DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

CERTIFIED MAIL – RESTRICTED DELIVERY
RETURN RECEIPT REQUESTED

Ref: 00-HFD-45-0912

SEP 27 2000

Jeffrey R. Levenson, M.D.
The Research Consortium, Inc.
9303 Seminole Boulevard, Suite D
Seminole, Florida 33772

Dear Dr. Levenson:

Between February 7 and March 1, 2000, Ms. Karen G. Hirshfield and Dr. Mathew T. Thomas, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol [ ] of the investigational drug Zyvox (linezolid), performed for Pharmacia and Upjohn Company. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report, the documents submitted with that report, and your written response dated April 6, 2000, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices. We note that at the conclusion of the inspection, Ms. Hirshfield presented and discussed with you the items listed on Form FDA 483, Inspectional Observations.

Your written responses to items 1.b.i, 1.b.v, 1.d, 1.e.ii, 1.e.iv, 1.e.v, 2.c, 2.d, 2.i, 2.j, and 5 (for subject #5410347), have been evaluated and accepted. However, your responses to the remaining items listed on the Form FDA 483 are unacceptable. Please note that the matters complained of in this letter follow a different numbering system from that used in the Form FDA 483.

We wish to emphasize the following:

I. FAILURE TO PERSONALLY CONDUCT AND SUPERVISE THE CLINICAL INVESTIGATION IN VIOLATION OF 21 CFR 312.60.

You failed to personally conduct and supervise the clinical investigation as you agreed to by signing the investigator statement (Form FDA 1572). Deviations noted in this study resulted from a serious lack of supervision of personnel involved in assisting you with the conduct of this study. You should recognize that although authority may be delegated, it is the principal investigator who is ultimately responsible for the conduct of a study.

II. SUMMARY OF PROTOCOL VIOLATIONS (21 CFR 312.60)

Our inspection revealed several significant deviations from the protocol.

A. You enrolled three subjects who did not qualify for inclusion in the study based on the amount of [ ] in their urine culture (protocol inclusion criteria, section 6.1.3). For example:

1. Subjects #5410201 and #5410345 had urine [ ] cultures [ ] and therefore did not qualify for inclusion even if they were symptomatic.

2. The sponsor's Clinical Project Manager provided written instruction to you on 4/26/99 amending the inclusion criteria and allowing the enrollment of subjects who had a urine [ ] culture of [ ] if they were symptomatic. On 5/8/99, you enrolled an asymptomatic subject #5410348 who had a [ ] culture of [ ] Your response to this observation in the Form FDA 483 does not provide any documentation to support your statement that this subject was symptomatic at the time of study enrollment.

B. You enrolled subject #5410356 in violation of the protocol inclusion criteria (section 6.1.4) that "Patients must be willing and able to complete all study-related activities and the follow-up visit(s)." On the day of enrollment (9/22/99 at 4:40 PM) a psychiatrist deemed this subject was mentally ill "angry, agitated, depressed" and "refusing needed care." Therefore, at 5:45 PM on 9/22/99 it was decided to continue treatment for this patient under the provisions of the "Baker Act." In your response you state that you examined this subject on the morning of the day of enrollment and found the subject alert and oriented. You also state that your study coordinator, a RN, examined that subject the same evening and found the subject alert and oriented to obtain informed consent. We do not wish to question your judgment regarding the mental status of this subject. However, because this patient was being medically treated under the provisions of the Baker Act, the patient should not have been enrolled as a subject in a research study that prohibited the enrollment of subjects who would not be able to voluntarily complete all study-related activities and follow-up visits.

C. Two subjects were administered, "Greater than [ ] hours of a potentially effective antibiotic in the last [ ] days prior to study entry or since the last positive blood culture," in violation of protocol (section 6.2.10).

1. Subject #5410202 had a blood culture on 02/10/99 that was positive for Enterococcus faecalis sensitive to amoxicillin. This subject was administered study drug from 2100 hours on 2/12/99 although the subject was being treated with amoxicillin every 6 hours from 2400 hours on 2/10/99 until 0600 hours on 2/13/99.

2. Subject #5410203 had a urine culture on 3/10/99 that was positive for Enterococcus faecium (sensitivity to antibiotics was not done). This subject was administered study drug from 03/13/99 although the subject was being treated with cefotaxime every 8 hours from 2300 hours on 3/10/99 until 0600 hours on 3/12/99.

D. The following laboratory samples were not collected as specified by the protocol (section 8.2.2. and appendix A):

1. End of treatment samples for subjects #5410121 (chemistry, hematology and urine culture), #5410122 (chemistry and hematology), #5410123 (chemistry, hematology &[ ] sputum culture), and #5410206 (chemistry, hematology & urine culture).

2. Long term follow-up urine culture for subject #5410201

E. You failed to submit to the sponsor detailed reports of serious adverse events (SAE) within 5 working days of the event, as required by protocol (section 8.3.6), for the following subjects:

Subject	SAE	Date of Event	Report Signed
#5410206*	Multi-system Organ failure/Death	3/5/99	5/4/99
#5410223	Cerebrovascular accident	6/15/99	7/17/99
#5410345	Deep Vein Thrombosis	4/13/99	6/18/99
#5410354	Acute Respiratory Failure & Death	9/7/99	10/12/99
#5410356	Respiratory Failure & Death	10/2/99	11/12/99

* On 3/31/99 you reported to your IRB that subject #5410206 died on 3/1/99.

