



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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May 27, 2009

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Myron Rosenthal, PhD
Vice Provost for Human Subject Research
University of Miami
1500 N.W. 12th Avenue JMT East
Suite 1002
Miami, FL 33136

RE: Human Research Protections under Federalwide Assurances FWA-176, FWA-2247, FWA-9025

Research Project: Trial to Assess Chelation Therapy (TACT) (IND #66,743)
Principal Investigator: Gervasio A. Lamas, M.D.
HHS Protocol Number: UOI-HL-092607

Dear Drs. Abraham, Rosenthal, and Oddone:

Thank you for your November 5, 2008 report in a joint response to our August 25, 2008 request that your institutions investigate allegations of noncompliance with Department of Health and

Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46). Also, we acknowledge, per the letter dated January 26, 2009 from University of Miami, that the primary investigator has resigned from the University of Miami and transferred the study back to Mount Sinai Medical Center, and that this study was only conducted at the University of Miami from September 2008 to January 26, 2009. We appreciate your investigations into the matters outlined in our request.

A. Determinations regarding the above-referenced research:

- (1) The complainant alleged that the informed consent documents for this study failed to describe accurately and completely all procedures to be followed and to identify any procedures which are experimental as required by HHS regulations at 45 CFR 46.116(a)(1). In specific, the complainant alleged that the informed consent documents falsely implied that the drug being used in the TACT study is approved for treatment of lead toxicity.

The informed consent documents from the inception of this study in 2003 up to the 5/20/2008 version stated that “The Food and Drug Administration has approved chelation therapy for treatment of lead poisoning; but not as treatment for heart disease. Chelation therapy has been practiced in the community for many years. The present chelation therapy also involves the use of high-dose antioxidant vitamins, minerals, and nutritional supplements taken by mouth.”

In our assessment, the above statement implies that the drug being used in this study is approved for lead toxicity. It does not clarify that the Food and Drug Administration (FDA) approved chelation therapy for lead toxicity involves the use of calcium disodium ethylenediamine tetra acetate (EDTA), while the test article used in the TACT study is a different substance, disodium EDTA. The 2006 investigator’s brochure cautions that the test article should not be confused with calcium disodium EDTA. The ambiguity of this distinction in the informed consent documents might engender unmerited confidence in subjects regarding the safety of the disodium EDTA. Therefore, we determine that the informed consent documents for this study failed to describe accurately and completely all procedures to be followed and to identify any procedures which are experimental as required by HHS regulations at 45 CFR 46.116(a)(1).

Corrective Action: Your response states that “the consent form would benefit by further clarifying that the disodium EDTA is not the FDA approved agent for chelation therapy in lead toxicity and also that the efficacy of this form of EDTA for coronary artery disease (CAD) treatment is being investigated in this study.” Your response also states that the informed consent document has been modified accordingly.

Required Action: In addition to the corrective actions you have already taken, which are appropriate, please provide a copy of the most current institutional review board (IRB)-approved informed consent document, verify that the informed consent documents at all study sites contain this clarification, and provide a plan that specifies the procedures the IRB for each study site will use to ensure that subjects who are currently receiving chelation therapy are informed that FDA approved the use of calcium disodium EDTA chelation therapy for lead toxicity, which is not the test article used in the TACT study.

- (2) The complainant alleged that the informed consent document for this study failed to include a complete description of the reasonably foreseeable risks and discomforts of the research as required by HHS regulations at 45 CFR 46.116 (a)(2). In specific, the complainant alleged that death was not mentioned as a possible adverse event in the list of events that may occur if the test article is infused too quickly.

Based on the information available to us, deaths resulting from chelation therapy are primarily caused by infusing EDTA too quickly. The TACT study recognized this as a reasonably foreseeable risk and sought to build in additional safety measures, including labeling the infusion bags and requiring investigator training on point. However, the informed consent document did not indicate this risk to subjects. We therefore determine that the informed consent document for this study failed to include a complete description of the reasonably foreseeable risks and discomforts of the research as required by HHS regulations at 45 CFR 46.116 (a)(2).

Corrective Action: We note that in response to this allegation, the principal investigator has chosen to modify the informed consent document under Risks and Side Effects to add that “death is a rare complication of EDTA infusions.” We believe that this corrective action appropriately addresses this determination.

- (3) The complainant alleged that there was a failure to ensure that risks to subjects are minimized and that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result as required by HHS regulations at 45 CFR 46.111(a)(1) and (2). In specific, the complainant alleged that:

- (a) The basis in the protocol for the claim that chelation may be a reasonable treatment for coronary artery disease is that the supposition that removing toxic heavy metals from the body will treat coronary artery disease, the “heavy metals” hypothesis. Calcium disodium EDTA, the form of EDTA used for treatment of lead poisoning would be consistent with this hypothesis and less dangerous than the disodium EDTA used as the agent in the TACT study. The use of disodium EDTA in this trial is more consistent with the “decalcification hypothesis” which has been demonstrated to be invalid.

- (b) Biochemical literature has demonstrated that the “heavy metals hypothesis” is implausible and demonstrates that the chelation mixture used in the TACT actually has pro-oxidant effects in vitro.
- (c) The trial was begun in the absence of prior supporting laboratory, animal, or human phase 1 or 2 studies, contrary to the usual requirements for a phase 3 trial.
- (d) Since the mid-1970's court documents and newspapers have reported at least 30 deaths associated with intravenous disodium EDTA.

