



WARNING LETTER

Food and Drug Administration
Rockville MD 20857

OVERNIGHT DELIVERY

Ref: No. 98-HFD-340-0802

AUG 27 1998

William C. Waggoner, Ph.D., FAACT
President and Chairman
Essex Institutional Review Board
10 Apgar Way
Lebanon, New Jersey 08833

Dear Mr. Waggoner:

On February 9, 1998, Ms. Jean M. Kelahan, an investigator with the New Jersey District of the Food and Drug Administration (FDA), performed a limited inspection of Essex Institutional Review Board (EIRB) to obtain copies of all documents pertaining to EIRB's initial and continuing review of Dr. Eduardo Caro Acevedo's clinical trials under [REDACTED]. The inspection was done secondary to a May - July 1997 inspection performed by Ms. Daryl A. DeWoskin and Ms. Maridalia Torres, FDA San Juan District, of Dr. Eduardo Caro Acevedo's (Dr. Caro) clinical study site.

Two clinical trials were performed by Dr. Caro and his subinvestigator, Maxuel Genao Encarnación, M.D. (Dr. Genao):

1. [REDACTED]
[REDACTED]
[REDACTED]
- and
2. [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

According to the May - July 1997 inspection performed by Ms. DeWoskin and Ms. Torres at the clinical study site, both studies were done at Dr. Caro's private office located at Calle Marginal 51 - #57, Bayamón, Puerto Rico, and at the Municipio De Bayamón Centro De Diagnostico y Tratamiento (Bayamón CDT). The majority of the research activities occurred at the Bayamón CDT, a public outpatient city clinic providing free health care to economically disadvantaged patients. Based on the statements of Dr. Miguel Rodriguez Reyes, Medical Director of the Department of Health of the Municipality of Bayamón, there has not been any authorization for investigational studies to be performed in the Bayamón CDT.

The agency has reviewed the documents and records in Ms. DeWoskin's and Ms. Torres' written report of the clinical trial site and the documents and records

relating to the IRB's responsibilities for the protection of human subjects of research contained in Ms. Kelahan's inspection report. The available documentation shows that EIRB has failed to adhere to pertinent federal regulations as contained in 21 CFR Sections 56. The agency's findings represent significant violations of the Federal Food, Drug, and Cosmetic Act.

SUMMARY OF EIRB MEMBERSHIP VIOLATIONS [21 CFR 56.107(a)]:

1. EIRB has failed to maintain a membership that is sensitive to community attitudes and is able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice.

Dr. Caro submitted for EIRB review, through [REDACTED] (the study monitor), a "Pattern Letter" (described in item 3 below), curricula vitae for himself and Dr. Genao, a copy of the informed consent document, and an advertisement for the recruitment of subjects. Dr. Caro's CV lists his current position as the Medical Director of the Out Patient Department at Bayamón CDT; Dr. Genao's CV lists his position as physician in the Out Patient Department. The advertisement gives a telephone number for Dr. Caro where he can be reached Monday - Friday, 8 AM - 4 PM, which is the number of the Out Patient Department at Bayamón CDT.

EIRB did not have a member or advisor with knowledge of the local conditions who, upon review of the information submitted, may have been able to discern Drs. Caro's and Genao's connection with Bayamón CDT and would also be familiar with the nature of Bayamón CDT's medical service to the community and its policy on clinical research studies.

SUMMARY OF IRB FUNCTIONS AND OPERATIONS VIOLATIONS [21 CFR 56.108(a)(1)]:

2. EIRB has failed to follow its written procedures for initial and continuing review which allows EIRB to use an advisor that would ensure that Essex IRB is aware of the local conditions and standards in the community in which the clinical studies are performed. This provision for determining local conditions and standards was not used during the review of Dr. Caro's submission.

SUMMARY OF CRITERIA FOR IRB APPROVAL OF RESEARCH VIOLATIONS [21 CFR 56.111(a)(3) and (b)]:

3. EIRB has failed to take into account the settings in which the research will be conducted. The written procedures do not require the investigator to state where the study will be conducted, if there are any restrictions on research at the site, and if any other institutional review board has jurisdiction.

We note that Essex IRB requires the submission of a "Pattern Letter" which is to be printed on the Clinical Investigator's letterhead and signed by the clinical investigator. The "Pattern Letter" states in part:

. . .Our office is appropriately equipped to handle adverse reactions should they occur. Further, the closest hospital, (name of hospital), is located (distance) from our office should extended treatment be needed.

To our knowledge there is no community attitude that could impact on the manner in which the study will be conducted. Selection of subjects for this study will be equitable.

As noted in item 1, Dr. Caro submitted the "Pattern Letter" with the above statement.

This letter presumes that the study will be done in the clinical investigator's office and does not request information on the actual study site(s). None of the other information submitted by Dr. Caro through the study monitor for EIRB review identified the site(s). We also note that other standard forms and letters used by EIRB refer to the clinical site without requesting or specifying the specific site.

It is clear from documents in Ms. DeWoskin's and Ms. Torres' report that [REDACTED] (study sponsor), [REDACTED] (study monitor) and [REDACTED] (study drug supplier) were aware that the clinical trials would be conducted at Dr. Caro's private office and at the Bayamón CDT. As the study monitor forwarded all documentation for the study sites to EIRB for review, it is unclear why specific site information was never requested or supplied.

4. EIRB has failed to assure that selection of subjects is equitable in that two vulnerable populations, economically disadvantaged subjects (adults and children) and pediatric subjects, were used as research subjects. The patients who attend Bayamón CDT are assigned to the clinic for their medical care based upon their residence and must see the physician on duty when they visit the clinic. They do not have the option of obtaining their medical care elsewhere.

5. EIRB failed to include additional safeguards to prevent coercion or undue influence on the vulnerable populations. As noted above, subjects do not have the option of changing their medical care provider. Many of the subjects interviewed by Ms. DeWoskin stated they received preferential treatment at the clinic and were placed ahead of other patients already waiting at the clinic as a result of their participation in the trial.

The above cited violations may not be all inclusive of the deficiencies in your IRB operation.

Page 4 - William C. Waggoner, Ph.D., FAACT

We have no assurance that your procedures are adequately protecting the rights and welfare of human subjects of research. For this reason, no new studies subject to Parts 50 and 56 of the FDA regulations should be approved by your IRB until this office has assurance that adequate corrections have been made. This restriction does not apply to the emergency use of an investigational material when the conditions described in section 56.102(d) exist and the procedures followed by your institution meet or exceed the requirements described in section 56.104(c). Neither does this restriction relieve the IRB from receiving and reacting to proposed amendments, reports of unexpected and serious reactions and routine progress reports from ongoing studies.

Please inform this office, in writing, within fifteen (15) working days from the date of receipt of this letter, of the corrective actions you have taken or plan to take to bring your IRB into compliance with FDA's regulations.

If you have any questions, please contact Ms. Mary-Jo Zollo at (301) 594-1026. Your response should be addressed to the following:

Mary-Jo Zollo, Acting Team Leader
Human Subject Protection Team, HFD-343
Division of Scientific Investigations
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

Sincerely yours,

A handwritten signature in dark ink, appearing to read "David A. Lepay" followed by a stylized flourish or initials.

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research