III. SUMMARY OF VIOLATIONS RELATED TO FAILURE TO REPORT ADVERSE EVENTS (21 CFR 312.64(a) and (b))

You did not report on the case report form the adverse events experienced, prior to the follow-up visit on 5/5/99, by subject #5410221 (e.g., anxiety on 4/22/99, tachypnea on 4/21/99 and 4/22/99, and respiratory distress on 4/22/99).

IV. SUMMARY OF VIOLATIONS RELATED TO REQUIREMENTS FOR INVESTIGATOR REPORTING TO IRB (21 CFR 312.66)

You did not promptly report to the institutional review board (IRB) changes in the research activity and unanticipated problems involving risks to human subjects or others, and made changes in the research without IRB approval. For example:

A. You did not obtain IRB approval for continuing study-related activities at neighboring hospitals or nursing homes (secondary institutions) to which subjects were transferred after their enrollment at the [ ] or the [ ] General Hospital [ ] We note that you did not seek IRB approval for continuing research at secondary institutions even after the [ ] IRB specifically informed you that they could not continue to serve as the IRB for a second institution. Instead you incorrectly informed the IRB that the secondary institutions were only providing "incidental care" and were not research sites, when in fact you were conducting research on subjects and collecting data at these secondary institutions.

You also did not inform the [ ] IRB about the transfer of subjects #5410223, #5410357 and #5410358 to secondary institutions during their study participation. Although your response states that subject #5410223 was not seen in a nursing home, we note that research data were collected from this subject at that nursing home. You have not provided documentation to support your statement that you subsequently notified your IRB about the transfer of subjects #5410357 and #5410358.

B. You did not submit the following SAE reports to the [ ] IRB within two weeks of the event, as required by the IRB:

Subject	SAE	Event Date	Report Signed
#5410121	Hyperkalemia & Hypotension	2/24/99	3/31/99
#5410121	Respiratory Failure & Death	3/1/99	3/31/99
#5410122	Renal Failure & Death	3/10/99	3/31/99
#5410205	Respiratory Failure & Death	3/4/99	3/31/99
#5410206*	Death (cause unknown)	3/1/99	3/31/99
#5410222	Multisystem Organ Failure & Death	5/30/99	6/30/99

* On 5/4/99 you reported to the sponsor that subject #5410206 died on 3/5/99.

V. SUMMARY OF VIOLATIONS RELATED TO INFORMED CONSENT PROCESS (21 CFR 50.20, 50.25(a)(1), AND 50.27)

A. You did not obtain legally effective informed consent for the following subjects:

1. Consent for study subjects #5410223 and #5410354 was not obtained from the subjects themselves or from individuals who were identified in the medical records as legally authorized representatives (LARs).

2. Study treatment was initiated for two subjects after obtaining verbal consent from LARs.

   a. Subject #5410207 was enrolled and treated on 3/5/99 after obtaining verbal consent from the subject's legal guardian, and the legal guardian's written consent was obtained only on 3/8/99.

   b. Subject #5410350 was enrolled and treated on 5/29/99 after obtaining verbal consent from the subject's brother. You also did not ensure that the subject's brother dated his signature to indicate when he provided written consent for the subject's study participation.

3. You did not ensure that the witness dated the signature while attesting that subject #5410203 provided informed consent by placing an "X" mark in place of the subject's full signature.

4. You did not ensure that subjects or their LARs (for subjects #5410121, #5410122, #5410201, and #5410205) dated their signature on the consent form. Your study coordinator recorded the date of signature on the consent form for subjects #5410121, #5410122, and #5410205.

5. You also did not ensure that subject #5410356 dated the signature on the consent form. Furthermore, the signature of this subject who was enrolled at [ ]was placed on a consent form page that contained erroneous information; the telephone number for obtaining answers to questions about a research subject's rights was that of the IRB Chairman at another study site [ ]

B. Research related data were collected from subject #5410223 after the subject's legally authorized representative withdrew consent for the subject's study participation. Your response states, "Consent was withdrawn after labs had been completed, but prior to being reviewed." This statement is incorrect because our inspection revealed that this subject's family withdrew consent on 6/15/99, while the follow-up laboratory data were collected on 6/16/99, and 7/8/99.

C. The consent form did not explain to study subjects that their research participation would continue, and that their data would be collected, in secondary institutions to which they were transferred during the study period.

We also wish to emphasize that, in your April 6, 2000, response to item 1.a. on the Form FDA 483, you inaccurately state that you enrolled ten other "seriously ill subjects who did survive." Data collected during the FDA inspection revealed that four of the cited subjects died (#5410121 in 31 days, #5410122 in 35 days, #5410123 in 42 days, #5410205 in 16 days), and one subject (#5410350) was lost to follow-up. In total, eleven of the twenty-seven subjects enrolled at your site died within 42 days of enrollment, potentially confounding the interpretation of safety data for this investigational drug because of the enrollment of several critically ill subjects.

Because of the departures from FDA regulations discussed above, please inform this office, in writing, within 15 working days of your receipt of this letter, of the actions you have taken or plan to take to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in further regulatory action without further notice.

Your written response and any pertinent documentation should be addressed to:

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Sincerely yours,

Stan W. Woollen

Stan W. Woollen
Acting Director
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