DEPARTMENT OF HEALTH & HUMAN SERVICES

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June 27, 2002

Thomas Q. Morris, M.D
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722 West 168th Street
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RE: Human Research Protections Under Multiple Project Assurance (MPA) M-1541

Research Project: Use of Noninvasive Techniques in Sickle Cell Disease
Principle Investigator: Darryl DeVivo, M.D.
CU Protocol Number: 5725

Research Project: Energy Homeostasis in Human Obesity
Principle Investigator: Rudolph Leibel, M.D.
CU Protocol Number: 8028

Research Project: Quantification of Regional Ventricular Wall Motion Using Magnetic Resonance Tagging
Principle Investigator: Beth Printz, M.D.
CU Protocol Number: 7789

Research Project: An International, Multicenter, Double-Blind, Randomized, Parallel, Placebo-controlled Comparison of the Safety and Efficacy of Chronic Subcutaneous UT-15 Plus Conventional Therapy to Conventional Therapy in Patients with Pulmonary Hypertension
Principle Investigator: Robin Barst, M.D.
CU Protocol Number: 8542

Research Project: Evaluation of Prostacyclin in Patients with Pulmonary Hypertension
Principle Investigator: Robin Barst, M.D.
CU Protocol Number: 6154

Research Project: Evaluation of Long Term Prostacyclin in Patients with Idiopathic

Pulmonary Hypertension
Principle Investigator: Robin Barst, M.D.
NYCDOH Protocol Number: 6166

Dear Dr. Morris:

The Office for Human Research Protections (OHRP) has reviewed your June 4, 2002 report regarding the above-referenced research conducted at Columbia University (CU) that was submitted in response to OHRP's April 25, 2002 letter.

Based on its review, OHRP makes the following determinations:

(1) Continuing Institutional Review Board (IRB) review of research must be substantive and meaningful. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

In its April 25, 2002 letter, OHRP expressed concerned that continuing review of research by the CU IRB may not be substantive and meaningful. In particular, OHRP found no evidence of discussion of individual protocols for continuing review in the minutes of the IRB meetings. The minutes usually stated the following: "Dr. Kornfeld then asked for any comments or questions on the protocols that were presented for renewal. There were no comments or questions on any of the protocols, and it was agreed that none of the protocols required more than annual review. A motion was made to approve each protocol for an additional 12 months. The motion was passed unanimously; 13 in favor, 0 opposed." This appeared to represent block discussion and voting for all protocols undergoing continuing review.

Corrective Action: OHRP acknowledges that the CU IRB has developed a new continuing review report form, assigns continuing reviews to primary reviewers with appropriate expertise in the area being studied, distributes all materials for continuing review to all IRB members prior to the meeting, and the primary reviewer leads the discussion at the convened meeting where individual votes are taken and recorded.
In addition, OHRP acknowledges numerous general improvements that the CU IRB has undergone, including a sectional scientific review to assist the CU IRBs with identifying the scientific issues and assist investigators with study design prior to submission to the IRB, plans to increase the IRB from the present two boards to a total of three boards, the development of a new manual and orientation program for all new members, and new office and conference space for the IRB. OHRP finds that these corrective actions appear to adequately address the above finding and are appropriate under the CU MPA.

(2) Department of Health and Human Services (HHS) regulations at 45 CFR 46.109(e) require

that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. The regulations make no provision for any grace period extending the conduct of the research beyond the expiration date of IRB approval.

OHRP finds numerous instances in which the IRB failed to conduct continuing review of research at least once per year.

If the IRB does not re-approve the research by the specified expiration date, subject accrual should be suspended pending re-approval of the research by the IRB. Enrollment of new subjects cannot ordinarily occur after the expiration of IRB approval. Continuation of research interventions or interactions in already enrolled subjects should only continue when the IRB finds that it is in the best interests of individual subjects to do so. OHRP and IRBs must address on a case-by-case basis those rare instances where failure to enroll would seriously jeopardize the safety or well-being of an individual **prospective** subject.

