Attachment 23: Phase IV Health Follow-Up IRB Approval Signature Pages

23.1). AHS Health Follow-Up Office of Protocol Services Continuing Review Approval under the AHS AutoImmuneII Protocol

23.2). AHS Health Follow-Up Copernicus Group IRB Continuing Review Approval under the AHS AutoImmuneII Protocol

23.3). AHS Health Follow-Up Office of Protocol Services Amendment Approval under the AHS AutoImmuneII Protocol

CLINICAL RESEARCH PROTOCOL **CONTINUING** REVIEW APPLICATION	PROTOCOL NO. 11-E-N196	PRINCIPAL INVESTIGATOR (NIH Employee Name, Inst/Br, Address, Telephone and email): Jane A. Hoppin, ScD, NIEHS/EB, 919-541-7622, P.O. Box 12233, RTP, NC 27709, hoppin1@niehs.nih.gov

PROTOCOL TITLE: Agricultural Health Study: Health Followup

PROTOCOL STATUS:
- ☐ Renew -Recruitment of participants has not yet begun.
- ☒ Renew -Participants are currently being recruited or enrolled.
- ☐ Renew -No longer recruiting or enrolling participants, subject follow-up only.
- ☐ Renew -Participants have completed study; study and data analyses ongoing.
- ☐ Renew -Clinical Hold/Recruitment or enrollment of participants suspended.
- ☐ Terminate -Study closed. Participants have completed study. Recruitment and data analysis complete.

SUMMARY OF PROTOCOL ENROLLMENT (Aggregate): Only when the NIH is the coordinating site, provide totals and enrollment table for other site.

NIH Site	Other Sites	Total	
0	89656	89656	Accrual ceiling by IRB
0	903	903	New subjects accrued since last CR
0	903	903	Aggregate total accrued

Are you currently recruiting healthy volunteers? ☐ No ☒ Yes
Will the protocol involve adults unable to give informed consent? ☐ No ☒ Yes

Have analyses by sex, racial/ethnic subgroups been conducted for Phase 3 Clinical Trials as required? ☐ No ☐ Yes (answer a and b) ☒ N/A

a. Have analyses been reported? ☐ No (explain in narrative) ☐ Yes
b. Have significant differences been found? ☐ No ☐ Yes

Have any non-NIH Investigators or sites been added since the last review?
- ☒ No
- ☐ Yes (Identify the persons or sites and describe the collaboration in the summary report)

WITH THIS REVIEW, I AM REQUESTING A CHANGE TO THE FOLLOWING:
*Include Name, Inst/Branch, Telephone, Address, e-mail. Check box if an NIH Employee and initial line. Attach sheet if necessary.

PRINCIPAL INVESTIGATOR:
Delete: _____
Add*: ☐ _____

EXTRAMURAL ADJUNCT PRINCIPAL INVESTIGATOR:
Delete: _____
Add: _____

MEDICAL ADVISORY INVESTIGATOR:
Delete: _____
Add*: _____

LEAD ASSOCIATE INVESTIGATOR:
Delete: _____
Add*: ☐ _____

RESEARCH CONTACT:
Delete: _____
Add*: ☐ _____

ASSOCIATE INVESTIGATOR(S):
Delete: _____
Add*: ☐ _____

IONIZING RADIATION USE (X-rays, e.g., CT; radioisotopes, e.g. PET, etc.) check all that apply:
- ☒ None
- ☐ Medically indicated
- ☐ Research indicated. Since the last review,
  - ☐ Research usage HAS NOT changed.
  - ☐ Research usage HAS changed. (Explain in summary report)

INVESTIGATIONAL NEW DRUG/DEVICE: ☒ None ☐ IND ☐ IDE
*If reporting more than one IND/IDE, list on attached sheet.

FDA No. _____
Name: _____
Sponsor: _____
Who is the manufacturer of the above entity? _____

Does the protocol involve a Tech Transfer Agreement? ☒ No ☐ Yes

Does the protocol involve a drug/device/product that may lead to you or the NIH receiving payment and/or royalties?
- ☒ No
- ☐ Yes (Append a statement of disclosure)

Have there been any amendments since the last review?
- ☐ No
- ☒ Yes (Describe briefly in the attached narrative.)

