November 5, 2008

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Dear Dr. Borror:

This is in response to your letter dated August 25, 2008 in which you request from Drs. William Abraham (Mount Sinai Medical Center), Eugene Oddone (Duke University Health System) and me (Myron Rosenthal – University of Miami) responses to allegations regarding the research project titled "Trial to Assess Chelation Therapy (TACT)". This study is funded by the NIH as protocol number U01-HL-092607 with Dr. Gervasio Lamas as principal investigator.

With your guidance (September 4, 2008), the decision was made to submit this letter of response jointly on behalf of the three institutions. In addition, copies of the complete IRB file for the research were requested from each institution. To fulfill this request, each institution has individually compiled its requested materials and these are being forwarded to OHRP separately from the three institutions [*note – this letter is accompanied by three CDs. One CD contains documents labeled as "General Appendix" materials. A second CD contains the "UM Specific Documents" and a third CD contains the "Duke Specific Documents". The documents requested from Mount Sinai Medical Center are being submitted in hard copy. If OHRP wishes the documents within the CDs also to be submitted in hard copy, please advise*].

Four allegations of noncompliance with federal regulations (45 CFR 46) were brought forth regarding the above-referenced study. In subsequent paragraphs, we will respond to each and, where appropriate, present our plans for corrective actions.

ALLEGATION 1 – **"Failure of the informed consent documents for this study 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 complaint alleged that the informed consent documents falsely imply that the drug being used in the TACT study is approved for treatment of lead toxicity"**

Response Overview: The study and the informed consent documents were originally approved by the convened IRB of Mount Sinai Medical Center whose IRB initially approved the study with that institution as the administrative-coordinating center. The study and informed consent documents were subsequently approved by the many other IRBs or ethics panels providing oversight to the research at its multiple sites. These IRB or ethics panels (total 32 with some having responsibility for multiple sites) include Sterling IRB and the IRB's of numerous hospitals and universities including Emory, Johns Hopkins, NYU and the Universities of Kansas, Arkansas and Missouri. A list of approving IRB's is provided within the "GENERAL APPENDIX" of this response as **GENERAL APPENDIX 1.**

Included in the list of approving IRB's is the University of Miami whose IRB reviewed and approved the study on May 20, 2008. This University of Miami review was required since Dr. Lamas transferred his academic appointment and changed the study's administrative/clinical coordinating center from Mount Sinai Medical Center to the University of Miami effective June 1, 2008. A copy of the consent document initially approved by the UM IRB is included as **GENERAL APPENDIX 2.**

Although included within the list of approving IRBs, the Duke University Health System IRB did not review/approve the informed consent since Duke University served as the data coordinating center and was not a site for subject recruitment (note – the Duke IRB approved the institution's role as the statistical coordinating center for this research program).

Prior to the receipt of allegations from OHRP, none of the IRB panels had identified any serious or continuing noncompliance or subject safety concerns that would have required the study be suspended. As appropriate, input into IRB decision-making was provided by the DSMB and other oversight mechanisms. Since the OHRP allegations were in large part directed to the informed consent, however, the Principal Investigator voluntarily agreed that enrollment of participants into this study should cease until the matters brought forth by OHRP are clarified. His request for voluntary cessation of enrollment was approved by the UM Assistant Provost for IRB Affairs (Dr. Stephen Richman) pursuant to UM IRB policy and Dr. Lamas then forwarded this restriction to all sites (see letters in **GENERAL APPENDIX 3**).

As a first step in the process of re-examining the informed consent documents, we (and also Sterling IRB) asked Dr. Lamas to review these documents with the study leadership and others and make recommendations. The specific question asked by Sterling IRB was whether he (Dr. Lamas) is aware of any information in the consent document which is inaccurate or whether there is any risk information that should have been included.

Dr. Lamas responded that he reviewed the documents with colleagues and with the DSMB Chair (Dr. Hodis), the NHLBI Project Officers (Drs. Boineau and Rosenberg) and the NCCAM Project Officer (Dr Nahin) and that the collective opinion was that the consent form is accurate and without a need for any additional risk information. He also

reported that neither he nor others listed above are aware of any information involving subject safety that has not been provided to the IRB (see letters in **GENERAL APPENDIX 4**).