Corrective Action: OHRP acknowledges that a new tracking system has been developed to closely monitor renewal periods to ensure timely review, a full-time monitor/auditor has been hired to audit studies to address and report these issues, it has been made clear to all investigators that extensions are not allowed, renewal notices are sent out beginning approximately two months prior to the study expiration, every letter from the CU IRB office includes a bolded reminder of the expiration date, study terminations are sent when there is a failure to renew in a timely manner, and a new assessment of the approval periods is made at continuing review. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the CU MPA.

(3) OHRP finds that the informed consent documents reviewed and approved by the IRB for the above-referenced studies failed to adequately address the following elements required by HHS regulations at 45 CFR 46.116(a):

(a) Section 46.116(a)(1):

(i) An explanation of the purposes of the research. For protocol #6154, the Sponsor's Protocol stated "[t]he purpose of this study is to determine if the administration of epoprostenol will allow an assessment of the degree of pulmonary vasoreactivity in PPH [primary pulmonary hypertension] patients as an important prerequisite to design of an individualized therapeutic regimen." The informed consent document stated "[t]he purpose of this study is to determine whether a substance called prostacyclin can be used to decrease abnormal high blood pressure...in the blood vessel that goes from the heart to the lungs....*I have been told that knowing whether prostacyclin will dilate this vessel will provide my doctors with useful information for planning my treatment program*." (Emphasis added). The hypothesis the researchers

were supposedly testing was that prostacyclin vessel dilation would be useful in treatment planning, but the usefulness of this dilation was not known at the time the research was proposed. In addition, the statement that the purpose is to determine if prostacyclin can decrease pulmonary hypertension remained in the informed consent document even after the FDA had approved prostacyclin for this indication.

(ii) a description of the procedures to be followed, and identification of any procedures which are experimental.

– A publication of the research conducted under protocol #5725 (Sano, M, et. al, "Neuropsychological Consequences of Sickle Cell Disease" Neuropsychiatry, Neuropsychology, and Behavioral Neurology; Vol. 9, No. 4, pp. 242-247, 1996) stated that a complete blood count was performed at the time of evaluation and that regional cerebral blood flow studies were performed. These procedures were not described in the IRB-approved protocol or the informed consent document for protocol #5725.

– For protocol #8028, a July 10, 1997 letter from Dr. Michael Rosenbaum to Dr. Donald Kornfeld (IRB chair) stated that DNA would be obtained from all subjects for future genetic testing. This was not described in the informed consent document.

– For protocol #8028, the protocol outlined that, while hospitalized, each subject would be prescribed physical activity that mimics the individual's usual physical activity. This was to be determined prior to admission by requiring the subject to complete a physical activity diary and wear an ergometer and accelerometer on at least 2 separate occasions. The protocol also discussed genetic testing of blood samples obtained. The protocol also stated "[I]n the case of subjects enrolling from locations outside the NY metropolitan area, close scrutiny of medical records and discussions with their physicians will be used in place of examination in our outpatient department." These procedures are not described in the IRB-approved informed consent document.

– Protocol #8542 stated that subjects may remain hospitalized until the investigator is confident that the subject can safely manage the administration of study drug and the delivery system. This was not described in the IRB-approved informed consent document.

– The IRB-approved informed consent for the "observational study" of

protocol #6166 (after the approval of prostacyclin by the FDA) did not make it clear what procedures were done for research and what procedures were done for clinical care.

– In January of 1999, the investigator for protocol #7789 developed an assent form at the request of NCRR. The form stated that, for the study, the subject would stay in the MRI machine for an additional 15 minutes. The informed consent form for adults and the parental permission form stated that the subject would stay in the MRI machine for an additional 20 minutes.

– There appears to have been a discrepancy as to whether or not sedation would be used for children in protocol #7789. A December 23, 1997 letter from the principal investigator to the CU IRB chair stated "[a]s in our previously approved protocol, we will be studying patients without sedation." However, the protocol stated "[t]hose patients who are below the age of 8 years will be sedated in accordance with standard protocol."