Have there been any changes in the informed consent process or documentation since the last review?
- ☐ No
- ☒ Yes (Describe in Summary report)

Have there been any changes in the subject population, recruitment or selection criteria since the last review?
- ☒ No
- ☐ Yes (Explain changes in the attached narrative.)

Have any unexpected complications or side effects been noted since the last review?
- ☒ No
- ☐ Yes (Identify and explain in the attached narrative.)

Have any subjects withdrawn from this study since the last IRB approval?
- ☒ No
- ☐ Yes (Discuss in the attached narrative.)

Has any information appeared in the literature, or evolved from this or similar research, that might affect the IRB's evaluation of the risk/benefit analysis of human subjects involved in this protocol?
- ☒ No
- ☐ Yes (Discuss in the attached narrative.)

Has the NIH IRP COI Guide been distributed to new NIH investigators?
☐ No ☐ Yes ☒ N/A

Has the NIH IRP COI Guide been distributed to new Non-NIH investigators?
☐ No ☐ Yes ☒ N/A

CONFLICTS OF INTEREST REVIEW?

Date submitted to IC DEC: 4/2/12 Date cleared by IC DEC: _____

SIGNATURE	Jane A. Hoppin Principal Investigator	Jane A. Hoppin, ScD Print/Type Name	Date e-Signed on 4/2/12 11:33 AM	Send to Accountable Investigator
RECOMMENDATION	Dale P. Sandler Accountable Investigator	Dale P. Sandler, Ph.D. Print/Type Name	Date e-Signed on 4/5/12 12:24 PM	Send to Branch Chief, or CC Dept. Head of Accountable Investigator
	Dale P. Sandler Br Chief/CC Dept. Head of Acct. Invest	Dale P. Sandler, Ph.D. Print/Type Name	Date e-Signed on 4/5/12 12:24 PM	Send to Clinical Director
APPROVALS	Frederick W. Miller Clinical Director	Frederick W. Miller, M.D., Ph.D. Print/Type Name	Date e-Signed on 5/4/12 1:41 PM	Send to Chair, Institutional Review Board
	David B. Resnik Chair, For Institutional Review Board	David B. Resnik, J.D., Ph.D. Print/Type Name	Date e-Signed on 5/7/12 5:17 PM	Send to Office of Protocol Services, through IRB Protocol Coordinator
COMPLETION	C.Bonds-Beeken Protocol Specialist	Date 5/11/12	Protocol & Consent Approved Effective	

	Signature Page	
	Title	SSS1-11-220_Hoppin_Jane_Approvals_2012-06-06
	Summary	Hoppin Jane

Signed By:	Reason:	Date/Time:
Ashley Jacobs	Authorized Signature	June 7, 2012 10:33:54 AM EDT

June 7, 2012

Jane Hoppin ScD
National Institute of Environmental Health Sciences (NIEHS)
111 T.W. Alexander Drive
Research Triangle Park, NC 27709

Re: Protocol #: 11-E-N196
IRB Tracking #: SSS1-11-220

Dear Hoppin,

Enclosed please find an Approval Notice dated June 6, 2012 for the above-mentioned protocol.

This is to inform you that the Copernicus Group IRB has approved the above-referenced study for another year. Please continue to use the latest IRB approved Site-Specific Subject Information and Consent Form(s). Note that any changes in the study must be communicated to the Copernicus Group IRB.

If you have any questions regarding the contents of this letter or your working relationship with Copernicus Group IRB, please do not hesitate to call us at 1-888-303-2224 or email us at irb@cgirb.com. To avoid delay in locating your records we ask that you refer to the IRB Tracking number located in the header of this letter. Send faxes for this project to 1-919-654-7197.

Copernicus Group IRB

cc: Elizabeth Long O'Connell, NIEHS (Web Portal)

IRB APPROVAL DATED:
June 6, 2012
STUDY EXPIRATION DATE: June 5, 2013

Protocol #: 11-E-N196
Investigator: Jane Hoppin ScD
Approval Includes:
Re-Approval of Study

Investigator Address: Jane Hoppin ScD

National Institute of Environmental Health Sciences (NIEHS)
111 T.W. Alexander Drive
Research Triangle Park, NC 27709

Sponsor: NIEHS

CRO: Social & Scientific Systems, Inc.

