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June 11, 2001

Michael H. Jang
Director
Institute for Scientific Analysis
Scientific Analysis Corporation
390 Fourth Street, 1st Floor
San Francisco, CA 94107

RE: OHRP Investigation Of Human Subject Protections Under Multiple Project Assurance (MPA) M-1020

Dear Dr. Jang:

The Office for Human Research Protections (OHRP) has reviewed your June 29, 2000 and May 7, 2001 letters responding to OHRP's concerns and requests for action regarding institutional review board (IRB) review of research conducted by the Institute for Scientific Analysis (ISA).

OHRP makes the determinations about ISA's program for protecting human research subjects:

(1) In response to OHRP's request in its November 23, 1999 letter, ISA reviewed all active protocols previously approved under an expedited review procedure and confirmed that these protocols qualified for expedited review in accordance with Department of Health and Human Services (HHS) regulations governing the protection of human research subjects at 45 CFR 46.110 and 63 FR 60364-60367.

(2) In its letter of November 23, 1999, OHRP expressed concern that protocols involving questionnaires to be administered to human subjects were approved by the ISA IRB without IRB review of the questionnaire, indicating that the IRB lacked sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. ISA acknowledged that IRB approval of protocols involving human subjects occurred prior to the development or review of finalized documents. ISA indicated that its IRB policy was to review and approve all documents, including pilot and finalized instruments, before they were administered to human subjects. OHRP finds its concern has been adequately addressed provided that ISA

continues to ensure that all final survey instruments are reviewed and approved by the IRB prior to enrollment of any human subjects.

(3) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

Corrective Action: OHRP finds that ISA's Handbook of Institutional Review Board Procedures (Revised June 22, 2000) incorporates the requirements of 45 CFR 46.115(a)(2).

(4) In its letter of November 23, 1999, OHRP expressed concern that on September 16, 1994 and October 13, 1995, the IRB appeared to discuss protocols by telephone rather than at convened meetings as required by 45 CFR 46.108(b). OHRP acknowledges ISA's response that the protocols involved in these telephone discussions were approved by expedited review. While OHRP strongly recommends that IRB meetings take place with all participating IRB members physically present, under certain circumstances IRB meetings conducted by telephone conference call may comply with the requirement under HHS regulations at 45 CFR 46.108(b) that IRBs review proposed research "at convened meetings". See OHRP document titled "IRB Meetings Convened via Telephone Conference Call" at http://ohrp.osophs.dhhs.gov/references/irbtel.pdf.

As a result of the above determinations and presuming that ISA ensures that all active research has current continuing review and approval, there should be no need for further involvement of OHRP in this matter, and OHRP is therefore closing its investigation of ISA.

At this time, OHRP provides the following additional guidance to ISA:

(5) OHRP notes that informed consent forms approved by the ISA IRB typically provide only the name of the principal investigator as someone subjects may contact for questions about the research and subjects' rights, or in the event of a research-related injury. OHRP recommends that subjects be offered a contact other than the investigator to discuss subjects' rights or potential research-related injuries, to avoid possible conflicts of interest. The contact could be another individual on the IRB, an ombudsman, or an ethics committee representative. See OHRP document titled "Informed Consent Tips" (3/93) at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/ictips.htm.

(6) HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each application or proposal for HHS support has been reviewed and approved by the IRB. The IRB's review should ensure that all research described in the application or proposal is entirely consistent with any corresponding protocol submitted to the IRB. This review need not be undertaken by every IRB

member; rather, a designated member may document that proposed research is consistent with any relevant protocol(s) submitted to, or previously approved by, the IRB. A copy of the HHS application or proposal should be retained among the IRB records and made available to any IRB member who wishes to review it.

(7) 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 notes that on occasions the ISA IRB filed to conduct continuing review at least annually.

Please note that if the IRB does not re-approve 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.)

(8) ISA's Handbook of IRB procedures states that the IRB regularly reviews research involving vulnerable subjects, including prisoners. Subpart C of the HHS human subject protection regulations (45 CFR 46.301 through 46.306) provides additional protections for prisoners participating in human subject research, including special findings the IRB must document before approving research involving prisoners. Please note that under 45 CFR 46.304, an IRB reviewing research involving prisoners must include at least one voting member who is a prisoner or a prisoner representative with appropriate background and experience to serve in that capacity.

(9) In conducting the initial review of proposed research, IRBs must obtain information in sufficient detail to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. These determinations include: (a) that risks to subjects have been minimized and are reasonable in relation to anticipated benefits; (b) that selection of subjects is equitable; (c) that appropriate safeguards are provided for vulnerable populations (children, prisoners, pregnant women, etc.); and (d) that adequate provisions exist to protect subjects' privacy and confidentiality. Materials should include the full protocol, a proposed informed consent document, relevant grant applications, the investigator's brochure (if one exists), and any advertising intended to be seen or heard by potential subjects. Unless a primary reviewer system is used, all members should receive a copy of the complete documentation sufficiently in advance of the IRB meeting date to allow review of the material.

(10) As stated in OHRP's letter of November 23, 1999, where HHS regulations require specific findings on the part of the IRB, such as (a) approving a procedure which alters or

waives the requirements for informed consent [see 45 CFR 46.116(d)]; (b) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (c) approving research involving prisoners [see 45 CFR 46.305-306]; or (d) approving research involving children [see 45 CFR 46.404-407], the IRB should document such findings. OHRP strongly recommends that all required findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding.

OHRP appreciates ISA's continued commitment to the protection of human research subjects.

Sincerely,

Carol J. Weil, J.D.
Compliance Oversight Coordinator
Division of Human Subject Protections

cc: Dr. Michael A. Carome, OHRP
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