(b) Section 46.116(a)(2): A description of any reasonably foreseeable risks or discomforts to the subject.

(i) For protocol #5725 the IRB-approved protocol stated "there are only minimal risks associated with the neuropsychological evaluation, risk factor analysis questionnaire, or chart review." However, the IRB-approved informed consent document stated "there are no risks involved in this study." OHRP found no mention of discomforts or potential confidentiality violations, which could be reasonably foreseeable risks for this research, in the IRB-approved informed consent document.

(ii) For protocol #8028 the risk of edema of the extremities was described in the IRB-approved protocol but not described in the IRB-approved informed consent document.

(iii) For protocol #8542 several risks were noted in the Sponsor's Protocol but were not described in the IRB-approved informed consent document, including fainting, abdominal cramping, dyspnea, fatigue, hypoxia, premature ventricular contractions, pulmonary hypertension, restlessness, sweating, warmness, catheter colonization, catheter dislodgement, and infection at the infusion site.

(iv) On June 2, 1998, a reviewer for protocol #8542 stated that study risks should include risks related to exercise (six-minute walk) and risks related to delaying prostacyclin intravenous therapy to participate in the study. These risks were not described in the IRB-approved informed consent document.

(v) The Primary Review Committee requested that the informed consent document for protocol #8542 state that the subject's condition may become worse while on the study drug and that the placebo group is expected to worsen. These risks were not described in the IRB-approved informed consent document.

(vi) The IRB-approved informed consent document for protocol #6154 did not describe the risks associated with abrupt termination of chronic prostacyclin infusion, such as death.

(vii) The Sponsor's Protocol for protocol #6166 listed numerous side effects of prostacyclin that were not described in the IRB-approved informed consent document, including abdominal pain, anorexia, back pain, cardiovascular collapse, chest pain, diarrhea, disorientation, fatigue, flushing, inability to move, lightheadedness, loss of consciousness, seizure, shortness of breath, warm extremities, weakness and weight loss.

(viii) Several serious adverse events (including death) occurred in protocol #6166 when prostacyclin was inadvertently withdrawn or reduced in dose. These risks were not added to the IRB-approved informed consent document.

(c) Section 46.116(a)(3): A description of any benefits to the subject or others that may *reasonably* be expected from the research.

(i) The minutes for the October 28, 1998 IRB meeting stated that the informed consent document for protocol #8542 should include a statement that the previous study of this drug was inconclusive regarding the possible benefit of the treatment. This was not included in the IRB-approved informed consent document.

(ii) Protocol # 6166 stated "[n]o additional study procedures will be performed for these patients....the benefit to the patients enrolled in this study is further assessment of the long-term effects of chronic intravenous prostacyclin in patients with primary pulmonary hypertension." It is not clear how the investigators could perform "further assessment" without doing "additional study procedures." Given that no additional study procedures were performed, it would be difficult to support a claim of direct benefit to the individual participants.

(d) Section 46.116(a)(4): A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. The IRB-

approved informed consent documents for protocols #6154 and #6166 did not disclose that prostacyclin was available outside of the trial after the date that FDA approved prostacyclin.

(e) Section 46.116(a)(8): A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. The IRB-approved informed consent documents for protocols #5725, #8028, and #7789 stated "your participation in this study is completely voluntary. You can refuse to participate or withdraw from the study at any time, and such a decision will not affect your medical care at Columbia-Presbyterian Medical Center...." This language was also in the "Sample format for the consent forms." OHRP notes that there can be penalties or loss of benefits other than an effect on the subject's "medical care at Columbia-Presbyterian Medical Center."

Corrective Action: OHRP acknowledges that the CU IRB has implemented a number of corrective actions to address this finding, including instructing the CU IRB members and new recruits that the review of the informed consent process is one of the crucial aspects of their duties as IRB members, the development of a new application form to help identify key issues, and a new electronic submission/review/tracking system that is being developed which has a consent builder module. OHRP finds that these corrective actions adequately address the above findings and are appropriate under the CU MPA.