Protocol Title: Agricultural Health Study Health Follow Up

Approval is granted subject to the following considerations:

- Responsibilities of the Principal Investigator as found in the Investigator Guidebook
- In the event that non-English speaking subjects are recruited, a certified translation of the informed consent must be approved by the IRB before recruitment.
- If subjects who cannot read are recruited, there should be an impartial witness to attest to the adequacy of the consent process and to the subject's voluntary agreement to be in the study. This witness should also verify the subject's signature or mark on the consent form.
- Please note that if revisions are required for any approved item (particularly advertisements), they must be approved prior to use.
- If pediatric subjects are to be enrolled then they should be re-consented when they become of legal age.
- Please note that CGIRB requires the reporting of any unanticipated problems involving risks to subjects or others as soon as possible, but in all cases within 10 business days in accordance with the applicable regulatory standards and CGIRB requirements.

IF YOU HAVE ANY QUESTIONS, CALL COPERNICUS GROUP IRB AT 1-888-303-2224

This signature certifies that the information contained in this IRB Approval Notice is true and correct as verified by the minutes and records of The Copernicus Group, Inc. It also certifies that The Copernicus Group, Inc. is in full compliance with FDA Code of Federal Regulations (21 CFR Parts 50, 56, 312, and 812 and 45 CFR) and ICH Guidelines.

Signature See appended electronic signature page IRB TRACKING # SSS1-11-220

Authorized Signature

Copernicus Group IRB
One Triangle Drive Suite 100
Durham, NC 27713
Mailing Address:
P.O. Box 110605
Research Triangle Park, NC 27709

Experience and Innovation in Ethical Review ™

Telephone: 919-465-4310
Toll-Free: 888-303-2224
Fax: 919-465-4311
E-Mail: irb@cgirb.com
Web: www.cgirb.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health
National Institute of
Environmental Health Sciences
P. O. Box 12233
Research Triangle Park, NC 27709
http://sharepoint.niehs.nih.gov/ohrc/default.aspx

DATE: June28, 2012

TO: NIEHS IRB Chair
Through: The Office of Human Research Compliance
Branch Chief, Dale Sandler, PhD
(Acting) Clinical Director, CRP, OCR

FROM: Jane Hoppin, ScD

SUBJECT: Expedited Amendment to Protocol # 11-E-N196 titled "Agricultural Health Study Health Follow-up"

An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from members of the IRB in accordance with the requirements set forth in 45 CFR 46.110. Additional information on determining the appropriate level of review for a submission can be found at http://ohsr.od.nih.gov/irb/Attachments/Chapter7.htm.

Note: *If an NIH investigator is added to the protocol, attach a signed/cleared Personal Financial Holding Clearance form along with an e-mail from the new investigator stating they are aware they are being added to the protocol.*

Expedited Amendment Summary and Justification:

We propose to amend the Agricultural Health Sstudy (AHS) Health Follow-up protocol to collect updated information on medical history and other important covariates through follow-up interviews of the cohort. Currently, we plan to contact cohort members to complete follow-up interviews allowing one of three modes of response: self-administered paper questionnaire, self-administered web survey (CAWI), and interviewer-administered telephone interview (CATI). We will contact proxy respondents if the participant is deceased or is unable to provide information. AHS participants were re-interviewed in 1999-2003 (Phase 2 follow-up). AHS farmers and their spouses were contacted again in 2005-2010 (Phase 3 follow-up). The AHS enrollment and previous follow-up questionnaires collected self-reported data on the participants' disease history to identify new cases of disease. Enrollment and subsequent follow-up interviews in the AHS was based on questionnaire return and consent was implied. Consistent with AHS and other cohort studies, additional written consent for this follow-up will not be obtained.

The planned Phase 4 follow up will continue this identification of newly reported non-cancer health outcomes from AHS participants in order to include in current and future validation efforts. Under this protocol, cohort members or their proxies will be re-interviewed in 2013 -2014 (Phase 4 follow-up). Individuals who were eligible for the Phase 3 interview will be contacted to complete Phase 4. The Phase 4 follow up is designed to take approximately 20 minutes to complete. OMB clearance for this follow up questionnaire will be obtained.

