



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

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

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CBER -- 07-- 06

Warning Letter

FEB - 1 2007

James V. Roberts, Jr., Chair
Patient Advocacy Council, Inc.
600 Bel Air Avenue, Suite 315
Mobile, Alabama 36606

Dear Mr. Roberts:

This letter describes the results of a Food and Drug Administration (FDA) inspection that was conducted from September 18 through 21, 2006. FDA investigators Patricia Smith and Jason Abel conducted an inspection of the Patient Advocacy Council (PAC) Institutional Review Board (IRB) to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 56. FDA conducted this inspection under the agency's Bioresearch Monitoring Program, which includes inspections designed to review IRB operations for clinical studies using investigational products, and for the protection of human subjects.

At the conclusion of the inspection, a Form FDA 483, List of Inspectional Observations, was issued and discussed with you, Ms. Sondra Wacker, Vice President of Operations, and Karen Pellegrin, President of Compass Point Research, Inc., the IRB's parent institution.

We received your letter dated October 19, 2006, in response to the Form FDA-483. Our comments on your response to the Form FDA-483 are included below.

We have determined that the IRB violated regulations governing the composition, operation, and responsibilities of Institutional Review Boards as published under 21 CFR 50 and 56 (available at <http://www.gpoaccess.gov/cfr/index.html>). The applicable provisions of the CFR are cited for each violation. We are addressing this letter to you under 21 CFR 56.120(a) as the current IRB Chairperson with responsibility for ensuring that the IRB takes the actions necessary to bring the IRB into full compliance with FDA regulations. Under 21 CFR 56.120(a) we are also sending copies of this letter to the responsible head of the IRB's parent institution, Compass Point Research, Inc. (formerly known as Discovery Alliance), because under 21 CFR 56.120(c), the parent institution is presumed to be responsible for the IRB's operations.

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. [21 CFR § 56.111(a)(3) and (b)].**

The IRB initially approved [REDACTED] studies of a [REDACTED] and related consent forms on 11/25/03. In a letter to the IRB dated 2/24/04, investigator [REDACTED] requested approval 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.

The IRB's meeting minutes of 3/2/04, show that the IRB approved the changes to the informed consent form. The IRB's "Amended Certificate of Approval" for the [REDACTED] studies indicates only that the IRB approved the revised consent form; it does not include documentation that the IRB specifically discussed, voted on, and approved the use of economically and educationally disadvantaged subjects for the [REDACTED] studies. The IRB did not record any consideration of the status of these additional subjects as economically and educationally disadvantaged subjects. Despite the IRB's duty to be particularly cognizant of the special problems of research involving vulnerable populations, the IRB did not request further information about the source of the vulnerable population. There is no indication that the IRB considered, among other issues, whether: (1) economically and educationally disadvantaged subjects were appropriate candidates for these studies; (2) the economically disadvantaged subjects would be vulnerable to coercion or undue influence by the \$150 monetary compensation for study participation; (3) the educationally disadvantaged subjects would be able to fully understand the requirements of the study and the potential risks to others; (4) the vulnerable populations came from settings where the administration of the [REDACTED] could be detrimental to the subjects or their close contacts; (5) the 19-page consent form containing complex medical and technical terminology was appropriate for educationally disadvantaged subjects; or (6) the revisions to the consent form would meaningfully add to the protection of the rights and welfare of the vulnerable subjects.

Your letter acknowledges that there is no documentation that "the IRB required additional information about the logistics of enrolling these patients or criteria for determining which subjects were considered economically or educationally disadvantaged." Your letter states that you will revise the written procedures regarding vulnerable populations. Please submit the revised procedures as part of your response to this letter.

2. The IRB failed to follow written procedures for conducting continuing review of research. [21 CFR § 56.108(a)].

The IRB failed to follow SOP 221 "Conducting Continuing Review" which states that "Particular attention is paid to new information, changes to the protocol, or if unanticipated risks were discovered during the research." In reference to one of the [REDACTED] studies, the IRB received reports of serious and unanticipated events, and reports of a total of 131 protocol deviations. Nevertheless, the IRB allowed the studies to continue without paying "particular attention" to this new information. In fact, the IRB meeting minutes simply state, "The Board reviewed and noted the deviations. No further action was required." Many of the protocol deviations were directly related to the economically and educationally disadvantaged subjects that the IRB had allowed to be enrolled into the [REDACTED] studies.

The IRB also failed to follow SOP #232, "Serious or Continuing Noncompliance" which states: "When PAC learns of an instance of noncompliance, the investigator will be sent a 'notification of noncompliance' that includes a description of the noncompliance and a deadline by which the investigator must submit a response." Instead of following the procedure prescribed here, on 3/30/04, the IRB voted to send [REDACTED] a letter requesting an explanation for the numerous reported protocol deviations, and for a description of the process put in place to keep such deviations from recurring. There was no documentation that the IRB followed up on their recommendation, and no record that the IRB sent such a letter to [REDACTED]. This non-compliance was significant because the violations involved the manner in which the informed consent was obtained from vulnerable populations.

Your letter acknowledges this violation, and states that you will implement improvements in operations and quality assurance procedures.

3. The IRB failed to make all records required by regulation to be fully accessible for inspection and copying by authorized representatives of the Food and Drug Administration (FDA). [21 CFR § 56.115(b)].

The administrative director of the IRB denied the FDA investigators full access to all study records and meeting minutes that related to studies reviewed by the IRB. Study binders were never provided for full review; instead, only limited, incomplete and redacted photocopies of minutes related to the [REDACTED] studies were provided to the FDA investigators.

We note that we expressed concern in the FDA 483 about the identity of an individual who voted and participated in deliberations at an IRB meeting. Your letter states that the individual is listed on a separate roster of alternate IRB members. Your response letter to the FDA 483 states that it has been the IRB's practice to list alternate members

on a separate roster. We recommend that the IRB maintain a single roster that lists both the regular and alternate members to avoid any confusion about the IRB membership.

This letter is not intended to be an all-inclusive list of deficiencies. It is incumbent upon you, the IRB, and the parent institution to not only correct the deficiencies cited on the Form FDA 483, and those described in this letter, but also to assure that all of the IRB's practices and procedures fully comply with the regulations.

Please notify this office in writing, within fifteen (15) business days of receipt of this letter, of the actions you have taken or plan to take to bring the procedures of your IRB into compliance with FDA requirements. Please include a copy of any revised documents, such as written procedures, with your response. Any plans of action should include projected completion dates for each action to be accomplished. We will review your response and determine whether the corrective actions are adequate to permit the IRB to resume unrestricted activities.

Your failure to adequately respond to this letter may result in further administrative actions against your IRB, as authorized by 21 CFR 56.120 and 56.121. These actions include FDA withholding approval of new studies reviewed by your IRB that are subject to Parts 50 and 56 of the FDA regulations, prohibiting the admission of new subjects to ongoing studies that are subject to 21 CFR Parts 50 and 56, terminating all ongoing studies approved by your IRB, and initiating regulatory proceedings for disqualification of your IRB.

Please send your written response to:

Patricia Holobaugh
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1488
Telephone: (301) 827-6221

We request that you send a copy of your response to the FDA offices listed below.

Sincerely,



Mary Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

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cc:

Compliance Oversight Branch
Office for Human Research Protections
U.S. Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852

H. Tyler Thornburg, District Director
New Orleans District
Food and Drug Administration
04 BNA Drive, Building 200, Suite 500
Nashville, Tennessee 37217