Pursuant to our re-examination of the informed consent documents, we concur with the view expressed above and also with the determinations of the IRB panels which reviewed and approved this study. We find that there was (and continues to be) compliance with federal regulations and with the IRB-related policies of our institutions. However, we are in agreement that at least some of the allegations presented by OHRP suggest that these documents, like most informed consent documents, can be improved and may be made more clear and precise. We address the specific sub-allegations and highlight the improving actions within paragraphs below

SUB-ALLEGATION 1.a -- Does the ICF describe all procedures?

The informed consent document specifically defines that the study includes:

1) Up to 28 months of intravenous infusions and oral treatments
2) 32 additional months of follow-up and additional pills
3) 40 intravenous infusions of a solution of vitamins and dissolved materials
4) a screening visit to complete a medical history and simple physical
5) blood testing for cell counts and kidney and liver functioning
6) questioning about health and emotional well-being, working status, education and income
7) the completion of a "confidential patient information form"
8) questioning at each visit related to heart problems and emotional status
9) blood pressure and simple physical exams at each visit
10) surveying participants to determine whether allergies to any of the compounds are a concern
11) after the infusions are completed, participants will be called every three months until the study is closed to determine their physical status
12) returning every year and at the end of the study for questioning about medical condition and a simple physical exam

Every IRB panel that reviewed and approved this study at our sites and others was convinced that this careful and complete listing of the procedures in the ICF is consistent with the protocol approved by the NIH (NHLBI) and describes all procedures. We concur with these determinations and conclude that the ICF provides a thorough and appropriate disclosure of the study's procedures to participants.

SUB-ALLEGATION 1.b - Does the ICF identify procedures that are experimental?

The informed consent documents approved earlier, and that approved in May (2008) by the UM IRB specifically state that this is a "research study" to test the effectiveness of chelation therapy. These documents clearly explain (and it states twice) that the FDA approved use of chelation therapy is for treatment of lead poisoning and not for treatment of heart disease. These consents also affirm that there is no evidence that chelation therapy or the vitamin supplements will benefit study participants.

In addition, the approved informed consent documents appropriately explain that the study is testing an unapproved use of chelation therapy. It describes that participants will be randomized into either a treatment or placebo group and that participants and investigators will not know to which group a participant is assigned. These latter statements further emphasize the experimental nature of the research program that comprises the TACT study.

Further identifying the experimental nature of this study, the ICF states that participants may or may not receive any medical benefit from participation in this study.

Although an amended informed consent document has recently been submitted which we believe improves upon the earlier document and enhances the clarity of issues raised by OHRP, we have no basis to disagree with determinations of the approving IRB panels that the consent documentation explicitly specifies that the procedures in the study (i.e. chelation therapy supplemented with high doses of vitamins) and the study itself, are experimental and that participants reading this document will be properly informed of the that they are volunteering to participate in an experimental study of experimental procedures.

SUB-ALLEGATION 1.c -- Does the ICF falsely imply that the TACT drug is approved for treatment of lead toxicity?

Although the current ICF clearly states that chelation therapy does not have FDA approval as a treatment for heart disease, the document does define that the FDA has approved chelation therapy for treatment of lead poisoning. Relevant sentences from the ICF are:

a) "the Food and Drug Administration has approved chelation therapy for treatment of lead poisoning, but not as a treatment for heart disease"

b) "EDTA, or ethylenediamine tetraacetate is in the chelation solution. It is approved for use by the FDA as a treatment for lead poisoning but not for coronary artery disease"

With regard to chelation therapy itself, the IRB panels correctly recognized that this therapy (using calcium disodium salt of EDTA) was initially approved by the FDA in 1953 for the treatment of lead poisoning; and, as affirmed in a 2008 FDA Public Advisory, the disodium salt of EDTA (marketed as "Endrate") was, at the time of IRB review, approved by the FDA for use in selected patients with high blood calcium levels (hypercalcemia) and for use in patients with heart rhythm problems due to intoxication with the drug, digitalis. We concur with that recognition and also that chelation therapy does not have FDA approval for the treatment of coronary artery disease.