In regards to allegations (a) through (d), we acknowledge your response that the “purpose of a clinical trial is to integrate all of the evidence and make a finding based on a public health need which will lead to clinical recommendations and a putative change in clinical practice,” as stated in your response. We also acknowledge your statement that you adhered to all regulatory obligations requiring that “...all serious adverse events, including deaths, were reported to the medical monitor, to the DSMB, the FDA and the IRB panels.” The test article used in the TACT study is under an IND issued by the FDA, which may consider the kind of information stated by the complainant in support of this allegation in the determination whether to issue an IND. Given this, our office is deferring the allegations noted above to FDA for appropriate investigation and/or action.

- (e) Several site co-investigators have been disciplined for substandard practices by state medical boards, several have been involved in insurance fraud, and at least three are convicted felons.

We note that your investigation revealed that in fact several of the TACT study investigators have been accused of substandard practices by state medical boards, involved in insurance fraud, and at least three are convicted felons. While concerning, these things do not automatically preclude an investigator from participating in research and do not automatically indicate a failure of risks to subjects to be appropriately minimized. The details and circumstances surrounding these incidents must be considered by the IRB when ascertaining the “acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice” as required by HHS regulations at 45 CFR 46.107(b). Based on the information available to us, we determine that, while true, the alleged facts in themselves do not give rise to a violation of 45 CFR 46.111. Please note the related recommendation at (C), below.

- (4) The complainant alleged that the informed consent document failed to provide subjects with a statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation, as required by

HHS regulations at 45 CFR 46.116(b)(5) and 46.115(a)(7). In specific, the complainant alleged that subjects should have been informed that the primary agent used in the TACT study is no longer FDA approved for any use and has been removed from the market because of safety concerns.

We note that the TACT study is testing disodium EDTA for atherosclerosis in post-myocardial infarction patients and that the use of disodium EDTA in this regard was never an approved indication. However, in 2008 FDA removed disodium EDTA from the FDA's approved list and withdrew of approval of new drug applications for disodium EDTA. We determine that subjects should have been informed of this information as required by HHS regulations at 45 CFR 46.116(b)(5) and 46.115(a)(7) as it may relate to the subject's willingness to continue their participation in this study.

Corrective Action: The UM IRB was informed of the de-listing of disodium EDTA from the FDA's approved list and of the FDA's withdrawal of approval of new drug applications for disodium EDTA submitted or held by three companies.

Required Action: In addition to the appropriate corrective action you have already taken, please modify the informed consent document to clarify that the TACT study is testing disodium EDTA for atherosclerosis in post-myocardial infarction patients and that the use of disodium EDTA in this regard was never an approved indication. Further, please provide a plan that describes whether and how the IRB for each study site plans to inform subjects who are currently enrolled in the TACT study of this clarification and that disodium EDTA is no longer approved for any use and has been removed from the market because of safety concerns.

Additional Required Actions:

- (a) We note that your response indicates the informed consent document for the TACT study was modified to incorporate the corrective actions noted above. Please submit a copy of the current IRB-approved informed consent documents.
- (b) Please ensure that a copy of this letter is sent to all participating study sites.

B. Additional questions and concerns regarding the above-referenced research

(1) [Redacted]

(2) [Redacted]

(3) [Redacted]

C. Recommendation

- (1) HHS regulations at 45 CFR 46.107(b) state that “the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.” We note that, as stated in (A)(3)(e), above, your investigations revealed multiple instances of substandard

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practices, insurance fraud, and felony activity on the part of investigators. We recommend that the IRBs that reviewed this research re-examine the processes for evaluating study investigators to determine they are obtaining sufficient site and investigator information that is adequate to comply with HHS regulations found at 45 CFR 46.107(b)

Please provide us with responses to the above determinations, questions, and concerns by June 30, 2009, including a corrective action plan for each of our determinations. If you identify any noncompliance during your review of the above questions and concerns, please describe any corrective actions that have been and will be taken to address the noncompliance. Feel free to contact me if you would like guidance in developing a corrective action plan.

We appreciate your institutions' continued commitment to the protection of human research subjects.

Sincerely,

Lisa R. Buchanan, MAOM, CIP
Compliance Oversight Coordinator
Division of Compliance Oversight

cc:

Ms. Yvonne Ortiz, IRB Coordinator, Mount Sinai Med Center
Dr. Jose A. Adams, IRB Chairperson, Mount Sinai Medical Center IRB
Dr. Kelly Insignares, Executive Director, University of Miami
Dr. Charles S. Carver, IRB Chairperson, Social and Behavioral Science IRB, University of Miami
Dr. Thomas Sick, IRB Chairperson, University of Miami IRB #1
Dr. Ofelia Alvarez, IRB Chairperson, University of Miami IRB #2
Dr. Dushyantha Jayaweera, IRB Chairperson, University of Miami IRB #3
Ms. Jody F. Power, Executive Director, Duke University Health System IRB
Dr. Joseph M. Farmer, IRB Chairperson, Duke University Health System IRB #1 & #2
Dr. George Parkerson, IRB Chairperson, Duke University Health System IRB #7 & #8
Dr. John Falletta, IRB Chairperson, Duke University Health System IRB #5 & #10
Dr. John Harrelson, IRB Chairperson, Duke University Health System IRB #3 & #4
Dr. Sally P. Green, IRB Chairperson, Sterling Institutional Review Board
Dr. Gervasio A. Lamas, University of Miami
Dr. Margaret Hamburg, Commissioner, Food and Drug Administration
Dr. Joanne Less, Food and Drug Administration
Dr. Thomas Puglisi, Office of Research Oversight, Department of Veterans Affairs
Dr. Sherry Mills, National Institutes of Health
Mr. Joseph Ellis, National Institutes of Health

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Dr. Elizabeth G. Nabel, Director, National Heart, Lung, and Blood Institute
Dr. Robin Boineau, National Heart, Lung, and Blood Institute
Dr. Josephine P. Briggs, Director, National Center for Complementary and Alternative Medicine