Our basic strategy involves: 1) mailing a letter to participants to inform them of the health follow-up; 2) include in the initial mailing a self-administered paper questionnaire; 3) provide a web link and login instructions for those who prefer completing the self-administered questionnaire via CAWI; and 4) contact those who do not respond by mail or web to complete the follow-up by CATI.

This amendment also contains minor changes to the validation effort language, allowing for more flexibility regarding case selection for saliva collection.

The specific requested revisions are detailed below:

I. Protocol

{Page number, section and detailed description of each change, if applicable}

All pages: in footer, protocol version date changed to 6/26/2012

Page 1: date changed from March 2012 to May 2012. Also, Laura Beane Freeman and Michael Alavanja of NCI were added as co-investigators

Page 2, Section A Precis, first paragraph: added language to include the purpose of the Phase 4 follow up

Page 2, Section A Precis, second paragraph: Updated the language regarding collection of saliva to read "We may also collect a saliva or cheek swab sample from cases….." instead of "We will also collect a saliva or cheek swab sample from all cases….." to allow investigators more flexibility in selection of cases for saliva collection.

Page 2, Section B.1 Background: The Agricultural Health Study, first paragraph: Added sentence "Under the current protocol, cohort members or their proxy who were eligible for the Phase 3 interview will be re-interviewed in 2013 -2014 (Phase 4 follow-up)."

Page 3, Section B.1 Background: The Agricultural Health Study, second paragraph, Added missing word from sentence "farming" and added new sentence "Of particular interest are non-cancer outcomes, as there are no formal registries for these important adult chronic diseases."

Page 3, Section B.1 Background: The Agricultural Health Study, third paragraph, last sentence: updated language to read "The AHS will continue to collect data……." instead of "The AHS has collected data……."

Page 3, Section B.1 Background: Validation of Disease Outcomes: Updated section name to "Health Follow-up and Validation of Disease Outcomes"

Page 3, Section B.1 Background: Validation of Disease Outcomes: first paragraph, added second sentence "This protocol will update information on medical history and other important covariates through follow-up interviews of the cohort."

Page 3, Section B.1 Background: Validation of Disease Outcomes: second paragraph, updated first two sentences to read "The Agricultural Health Study enrollment and previous follow-up questionnaires collected self-reported data on the participants' disease history to identify new cases of disease. The planned Phase 4 follow up will continue this identification of new cases of disease."

Page 4, Section C Objectives: Added last sentence "The Phase 4 follow-up will allow us to identify newly reported non-cancer health outcomes among AHS participants in order to include in current and future validation efforts."

Page 5, Section D.1 General Design: added new first paragraph describing the general design of the follow up and added "In addition…" to beginning of second paragraph and "Finall…." to third paragraph.

Page 6, Figure 1: added "for some" to buccal/saliva collection bubble.

Page 7, Section D.1.3 Design: Initial Contact: Added last sentence . "We will receive updated contact information that may be obtained by the outside investigator as well as participation outcomes in order to assist in cohort maintenance."

Page 7, Section D.2 Study Team: Added "co" to co-PI to describe Dr. Hoppin's role on AHS.

Page 8, Section D.2 Study Team: Added "Drs. Alavanja and Beane Freeman of NCI are both co-PIs of the AHS and are the lead investigators on cancer in the cohort.

Page 8, Section D.3 Project Timeline: added last sentence indicating that the Phase 4 follow up would begin in the first quarter of 2013.

Page 8, Section D.4 Population and sampling: added second sentence indicating that the Phase 4 follow up would begin in the first quarter of 2013 and updated third sentence indicating that we plan to use self-reported information from enrollment and all follow-up interviews to identify possible cases for validation.