A second issue raised within this allegation, relating to the specific TACT drug and its FDA approval, is more problematic. Background is that EDTA is available in two salts, disodium EDTA and calcium disodium EDTA. In the RFA released by the NIH (NCCAM and NHLBI) to which the present study became the selected respondent, the statement was made that "for chelation therapy, the most widely used formulation is a protocol recommended by the American College for Advancement in Medicine (ACAM) that includes disodium EDTA and magnesium chloride". Although calcium disodium EDTA is still approved for lead toxicity, the investigators of this study selected to apply for this NIH program with a protocol based on the use of the disodium salt of EDTA. They explained in their grant application and related documents that this choice was made with reference to common practice and clinical evidence which was described in the application to NIH. The use of disodium EDTA was subsequently approved by the NIH Special Emphasis Panel that scored this application highly and that recommended funding for the TACT study; and this decision to use the disodium EDTA was ratified by the Protocol Review Committee composed of NIH scientists and the investigative team. The decision was known to, and approval was given by, the DSMB providing oversight to the study, the FDA which granted an IND and the multiple IRB panels which approved the study and its consent documents.

Improved ICF: Although the wording of the ICF was approved by the DSMB, FDA scientists and multiple IRB panels, our re-review of the consent documents with the principal investigator was in agreement with the suggestion 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. As a result, a revised ICF has been drafted which deletes all mention of lead toxicity. An amendment seeking approval of this revision has been forwarded by the Principal Investigator to the UM IRB. This amendment will not require revision of the listed side effects since those were already included for the disodium salt. If approved, an amended consent document will be forwarded to each IRB approving the study at specific sites for approval to be used by future participants at those sites prior to any lifting of the current voluntary

suspension of participant enrollment. In addition, approval of this amendment will require that the UM IRB determine whether previously consented subjects must be re-consented. A copy of this submitted ICF, in draft form, is enclosed as **GENERAL APPENDIX 5**. If such an amendment is approved by the UM IRB, an approved copy will be provided to OHRP.

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

We interpret this allegation to consist of two sub-allegations for which responses are included in paragraphs below:

SUB-ALLEGATION 2a -- Does the ICF describe reasonable risks and discomforts?

The ICF contains two single-spaced pages under the heading "Risks and Side Effects" which lists known side effects and cautions that "there may be some side effects that we cannot predict."

Among the known side effects defined in the ICF are:

a) allergies or kidney problems (these are defined as occurring "rarely")

b) symptoms of low blood calcium such as tingling, muscle cramps, lightheadedness, severe muscular spasms, heart rhythm problems and low blood pressure (defined as occurring "rarely, with a correctly-administered infusion")

c) flu-like symptoms such as low-grade fevers, sneezing, muscle and joint aches, headaches and watery eyes (defined also as rare and occurring usually with high EDTA doses or too rapid infusion)

d) low blood sugar (defined as possible in diabetics)

e) a "burning-like" sensation at the site of the infusion or through the vein

f) fatigue, dry skin, tingling in hands and feet, skin rash, diarrhea and constipation

g) reduced effectiveness of some medications taken by participants

h) heparin-induced bleeding or blood clots

i) procaine-induced allergy

j) fluid in the lungs, ankle swelling, rapid weight gain and heart failure (this is defined as a risk to participants whose hearts are weak)

k) discomfort at the needle puncture site including bruising, swelling, redness and ("rarely") a serious blood infection

l) beta-carotene-induced increased cancer risk in participants who smoke

The ICF assures participants that they will be informed in a timely manner if new risk information becomes available that may affect willingness to continue participation in the study and it cautions that there may be serious unanticipated side effects that cannot be predicted.

The risk information in this ICF has been reviewed and approved by many IRB panels. From our re-examination of this ICF, we concur with those decisions.

SUB-ALLEGATION 2.b - should death be listed as a possible risk in the ICF?