OHRP notes that protocol numbers 8028, 7789, 8542, 5725, and 6166 have been terminated. It is not clear whether or not protocol # 6154 has been terminated. OHRP assumes that if this protocol is ongoing, the IRB has reviewed and approved a revised informed consent document that addresses the above findings.

(4) HHS regulations at 45 CFR 46.116 require that informed consent information be in language understandable to the subject or the subject's legally authorized representative. OHRP finds that the informed consent documents approved by the IRB for the above-referenced studies included complex language that would not be understandable to all subjects or their representatives. The language of the informed consent document was fairly complex, including phrases such as idiosyncratic, apnea, agitation, ingestion, plateau, expenditure, electrodes, circumferences, fuel utilization and cardiac arrhythmias.

Corrective Actions: OHRP acknowledges that CU has required education on human subject protections for all investigators and key personnel which emphasizes the use of lay language, IRB members now use a web glossary of medical terms with lay translations, and the consent builder module will assist in improving the quality of informed consent documents and may be used to assess the grade level of language. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the CU MPA.

(5) HHS regulations at 45 CFR 46.408(a) require that, if children are involved as subjects in research, the IRB determine that adequate provisions are made for soliciting the assent of the children, when in the judgement of the IRB the children are capable of providing assent. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research.

(a) It appears that for protocol #5725 there was no provision for soliciting the assent of child subjects. OHRP can find no evidence that the IRB made the findings necessary to waive the assent requirement. In its April 25, 2002 letter, OHRP expressed concern that assent may not have been waivable under 45 CFR 46.408(a), since all children were over the age of 6 and there is no evidence that any benefit to the children from the research was only available in the context of the research.

(b) It appears that for protocols #8542 and #6154 there was no provision for soliciting the assent of children subjects, although the National Center for Research Resources (NCRR) requested assent forms at an audit. OHRP found no evidence that the IRB found that the capacity of the children was so limited that they could not be consulted or that these studies provided a benefit for subjects that is not available outside of the context of the research.

Corrective Action: OHRP acknowledges that CU has taken numerous corrective actions to address this finding, including development of guidance and sample assents for investigators regarding the solicitation of assent from children, taking a strong stance on requiring assent from children between the ages of 8 and 17, and routinely holding investigators responsible for drafting and submitting parental permission forms along with a pediatric assent form. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the CU MPA.

(6) In its April 25, 2002 letter, OHRP expressed concern that when reviewing protocol applications, the CU IRB on occassion appeared to lack sufficient information to make all of the determinations required for approval of research under HHS regulations at 45 CFR 46.111. For example, OHRP notes the following:

(a) Protocol #5725 included a battery of neuropsychological tests for children. It appears that the CU IRB did not review these instruments, except for the Stroke Risk Factors test.

(b) Some procedures were listed in the IRB-approved informed consent document for protocol #8028 but did not appear to be described in the IRB-approved protocol (test

of fuel utilization of fat muscle with injection of nitroprusside and isoproterenol subcutaneously).

(c) The protocol for #6166 approved in 1998 was only 2 pages.

Corrective Actions: OHRP acknowledges that the current CU IRB procedures provide for review and approval of all questionnaires/tests/surveys and clarify that in addition to the sponsor/group/multicenter protocol the IRB protocol should provide a synopsis of the larger protocol, the new protocol application is much more detailed, and increased education and orientation helps to focus members on their duties while a third IRB has relieved overwork. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the CU MPA.

(7) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited review procedures for review of minor changes in previously approved research during the period (of one year or less) for which approval is authorized. OHRP finds that the IRB employed expedited procedures to review changes to the protocol that appear to exceed this limitation. In particular, OHRP notes the following:

(a) A change to protocol #8028 to include a new subject population of obese subjects whose obesity is due to mutations in certain genes and who were to be hospitalized to undergo a subset of the tests that the other subjects undergo. This amendment was reviewed in an expedited manner.

(b) For protocol #8542 the decision to waive assent was made by the IRB Chair and not the convened IRB.