Page 9, Section D.5 Methods: added new first paragraph to describe the Phase 4 and other subsequent health outcome follow-up efforts.
Page 11, Section E. Inclusion and Exclusion Criteria: Changed first paragraph to read "All members of the AHS cohort who were eligible for the Phase 3 interview will be eligible for the health follow-up and disease validation study. Individuals who only completed the enrollment questionnaire were excluded from Phase 3 eligibility. For individuals who are unable to provide information, we will allow a proxy to provide that information." and clarified that the second paragraph describes criteria for the validation efforts.
Page 11, Section F Montioring Subjects and Criteria for Withdrawal of Subjects from the Study: first sentence added "….health follow-up and…."
Page 11, Section G Analysis of the Study: first sentence, added "….update the medical history and other important covariates, and to….".
Page 11, Section G.1 Statistical Analysis: Added "The health follow-up interviews will aid in the identification of new cases of all diseases, thus increasing the overall power of the AHS to look at incident disease, for both rare and common outcomes."
Page 12, Section Rationale for Subject Selection: added first sentence "For the health follow-up interview, we will conduct the study among all participants who were Phase 3 eligible." and edited following paragraph to refer to validation efforts.
Page 13, Section H.2 Strategies and Procedures for Recruitment: moved sentences 4-6 to paragraph 3, added paragraph 2 to describe strategies and procedures for recruitment for the follow up. Added "For the validation efforts" to the third and fourth paragraphs for clarity.
Page 14, Section H.3 Justification for Exlcusions: second paragraph, added "…into a validation effort" for clarity.
Page 14, Section H.4 IRB Review and Approval: second paragraph, frist sentence, added "Health follow-up and…." Added last sentence "OMB clearance will be sought for the health follow up." and clarified that OMB exemption was obtained for the validation efforts.
Page 15, Section H.6 Consent Processes and Documents: added new first paragraph regarding the health follow up.
Page 15, Section H.6 Consent Processes and Documents: second paragraph, updated second sentence from "…..the telephone recruitment call by…." to "…..all subsequent contacts with….".
Page 15, Section H.6 Consent Processes and Documents: third paragraph, added reference to linkage with National Death Index.
Page 15, Section H.6 Consent Processes and Documents: updated paragraphs 5 and 6 to include reference to the validation efforts.
Page 15, Section H.6 Consent Processes and Documents: added final paragraph "For initial contact efforts, the outside institution conducting the research is responsible for obtaining consent in accordance with their Institutional Review Board."

II. Consent(s)
{Document title, page number, section and detailed description of each change, if applicable}

III. Recruitment Material/Participant Information Sheet
{Document title, page number, section and detailed description of each change, if applicable}
Health Follow up Phase 4 initial invitation mailing to participant - new
Health Follow up Phase 4 second invitation mailing to participant including website - new
Health Follow up Phase 4 invitation mailing to next of kin - new

IV. Other

{Document title, page number, section and detailed description of each change, if applicable}
Health Follow up Phase 4 questionnaire - participant - new
Health Follow up Phase 4 questionnaire - proxy - new

Jane Hoppin, ScD
Principal Investigator, NIEHS

I authorize the above changes to my study and have included updated edited and clean versions of all revised documents as attachments for submission via my NIH e-mail account to the NIEHS Office of Human Research Compliance.

For Approving Official Use Only:

The attached expedited amendment request is a minor change in the research that does not increase risks to subjects or reduce potential benefits and falls within the OHRP Categories of Research that May be Reviewed by the IRB through an expedited review procedure. Approval is hereby granted.

N. Almodovar	8/13/12	F
Protocol Specialist Office of Protocol Services	Date	Amendment Letter

Protocol eSign History

Protocol Number: 11-E-N196 Review: Amendment 06/29/2012 (6)

Date/Time	User	Type	Action
06/29/2012 4:02 PM	Jane Hoppin	Electronic signature access	eSignature Verified Principal Investigator
06/29/2012 4:31 PM	Dale Sandler	Electronic signature access	eSignature Verified Accountable Investigator
06/29/2012 4:31 PM	Dale Sandler	Electronic signature access	eSignature Verified Branch Chief
07/15/2012 8:37 PM	Bruce Androphy	Electronic signature access	Date/Time Cleared by IC DEC: Sun Jul 15 20:37:36 EDT 2012
07/16/2012 11:12 AM	Frederick Miller	Electronic signature access	eSignature Verified Clinical Director
07/17/2012 12:03 PM	David Resnik	Electronic signature access	eSignature Verified IRB Chair