Although reports of death have appeared in the literature, death is not listed in the current FDA-approved product labeling for disodium EDTA. FDA literature addresses confusion between the two EDTA drugs which require different rates of administration. It is these confusion-based medication errors which may, in some cases, have caused serious adverse reactions or death. The FDA explained (1/16/2008) that 9 deaths associated with edetate disodium were reported between 1971-2007 (2 in 2003, 2 in 2005 and 1 in 2007) and that another two deaths were also reported but the specific EDTA drug was not identified. Subsequently, the FDA warned about medication errors particularly with regard to dispensing the two salts of EDTA.

Despite the known risks and lack of controlled trials demonstrating efficacy, disodium EDTA continues to be used off label for chelation for various conditions, including post-MI.(myocardial infarction). Recognizing the public health impact of the continued off-label use of disodium EDTA, the NIH (NCCAM and NHLBI) published an

RFA in April 2001 for a multi-site, randomized, double-blinded, placebo-controlled trial investigating the efficacy and safety of EDTA chelation therapy in individuals suffering from coronary artery disease (CAD) and subsequently decided to support this study to define the safety and efficacy of disodium EDTA. These agencies and the FDA identified the need for evidence from a controlled trial to define what, if any, efficacy was realized in post-MI patients, and what the risk of harm, including death, is in this population.

The study's consent form was reviewed and re-reviewed by the NIH, the DSMB, the FDA (within the application for an IND) and by the IRB panels. None of these reviews required information about death or the inclusion of death as a risk factor. The Principal Investigator has explained that the TACT leadership originally decided not to include death in the TACT consent form unless so required by the NIH or FDA or DSMB or the approving IRB panels. This view was based on their belief that reported deaths associated with chelation therapy were not applicable to TACT since they involved mostly children (a vulnerable population ineligible for this study) and/or they were mostly reported to be due to confusion between the two EDTA drugs (Versenate and Endrate). With regard to the latter risk, the PI noted that infusion bags used in the TACT study are clearly labeled as TACT study bags approved under an IND and that the EDTA drug is administered by trained personnel.

Nevertheless, our re-review of the consent form with the principal investigator led to the suggestion that there is benefit to clarifying for study participants that death has occurred in association with disodium EDTA infusion. Therefore, the PI has drafted a revised ICF and submitted an amendment seeking IRB approval of this revision which includes death as a "risk and side effect" of the treatment (c.f. **GENERAL APPENDIX 5**). If approved, the amended consent document will be forwarded to each IRB approving the study at specific sites for approval to be used at those sites.

ALLEGATION 3 – "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(1)(1) and (2)."

There are five sub-allegations defined within this section. Responses are provided in the following paragraphs:

SUB- ALLEGATION 3.a – "The basis in the protocol of the claim that chelation may be a reasonable treatment for coronary artery disease presented is that removing toxic heavy metals from the system will treat coronary artery disease. Calcium-sodium EDTA, the form of EDTA used for lead poisoning, would be consistent with that hypothesis and less dangerous

than disodium EDTA, but disodium EDTA is the agent used. The use of disodium EDTA in this trial is more consistent with the "decalcification hypothesis" which has been demonstrated to be invalid."

This and the next two sub-allegations relate to the scientific background and hypothesis of the TACT study. In response, we emphasize that this trial was reviewed and approved by experts at the National Institutes of Health (NCCAM and NHLBI) who believed it addressed an important scientific question. The reviewers found the scientific merit and trial design of the TACT application to be the strongest among those reviewed, as evidenced by the priority score of 180. Since the funding mechanism was a U-01 Cooperative Agreement, NIH Project Officers participated in all TACT decision-making committees (including the Operations Committee and Steering Committee).

The hypothesis of this study was presented by the Principal Investigator in the RFA application and in applications to the various IRB panels which approved this research. Certainly, there is literature supporting this hypothesis and there is literature which does not. 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. If all questions or issues were resolved, there would be no need for a clinical study such as TACT.