Corrective Actions: OHRP acknowledges that (i) the CU IRB now uses a new review audit tool to document and track the appropriate use of expedited review procedures, (ii) increased education and orientation has raised the bar on knowledge and quality of review, (iii) expanded use of IRB member designees helps provide specific expertise when conducting expedited reviews, and (iv) the CU IRB has clarified which kinds of amendments would be considered expeditable and which would need to be reviewed by the convened IRB. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the CU MPA.

(8) A July 10, 1997 letter from Dr. Michael Rosenbaum to Dr. Donald Kornfeld (IRB chair) for protocol # 8028 stated "I obtain a complete medical history from students by telephone prior to admission." OHRP finds that the investigators obtained private, identifiable information from prospective subjects and was thus conducting human subject research prior to obtaining and documenting informed consent, in contravention of the requirements of HHS regulations at 45 CFR 46.116.

Corrective Action: OHRP acknowledges that the CU IRBs would now require such screening to be considered research requiring informed consent or appropriate waiver, and that IRB members have been provided with ongoing education and have been sensitized to the definition of human subject research. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the CU MPA.

(9) In its April 25, 2002 letter, OHRP expressed concern that the procedures for enrolling subjects for protocol # 8028 may have failed to minimize the possibility of coercion or undue influence as required by HHS regulations at 45 CFR 46.116. The control subjects for this study included work-study students. A July 10, 1997 letter from Dr. Michael Rosenbaum to Dr. Donald Kornfeld (IRB chair) stated, "Students will function both as subjects in this study and also participate in conducting a research project in our laboratory."

Corrective Action: OHRP acknowledges that the students were not CU students but were summer interns from other colleges. OHRP also acknowledges that the CU IRB prohibits direct solicitation of students and subordinates for research and provides education on this policy. OHRP finds that this corrective action adequately addresses the above finding and is appropriate under the CU MPA. OHRP notes that these interns did conduct research projects in the principal investigator's laboratory and therefore were subordinates of the investigator. OHRP assumes that CU would, in the future, consider such an arrangement to be coercive and in violation of CU policy.

As a result of the above determinations, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

At this time, OHRP provides the following additional guidance regarding the CU IRB policies and procedures.

(10) Written IRB policies and procedures should provide the operational details for each of the following procedures required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow (i) for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and (ii) for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

(b) The procedures for ensuring prompt reporting to appropriate institutional officials, OHRP and the Department or Agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (ii) any suspension or termination of IRB approval.

OHRP notes that the "Institutional Review Board Application Packet" includes an assurance by the investigator that the investigator will adhere to the requirements under finding (10) (a). OHRP suggests that a notation of the inclusion of this statement in this form could be written in the policies and procedures. Please see http://ohrp.osophs.dhhs.gov/humansubjects/guidance/wirbproc.pdf for additional guidance on preparing written IRB procedures.

(11) Regarding the CU policies and procedures section on "verbal consent," OHRP notes that HHS regulations at 45 CFR 46.117(c) require specific findings on the part of the IRB for waiver of the usual requirements for the investigator to obtain a signed consent form from all subjects. The IRB must find either (1) that the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality (each subject should be asked whether the subject wants documentation linking the subject with the research); or (2) that the research presents no more than minimal risk of harm to the subjects *and involves no procedures for which written consent is normally required outside of the research context*. OHRP recommends that the CU IRB revise its written procedures to address this requirement.

(12) Regarding the "Institutional Review Board Application Packet," OHRP recommends that under "11. Expedited Review" the form define "retrospective" and "prospective." OHRP notes that HHS regulations at 45 CFR 46.101(b)(4) state that research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects is exempt from HHS regulations at 45 CFR 46. OHPR interprets "existing" to mean "existing at the time the research is proposed." OHRP also recommends that the "Special Populations" section include a choice of "other," since it is possible that other populations than those listed may be vulnerable.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Human Subject Protections

cc: Mr. Paul Papagni, CU
Dr. Andrew Wit, CU IRB I Chair
Dr. James Garvin, CU IRB II Chair
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