



DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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October 30, 2009

William M. Abraham, Ph.D.  
Director, Research  
Mt. Sinai Medical Center  
Department of Research  
4300 Alton Road  
Miami Beach, FL 33140

**RE: Human Research Protections under Federalwide Assurances FWA-176**

**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 Dr. Abraham:

Thank you for your July 31, 2009 report in response to our May 27, 2009 determination letter regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46). We appreciate your investigations into the matters outlined in our request.

In our May 27, 2009 letter we made the following determinations regarding the above-referenced research:

- (1) We determined 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, we determined that the informed consent documents falsely implied that the drug being used in the TACT study is approved for treatment of lead toxicity.
- (2) We determined 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). In specific, we determined 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.

**Corrective Actions:** In addition to the corrective actions described in your November 5, 2008 report, which were appropriate, we have reviewed the revised informed consent document and the proposed “Dear Participant” letter provided with your July 31, 2009 report. We note that the revised informed consent document clarifies that “the use of disodium EDTA as treatment for heart disease or hardening of the arteries in patients that have suffered a heart attack has never been an approved indication for the drug,” and that “...the Food and Drug Administration has not approved chelation therapy as an effective treatment for heart disease.” We also note that that the “Dear Participant” letter that will be provided to subjects who are currently receiving intravenous treatments provides the same clarifications that were included in the revised informed consent document, as well as pointing out that the additional “...information is being provided to you because we want to make sure you understand that the research drug being used, disodium EDTA, is not currently indicated to be used for heart disease.” We also acknowledge that the informed consent continues to state that “...there is no reliable evidence of [chelation therapy’s] effectiveness.”

These corrective actions adequately address the above determinations and are appropriate under Mt. Sinai University’s FWA.

In our May 27, 2009 letter, we asked “whether any of the infusions that took less than three hours were completed infusions and explain why they were completed in less than three hours, and to provide a summary of any unanticipated problems involving risks to subjects revealed by your investigations that have not been reported to our office.” We noted that the TACT protocol specified that infusions should be completed in no less than three hours to allow for safe infusion rates, and we asked you to provide additional clarification regarding the reasons for “shorter-than-recommended” infusions and referenced 35 subjects across 26 study sites where this occurred. In the context of these shorter-than-recommended infusions, we also asked you to provide a summary of any unanticipated problems involving risks to subjects revealed by your investigation that have not been reported to our office. In response to our concern that the October 28, 2008 DSMB report indicated 440 instances (involving 251 subjects) of “Infusions shorter than recommended” across 63 sites, you provided the following summary of the reasons for shorter-than-recommended infusions that occurred during the conduct of the TACT study:

“The reasons for the shorter-than-expected duration of infusions in these 440 subjects were as follows:

- a. Infusion terminated early at subject’s request, [sic](subject has an appointment, etc.): 54

- b. Infusion terminated early due to problems with intravenous access (access lost, IV repositioned, swelling at infusion site etc.[sic]): 128
- c. Technician Error (rate calculation error, transcription error, etc.): 100
- d. Infusion terminated early due to other causes:
  - i. Symptoms of congestive heart failure (shortness of breath, etc.) (consistent with underlying disease): 2
  - ii. Weakness and/or malaise (consistent with underlying disease): 1
  - iii. Symptoms consistent with hypocalcemia (tingling, numbness): 2
  - iv. Miscellaneous causes (unrelated to research and/or consistent with underlying disease)(e.g., rales; dizziness; weight gain; chest pain; low blood pressure; ‘not feeling well’): 10
  - v. Unknown: 143.”

You further explained in your report that your review indicated that, relying upon our January 15, 2007 guidance entitled “Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events,” none of the instances of shorter-than-recommended infusions identified in your review were associated with unanticipated problems involving risks to subjects. Your analysis focused in particular on events referenced in paragraphs (d)(i), (ii), and (iii) above, noting that none of these events were considered unexpected.

At this time, we would like to offer the following additional guidance. As we explained in our January 15, 2007 guidance, an incident does not need to result in actual harm to a subject in order of the incident to be considered an unanticipated problem involving risks to subjects or others (see Appendix B in our guidance). While we agree with your analysis of the particular events referenced in paragraphs (d)(i), (ii), and (iii) above, please note that some subset of the events associated with technician error (paragraph (c) above) or for which the cause was unknown (paragraph (d)(v) above) may have represented unanticipated problems involving risks to subjects. Moreover, the overall pattern of events in which many subjects were receiving shorter-than-recommended infusions and for which corrective actions were taken to prevent such incidents also may have represented an unanticipated problem involving risks to subject.

We acknowledge, per your report, “that the case report forms will be modified to require a detailed report of the reason for any infusion which is shorter than recommended,” and that you are continuing efforts to retrieve data about these occurrences and will follow-up [with] OHRP.”

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Should any information be discovered that previously should have been reported to OHRP, please notify us promptly.

At this time, there should be no need for further involvement by our office in this matter. Please notify us if you identify any new information which might alter this determination.

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

Sincerely,

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

cc:

Mr. Fredrick Hamilton, Chief Compliance Officer, Mount Sinai Medical Center  
Ms. Yvonne Ortiz, IRB Coordinator, Mount Sinai Medical 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  
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

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**Note:** Copies of this letter were also sent to Dr. Eugene Z. Oddone, Vice Dean for Research, School of Medicine, Duke University Health System, Inc. and Dr. Myron Rosenthal, Vice Provost for Human Subject Research, University of Miami.