SUB-ALLEGATION 3.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"

Quality, hypothesis-driven research is often conducted to resolve mechanistic controversies. In fact, we contend that meritorious research should address such controversies rather than avoid them. Certainly there is literature to support the views expressed in the allegation; but there is literature supporting other views. The fact that some literature demonstrates one viewpoint while other literature demonstrates a conflicting viewpoint was made known to reviewers at the NIH, FDA, DSMB panel and the IRB groups that are providing oversight to this study. The key issue is not whether a reviewer agrees with one viewpoint or another but whether he/she believes the study is worthwhile for funding, for IND approval and for IRB approval. We concur with the approval decisions of each group.

SUB-ALLEGATION 3.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

The process of clinical trials wherein bench-top, laboratory investigations are followed by studies in experimental animals and then by Phase 1 through Phase 4 studies which hopefully lead to new therapy is consistent with the steps needed for regulatory approval of a new molecular entity. However, once a drug is FDA approved, off label use or clinical observations often lead directly to phase III-type studies designed to define safety and efficacy in a controlled trial. In this case as in other similar situations, the study was conceived in good faith by the NIH in response to questions about a therapy that is already in active clinical practice. For example, NCCAM estimated that more than 800,000 visits for chelation therapy were made in the United States in 1997. This estimate supports the view that chelation therapy is not a rarity and it lends credence to those who recognize the need for evidence-based decision-making about chelation therapy. With the drug already in clinical use, there was no identified need for further preclinical or early phase data. Instead, as identified by the NIH, the need was for a controlled trial to define safety and efficacy.

SUB-ALLEGATION 3.d – "Since the mid-'970's, court documents and newspapers have reported at least 30 deaths associated with intravenous disodium EDTA"

This fact, and an improving action, is included within the response to "Allegation 2.b". In addition to that response, we note that the RFA which provided the basis for this study listed side effects of EDTA considered "common" and others that were considered "rare". This list did not include death.

A constant worry in clinical medicine and medical research is the improper use of virtually all medications which brings risk and adverse events that may include death. Of special concern to clinical trials in medicine is that participants are often infirmed and inflicted with the ailments that the trial addresses. An unfortunate consequence is that the death of participants sometimes occurs with cause that may be linked to trial medications or to the illness or both. Such is the case in the TACT study. Over 44,000 infusions have been given to date (approx 22,000 being the disodium EDTA) in this study. Although the study involves a vulnerable population in which deaths at a rate of 2-4% per year are expected due to their medical condition, only one death was considered to be possibly related to the infusion. Whether this participant received the disodium EDTA or placebo is unknown. Nevertheless, all serious adverse events including death were reported to the medical monitor, to the DSMB, the FDA and the IRB panels, all of which recommended no changes in the study protocol. **GENERAL APPENDIX 6** contains reports from the medical monitor.

We concur with the many determinations by the NIH, FDA, DSMB and IRB panels that safeguards to minimize risk, especially death, are adequate in this study. Confusion between EDTA salts is non-existent since only the disodium salt is being administered. Site investigators are adequately trained in the procedures of intravenous

EDTA infusion including dose and infusion rates; and they are experienced in managing the medical issues of participants.

SUB-ALLEGATION 3.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. Most site co-investigators continue to promote chelation while the trial is in progress, even though the intervention has not been shown to be effective"

Since 2003, 185 investigators have participated in the TACT study. When this study was initiated, potential investigators were pre-screened by the principal investigator. This process required investigators to submit a signed copy of their curriculum vitae and a copy of their medical license and to answer questions regarding their professional history. The screening by the study leadership and by the many IRB panels which approved the study did not include criminal or civil background checks which are not standard practice for engagement in research.

The principal investigator has assured the IRB panels that site investigators were (and remain) properly licensed as physicians within their communities and that they underwent rigorous training in the study protocol and in the policies and regulations that govern the conduct of the study.

