based on the review of [redacted] studies reviewed by the IRB in 2003-4. These studies involved the administration of an investigational [redacted] associated with potentially significant adverse events to healthy volunteers who had limited expectations for benefiting from the [redacted] These studies were not selected for review during the January 2006 inspection, which focused on more recent investigations reviewed by PAC. However, the November 2006 inspection raised significant issues concerning the IRB's oversight of these studies enrolling vulnerable populations.

Regarding Item 1 ("The IRB failed to assure that selection of subjects is equitable while being particularly cognizant of the special problems of research involving vulnerable populations and failed to require additional safeguards to protect the rights and welfare of economically or educationally disadvantaged persons included as subjects in research"), as noted in our Warning Letter, we agree that the 3/2/04 meeting minutes document that the IRB addressed the request to enroll economically and educationally disadvantaged subjects into those [redacted] studies, and to amend the informed consent document by adding a signature line for an impartial witness. Our concern is that the IRB did not appear to be cognizant of the special problems presented to vulnerable populations by these particular studies, in light of the risks, precautions, and contraindications described in the Investigator's Brochure and other documents, such as the "Risk Sheets" the IRB reviewed and approved for the studies. Your letters did not directly address any of the six concerns listed in our letter specifically related to these [redacted] studies. However, your 2007 changes to written procedure #220 show that you now understand our concerns. The revised procedure appears to be adequate to ensure consideration of the special problems and potential additional safeguards for future studies that may involve vulnerable populations.

Regarding Item 2 ("The IRB failed to follow written procedures for conducting continuing review of research"), this item had two components: review of information regarding risks to human subjects in the study, and the IRB's response to reports of investigator noncompliance.

The Warning Letter noted that SOP 221 required that "particular attention is paid to new information, changes to the protocol, or if unanticipated risks were discovered during the research," and that the IRB had not followed this procedure. Your statements that "PAC received no reports of "serious and unanticipated events" occurring at the research sites," and that all three categories of serious events were anticipated, is not supported by the record. We disagree that a hospitalization for somatic transformation was an anticipated event because this type of reaction was not described in the Investigator's Brochure. Shortly after two myocardial events were reported to the IRB, the sponsor halted the studies due to the hospitalization for acute myocarditis that occurred in one of the sites PAC oversaw. The 2004 version of SOP 227 similarly required that the primary reviewer review adverse event reports and report any significant changes or findings, at which time these are discussed among the Board and appropriate action or follow-up is taken" (emphasis added).

With regard to investigator noncompliance, we agree that the version of SOP 232 in effect in March 2004 did not require that the IRB send a notification of noncompliance to the investigator. However, SOP 219, in effect in March 2004, stated that the IRB member serving as primary reviewer for the study was expected to review safety reports and "discuss their findings and any unusual activity and any necessary action that needs to be taken". Moreover, as described in the Warning Letter, the IRB failed to follow through on its own determination on 3/30/04 to send a letter to the clinical investigator requesting an explanation for the numerous reported informed consent process deviations, and for a description of the process put in place to keep such deviations from recurring. The IRB was concerned enough about the 21 subjects who had no witness signature on the consent forms, reported by the clinical investigator for the [redacted] studies in letters dated 3/17/04, that you planned to request an explanation and action plan.

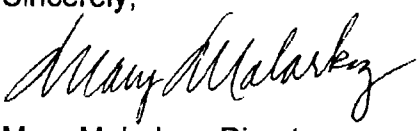
Further, we believe that protocol deviations that might initially appear to be routine or nonsignificant may be significant in vulnerable populations. Although it is not uncommon for subjects to miss scheduled study visits, the clinical investigator and IRB bear additional responsibility to ensure that educationally and economically disadvantaged subjects be seen for study visits. Educationally disadvantaged subjects simply might not have understood the importance of each visit to make sure that they were appropriately followed for recognized complications associated with the studies. An assessment of these violations in the vulnerable population may have indicated that vulnerable populations should not be recruited for these studies. Although we have not linked specific deviations to specific members of vulnerable populations, given the

responsibility to be "particularly cognizant", the IRB should be especially concerned about informed consent and protocol deviations occurring in clinical trials where vulnerable subjects are enrolled.

Regarding Item 3 ("The IRB failed to make all records required by regulation to be fully accessible for inspection and copying by authorized representatives of . . . FDA"), we have reviewed your affidavits and statements regarding your provision of records during FDA inspections. We recognize that, in these documents, you affirm the importance of making records appropriately available to FDA. We believe that additional argument on this point will not be fruitful. We welcome your cooperation in future inspections.

Thank you for letting us know your concerns about the manner in which the inspection was conducted. Please be assured that every action taken by FDA is carefully considered based on a review and analysis of records collected at the site or otherwise submitted to the agency. As an agency we are committed to conducting fair inspections and taking follow-up actions that are consistent with our responsibilities to protect the public health. The FDA believes the inspection process, employees, and the actions taken subsequent to this inspection met this intent.

Sincerely,



Mary Malarkey, Director
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cc:

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