



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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January 12, 2011

Peter J. Snyder, PhD
Vice President Clinical Research
Rhode Island Hospital
593 Eddy Street
Aldrich Building Suite 132
Providence, RI 02903

RE: Human Research Protections under Federalwide Assurance FWA-1230

Research Project: A Novel, Population-based Prospective Inception Cohort of Inflammatory Bowel Syndrome. Ocean State Crohn's and Colitis Area Registry (OSCCAR)

RIH Principal Investigator: Samir Shah, MD

Sub Recipient: Rhode Island Hospital

Prime Awardee: Massachusetts General Hospital

NIH Grant Number: 5R21DK078555-02

Dear Dr. Snyder:

Thank you for your June 9, 2010 report in response to our May 3, 2010 request that Rhode Island Hospital (RIH) investigate allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46). Based on review of your response, we make the following determinations:

A. Determinations regarding the above-referenced research.

- (1) The complainant alleged that protocol changes were made without institutional review board (IRB) review and approval. Specifically, it was alleged that in October 2008, a filming about the above study aired on television and a study website went live prior to IRB review and approval. It was alleged that protocol changes were implemented, "batch[ed]," then forwarded to the IRB for review. HHS regulations at 45 CFR

46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. We reviewed your responses and the materials provided and determine the following:

- (a) With respect to the allegation that protocol modifications were made without IRB approval, the documentation provided indicates that the Lifespan IRB reviewed and approved these changes before they were implemented by the RIH principal investigator (PI). Given the facts at our disposal, we determine that this allegation is unproven.
- (b) With respect to the allegation that a subject was “filmed” (interviewed) by a local news station to recruit subjects for this study, we reviewed the materials provided and note that the Lifespan IRB was informed in advance of the interview and determined that the interview only provided general awareness of inflammatory bowel disease to the community, and was not for recruitment purposes. Given the facts at our disposal, we determine that this allegation is unproven.
- (c) With respect to the allegation that the study website went live without IRB approval, we reviewed your responses that indicate that the website was created with the information from the IRB approved study brochure. However, we note that in some cases, the information provided on websites may constitute the earliest components of the informed consent process. While websites that provide *only* directory listings with basic descriptive information about the research study do not need to be reviewed by an IRB, OHRP consistently has interpreted HHS regulations to provide IRB authority and responsibility for review of study recruitment material, including advertisements. Although websites use a different medium than traditional print or broadcast advertisements, the requirements are the same if the website contains more than just basic descriptive information about the research study. For more information about which websites require IRB review, please refer to OHRP’s “Guidance on Institutional Review Board Review of Clinical Trial Websites” at <http://www.hhs.gov/ohrp/policy/clinicaltrials.html>. We determine that the plan for the study website and a description of the proposed content should have been reviewed by the IRB prior to its activation in accordance with HHS regulations at 45 CFR 46.103(b)(4)(iii) which require that the IRB review and approve all proposed changes in a research activity during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects.

Required Action: Please provide a plan to ensure that the IRB reviews and approves all recruitment plans and materials (including plans to use websites for study recruitment and a description of the proposed content of such websites, if the websites provide more than basic descriptive information about the research study)

and proposed changes in research prior to the implementation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects.

- (2) The complainant alleged that outdated study brochures that did not reflect the current IRB approved inclusion criteria and other study materials were distributed for approximately 4-6 months to approximately 100 physicians, 27 physician practices, and patients. We have reviewed the materials provided along with the written attestation from the PI that the new brochures were distributed as approved by the IRB and that the older versions of the brochures were “swapped out.” No evidence was presented to us indicating that outdated study brochures were distributed after the IRB approved updated brochures. Given the facts at our disposal, we make no determination regarding this allegation.
- (3) The complainant alleged that the investigator failed to report complaints from parents of subjects to the IRB in violation of HHS regulations at 45 CFR 46.103(b)(5), which require prompt reporting to the IRB appropriate institutional officials, and the department or agency head of, among other things, any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB. We note that although the continuing review submission form asks whether “the study receive[d] any complaints,” the PI indicated in the continuing review form (signed by the PI on June 17, 2008) that there had been no complaints. We further note that your April 2009 audit revealed that a co-investigator received a complaint on June 11, 2008 - a subject’s parent had made the complaint, and it was not reported to the IRB. When asked why the complaint was not reported to the IRB the auditor was informed by the PI that “the Co-I did not inform the PI of the complaint in time for the continuing review report in 2008.” The IRB became aware of this subject’s complaint via the 2009 audit report. HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) require that unanticipated problems involving risks to subjects or others or serious or continuing noncompliance or suspensions or terminations of IRB approval be reported to the IRB. We reviewed your response and note that complaints do not necessarily constitute an event that must be reported to the IRB. The Lifespan IRB did require a “deviation report” to explain omission of this information; it did not consider the omission to be serious or continuing non-compliance. Given the facts at our disposal, we determine that this allegation is unproven.
- (4) The complainant alleged that the parental permission document failed to provide a complete description of the procedures to be followed in this research as required by HHS regulations at 45 CFR 46.116(a)(1). We note that this allegation pertains to the parent’s complaint referenced in item #3 above. Specifically, a subject’s parent complained that they were unaware that study questionnaires would be administered to their children when they were not present. The complainant also alleged that other complaints were made by subjects regarding the stipends for subjects’ participation. No evidence was presented to us specifying complaints made in regards to stipends; however, based on the information provided, we determine that the parental permission

document did not clearly describe the procedures to be followed in violation of HHS regulations at 45 CFR 46.116(a)(1).