As a supplement to the information above, we were informed of the following:

a) two TACT site investigators have been charged with misdemeanor offences Study enrollment has been suspended at the site of the former investigator but the site remains active with enrolled subjects; a licensed physician is collaborating at the site as a sub-investigator. The site of the latter investigator has been closed with one patient transferred.

b) four other TACT site investigators have been named in federal civil actions. One of these investigators has retired but the site remains open with another investigator. Another investigator disclosed this matter at the time of the initial application. This site is now closed and no subjects were enrolled. The sites of the other two investigators are closed with zero enrollment.

c) Until this time when notified of the OHRP allegations, neither the Mount Sinai IRB, the Duke University Health system IRB nor the University of Miami IRB received any information indicating that potential or approved TACT investigators had criminal convictions. However, three individuals did disclose criminal convictions to the IRB of record for their sites, which was the Sterling IRB, at the time of their application to participate as site investigators in TACT. All of the conviction-related events occurred prior to

participation in the TACT study. The IRB of record for these sites (Sterling IRB) and the TACT Clinical Coordinating Committee reviewed the investigators' CVs, verified their active medical licenses and examined their answers to questions in the screening forms and considered any additional information obtained from discussions with the TACT principal investigator. In one of these cases, discussions were also conducted with the NIH Project Officer and the TACT Operations Committee. These deliberations led to determinations that these individuals held state medical licenses and were appropriately qualified to serve as TACT site investigators. It should be noted, however, that the site of one investigator was closed for reasons unrelated to the conviction and without participant accrual; the other sites are active with Sterling IRB approval and the investigators hold current medical licenses from their respective states.

Eight of the nine investigators discussed above had subsequent State Board actions pursuant to the above-mentioned matters. Seven additional site investigators are known to have had State Medical Board actions against them. Details include:

a) Five investigators were the subject of State Board actions after they began participating in the TACT study. The sites of three of these investigators have been closed and their patients were transferred to another clinical site for continued follow-up. Another investigator currently holds a valid state medical license and continues as a site investigator in TACT. The fifth investigator is closing his site and the patients will be transferred for follow-up at another clinical site.

b) Two investigators reported State Board actions at the time of their initial screening into the TACT study. One of these sites has been closed (no subjects were enrolled). The other investigator continues as a site investigator with a current, active medical license.

In summary, we are aware of no current site investigator who is without proper licensure or who is debarred from receiving federal funds for research. Therefore, we concur in the belief that no further action regarding the participation of site investigators is required at this time. However, our discussions with the Principal Investigator led to the conclusion that a plan should be implemented that provides for enhanced monitoring of State Board actions. Therefore, the Principal Investigator has developed a plan that requires checking with the State Boards at least bi-annually. Within this plan, all disclosed or undisclosed State Board Actions will be brought to the TACT Operation Committee for review and imposition of corrective actions when deemed necessary. Examples of such corrective actions may include enhanced monitoring, changing the site

or closing the site. The Principal Investigator's corrective action plan will be presented to the UM IRB and implemented per IRB determination as soon as possible. A first draft of this plan is included here as **GENERAL APPENDIX 7.**

We interpret that a key issue in this regard is not the professional licensure of site investigators but rather the perception that there may be a putative predisposition of site investigators favoring chelation therapy. This has been discussed by the UM IRB and likely by many other IRB panels. In response, we believe that it would be difficult, if not impossible, to conduct this study if only investigators unfamiliar with chelation therapy were engaged and if only participants not inclined to this treatment modality could be enrolled. In deliberating upon this issue, we also took note of well-considered views that chelation therapy should be used only under the direct supervision of a qualified health care provider. In light of these issues, therefore, we are unable to define a reasonable means to conduct this study while excluding from involvement those investigators and participants who are experienced in, or inclined toward, chelation therapy.

In discussing this concern with the principal investigator, he referred to the 1995, $15M, NHLBI-sponsored trial ("Mode Selection Trial in sinus Node Dysfunction – MOST) which compared dual chamber ventricular pacing with single chamber pacing. At that time, most physicians utilized dual chamber pacing which they believed was superior and views were expressed that a trial was unnecessary. Yet this trial did occur and physicians whose pre-beliefs and practices were directed to dual chamber pacing became investigators in the study which improved understanding of the physiology of pacing and did not support the superiority of dual chamber pacing.

The Principal Investigator described another analogous situation when the efficacy of percutaneous coronary intervention was tested. He noted that interventional cardiologists who supported and practiced this therapy became investigators in the study which found that the therapy did not benefit patients.

We interpret the commitment of the NIH to create and fund this study and the commitment of the FDA, DSMB and the many IRB panels which approved the study to be based on the assessment that the pre-study beliefs of site investigators should not affect the care of participants or the interpretation of clinical events if the trial is set-up properly and the therapy is blinded. We note that the study is well monitored and that the DSMB and data coordinating center is experienced in clinical trials and aware of the concerns of putative investigator bias. We agree that there is no reason to believe other than that proper safeguards are in place and, therefore, we concur with the decisions of the IRB panels.

ALLEGATION 4 – Failure 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 will be provided to the subject as required by HHS regulations at 45 CFR 46.116(b)(5) and 46.115(a)(7). In specific, it is alleged that subjects should have been informed that the primary agent used in the TACT, is no longer approved for any drug use and have been removed from the market because of safety concerns (See http://edocket.access.gpo.gov/2008/pdf/E8-13273.pdf)."

We interpret this allegation to consist of three sub-allegations for which responses are provided in the following paragraphs.

SUB-ALLEGATION 4.a – "Failure to provide subjects with a statement that significant new findings developed during the course of the research which may relate to the subjects' willingness to continue participation will be provide to the subject"

The consent form contains the following statement which we believe adequately addresses the concern in this sub-allegation:

> "You will be informed in a timely manner if new information becomes available that may affect your willingness to continue participation in this study"

SUB-ALLEGATION 4.b– "Subjects should have been informed that the primary agent used in the TACT, is no longer approved for any drug use and have (sic) been removed from the market because of safety concerns"

The primary agent used in TACT, disodium ETDA, remains FDA approved and available on the US market. Notwithstanding safety concerns for this drug (as for many approved drugs on the market), the primary agent used in the TACT continues to hold an IND which has not been withdrawn by the FDA and the drug (disodium EDTA) not only has not been removed from the market but it remains available for purchase. In fact, it is because this drug is so available and so often used that we believe the NIH has created and funded this randomized trial to support or refute its use.

With regard to safety concerns, the FDA issued a Public Health Advisory on January 16, 2008 which warned that children and adults have died when they were mistakenly given disodium EDTA instead of calcium disodium EDTA or when disodium EDTA was used for therapies or other uses that are not approved by the FDA. Although the FDA did not remove the drug from the market, it did state that it was reviewing the benefit/risk profile of disodium EDTA to determine if the benefits for its intended use continue to outweigh the serious risks.

The Principal Investigator of the TACT study has explained that he and all involved in study leadership were aware of this FDA concern and that he inquired to the FDA if there were any changes that were being proposed for the TACT trial based on the FDA's knowledge and advisory. The FDA responded that no changes were necessary to the IND at that time. Nevertheless, the investigators developed a fact sheet for TACT sites to be aware of ongoing FDA concerns.

SUB-ALLEGATION 4.c– "Subjects should have been informed that the primary agent used in the TACT ... have (sic) been removed from the market because of safety concerns"

The primary agent of TACT has not been removed from the market. Instead, on a date subsequent to the most recent IRB reviews of this study (June 12, 2008), the FDA announced that it is withdrawing approval of new drug applications (NDAs) for edetate disodium EDTA submitted or held by Hospira Inc, Apotex Inc and Bioniche Pharma. These companies have now removed their EDTA product from the market. The FDA announcement confirmed that this agent was effective for the treatment of hypercalcemia and for the control of ventricular arrhythmias associated with digitalis toxicity but it explained that there have been fatal medication errors and reports of serious adverse reactions associated with this product.

As also for the sub-allegation 4.b (response above), the Principal Investigator of the TACT study has explained that he and all involved in study leadership were aware of this FDA announcement. He noted that the FDA, the site investigators, the DSMB and the IRB panels were aware of the FDA's issues. He explained that the editate disodium EDTA (marketed as Endrate sodium) is supplied to the TACT study only by Akzo Nobel under the trade name Dissolvine NA2-P. Although to our knowledge, Akzo Nobel does not otherwise distribute this drug for use in the U.S., the fact of its supply to TACT by Akzo Nobel is defined in the IND documents and therefore this distribution to TACT is allowed under the terms of the on-going IND which permits its use as part of TACT.