Corrective Action: We note that the Lifespan IRB, upon its review of the incident described above, required changes to the consent to specifically discuss and inform parents that their children may be asked to complete the study questionnaires in their absence. At that time, stipend information was made more specific as to the timing of payments for participation. This corrective action adequately addresses this determination.

- (5) The complainant alleged that an Exercise Physiologist who lacked proper training conducted blood draws in violation of HHS regulations at 45 CFR 46.111 that require the IRB to determine that risks to subjects are minimized. No evidence was presented to us indicating that this individual lacked proper training. We note that a copy of this individual's phlebotomy training certificate was included in your response. Given the facts at our disposal, we determine that this allegation is unproven.

B. Determinations regarding your institution's system for protecting human subjects.

In addition to the matter complained about, we make the following determination:

- (1) We have reviewed the research protocol referenced above and note that the study protocol includes a section titled "Identification of Unreferred Incident Cases" that involves accessing and reviewing medical records of individuals diagnosed with Irritable Bowel Syndrome that did not enroll this study "to get accurate incidence rates." Per your response, a "portion of the study [the "Identification of Unreferred Incident Cases" portion]... calls for retrospective collection of de-identified patient data and does not involve interaction with human subjects...and did not become active at RIH until September 2009."

Based on the information provided, medical records (which included individually identifiable information) were accessed for research purposes by members of the research team. As such, this activity involves human subject research and unless waived, informed consent is required. If the accessing had been done by, e.g., medical records personnel, who passed on only information stripped of identifiers, to the research team, then this would not have met the definition of being research with human subjects.

Your response also states that "this portion of the study was determined to be research exempt from IRB review pursuant to 45 CFR 46.101(b)(4)." This exempt determination is incorrect. HHS regulations at 45 CFR 46.101(b)(4) exempts research that only involves the collection or study of *existing* data, documents, records, pathologic specimens, or diagnostic specimens provided specified conditions are met. Please note that data and specimens exempt under this category must exist at the time that the research is submitted to the IRB.

Further, we note that all versions of the protocol since the study's initial review included the section titled, "Identification of Unreferred Incident Cases." This part of the protocol should have been reviewed as part of the whole research proposal, as opposed to separately, and informed consent should have been obtained from those subjects whose medical charts were reviewed--or if appropriate, waived. HHS regulations at 45 CFR 46.116 state that no investigator may involve a human being as a subject in research covered by the regulations unless (a) the investigator has obtained the legally effective informed consent of the subjects or the subject's legally authorized representative, or (b) the IRB has waived the requirements to obtain informed consent in accordance with 45 CFR 46.116(c) or (d). We determine that your institution inappropriately exempted human subjects research and conducted human subject research without obtaining legally effective informed consent of subjects and without the IRB appropriately waiving these requirements in violation of HHS regulations at 45 CFR 46.116(c) or (d).

Required Action: Please provide a corrective action plan to ensure that your institution appropriately applies HHS regulations at 45 CFR 46.101(b)(4) in making exemption determinations, and conducts human subject research with the legally effective informed consent of subjects, unless the IRB appropriately waives these requirements in accordance with HHS regulations at 45 CFR 46.116(c) or (d).

Please provide us with responses to the above determinations by February 21, 2011, including a corrective action plan for each of our determinations. Feel free to contact me if you would like guidance in developing a corrective action plan.

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

Sincerely,

Lisa Buchanan, MAOM
Compliance Oversight Coordinator
Division of Compliance Oversight

cc:

Dr. James Linakis, Chairperson, Lifespan IRB/Rhode Island Hospital
Dr. Janice Muratori, Associate Chairpersons, Lifespan IRB/Rhode Island Hospital Panel #1
Dr. Ronald Seifer, Associate Chairpersons, Lifespan IRB/Rhode Island Hospital Panel #1
Dr. William Sikov, Associate Chairperson, Lifespan IRB/Rhode Island Hospital Panel #2
Dr. Jennifer Friedman, Lifespan IRB/Rhode Island Hospital Panel #2
Ms. Patricia E. Houser, Manager, Lifespan IRB/Rhode Island Hospital
Dr. F. Richard Bringham, Sr., VP of Medicine & Research Management,
Massachusetts General Hospital

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Dr. Griffin P. Rodgers, Director, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Dr. Marilyn S. Radke, Director, OSRS, Centers for Disease Control

Dr. Sherry Mills, National Institutes of Health

Mr. Joseph Ellis, National Institutes of Health