The FDA is aware of the IND and the fact that Akzo Nobel supplies the disodium EDTA to the TACT investigators since this is reported annually in the IND documentation. The FDA has not withdrawn or required modifications to the IND. Nevertheless, we agree that the UM IRB should be informed of the de-listing of editate disodium EDTA from the FDA's approved list and of the FDA's withdrawal of approval of new drug applications for editate disodium EDTA submitted or held by three companies, even if these companies are not suppliers to the TACT study. This will be done prior to any change in the current status of the TACT study so that, among other matters, the IRB may consider whether the consent form makes clear that the TACT study is testing disodium EDTA for atherosclerosis in post-MI patients and that the use of disodium EDTA in this regard was never an approved indication.

SUMMARY:

Despite the fact that chelation therapy is currently being used for the treatment of cardiovascular disease, until TACT there have been no definitive scientific studies to determine whether this treatment is safe and effective. It was to make this determination that the NIH (NCCAM and NHLBI) requested proposals for a placebo-controlled, double-blind study involving participants age 50 years and older who have had a heart attack, With an expected total enrollment of approximately 2,000 subjects representative of the U.S. population, the study was conceived to provide a definitive answer to whether chelation therapy offers benefit to patients with coronary artery disease.

It was in response to this NIH request that the TACT study was conceived, peer reviewed and awarded financial support. We believe that the review and oversight processes that took place at the NIH, FDA and within the DSMB and over 30 IRB panels carefully weighed the important benefits of this study as defined above with the risks when each made the decision(s) to approve the initiation and continuance of this research.

We also believe that the IRB panels understood, with the NIH and the FDA, that the study is important not only to define whether chelation therapy is effective but also to define whether it is ineffective since, in the latter situation, the use of chelation therapy may deter or deprive patients of the benefit of other treatment methods.

The allegations brought to and forwarded by OHRP are well considered and address essential subject safety issues that must be managed pursuant to IRB determinations in compliance with regulations and institutional policies. However, we interpret that the allegations have another (albeit unspoken) underlying basis which centers around the appropriateness of the NIH decision to fund this study and whether the public health benefit of the TACT study is worth the cost in dollars, professional effort and participant risk.

With regard to the NIH decision to initiate this study, this is a matter over which the IRB panels have no control although we believe that the IRB panels share with others in the scientific community the principle that science, by its nature, is often controversial. The fact that controversy exists should not, itself, be a determinant of a study's merit. Rather, we believe in the shared responsibility for determining scientific merit by peer review and hope that the peer review system, exemplified by the NIH, is never supplanted by a funding system based on popularity or public pressure.

With the above in mind, we note that IRB panels are authorized and should be encouraged to seek consultative support or other relevant information whenever such is deemed useful to good decision-making. In this case, the IRB panels were aware that the TACT study had undergone rigorous peer review at the NIH and that scientists and administrators at the NIH and FDA had considered the benefits of the study to be worth supporting and worth the manageable risks to participants.

Corrective and Improving Actions: With regard to IRB determinations, our re-examination confirms the determinations of multiple IRB panels that appropriate subject safety controls have been in place. Nevertheless and as always, we should continue to seek to improve these controls and to improve the management of this study from the regulatory and IRB view. Together with the principal investigator, therefore, an amended ICF has been submitted to the UM IRB for review. If approved by the UM IRB, the amended ICF will be forwarded to the other approving IRB panels for their review and approval. Once approved, this shall be the ICF for the study. In addition, a plan is proposed to ensure timely assessment of any state board actions relative to site investigators. This plan also will be brought to the UM IRB for approval. Following these putative determinations/approvals, we believe that from a regulatory standpoint, we shall have no reason to do other than permit the principal investigator to lift his voluntary suspension of enrollment into TACT and to permit the study to continue contingent upon IRB determinations.

We hope that this response and prompt actions emphasize the commitment of our institutions to the protection of human subjects in research. If OHRP has any suggestions or needs further information regarding this matter, please advise.

Yours sincerely,

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cc: Commissioner, FDA