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

23.1) AHS Health Follow-Up Office of Protocol Services Continuing Review Approval

23.2) AHS Health Follow-Up Copernicus Group IRB Closeout Report

DATE: January 22, 2015

TO: Dale P Sandler, Ph.D.
Principal Investigator

THROUGH: Michael W Roberts, D.D.S., M.Sc.D.
Primary Reviewer

FROM: Resnik David, J.D., Ph.D.
Chair, NIEHS IRB

SUBJECT: IRB Review of Continuing Review 3/5/2015 for Protocol 11-E-N196: "Agricultural Health Study: Health Followup"

Your Continuing Review 3/5/2015 was approved without stipulations by the NIEHS Institutional Review Board (IRB) at the January 08, 2015, meeting.

DISCUSSION:
Pesticides are a common environmental exposure due to their widespread use for agricultural, residential, and public health purposes. Farmers and their families represent a unique population for studying the chronic health effects of pesticides because farmers know what chemicals they use, furthermore, farmers tend to remain at the same location over most of their adult life. The Agricultural Health Study (AHS), a cohort of ~89,000 pesticide applicators and spouses from Iowa and North Carolina, is the largest US cohort study of individuals working with pesticides. The AHS cohort was enrolled in 1993 to 1997 to assess human health effects associated with well characterized exposures to pesticides and other agricultural factors. Detailed exposure data were collected at enrollment and in two five-year follow-up interviews. As a result, the AHS has a wealth of information on pesticide use by both farmers and their spouses, as well as the ability to account for changes in pesticide use over time. Information on medical history and important covariates was also collected at enrollment and in the follow-up interviews, and will continue to be collected over time. Only mortality and cancer incidence are updated annually through linkage to vital statistics and cancer registries; all other health outcomes are based on self-reported information from participants. The accuracy of self-reported health outcome information can vary from quite good (e.g., asthma) to poor (e.g., rheumatoid arthritis). In order to ensure high quality epidemiologic analyses, validation of self-reported disease is necessary prior to statistical analysis. To date, several health endpoints have been validated through follow-up with AHS participants and their physicians. The purpose of the current protocol is three-fold: 1) update information on medical history and other important covariates through follow-up interviews of the cohort; 2) validate self-reported diseases among cohort participants over the duration of cohort follow-up (at least through 2020); and 3) complete initial contact of potential participants to inform them of other health outcome studies being conducted by an outside institution.

Currently, investigators plan to contact AHS cohort members to complete a follow-up interview allowing one of three modes of response: self-administered paper questionnaire, self-administered web survey (CAWI), and interviewer-administered telephone interview (CATI). Study staff will contact proxy respondents if the participant is unable to provide information.

While the characteristics of the diseases may vary, the strategy for disease validation is similar. Validation efforts will include a phone call to the participant to confirm the self-report, a short questionnaire about disease characteristics, a request for permission to contact the participant's physician, and contacting the physician's office to obtain the relevant medical information. Study staff may also collect a saliva or cheek swab sample from cases who confirm their self-reported

disease to allow for future genetic and DNA analyses. These may include polymorphisms that influence disease susceptibility, response to xenobiotic agents, and innate immune response. Investigators will contact proxy respondents if the participant is unable to provide information. Currently study staff plan to contact participants who have reported a history of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and Sjogren's syndrome (SS). Over time, investigators plan to validate other diseases as they accrue in the cohort.

Research progress and rationale for continuation of the study:

A total of 317 subjects completed screening for the Parkinson's disease validation. Of these, 54 denied disease, 259 confirmed disease and for 3 disease status was uncertain at screening. Of those confirming disease, 117 agreed to medical record release and saliva collection, 121 agreed to medical record release only, 3 agreed to saliva collection only, and 22 refused medical record release and saliva collection. Checklists have been returned by 61% of the physicians who were mailed these requests. No subjects have withdrawn from the Parkinson's disease validation. There are still plenty of subjects to contact from the 89,000 originally enrolled in the larger study. Research is progressing as expected and the study may continue.

Changes in previously approved research:

Four amendments were approved during the past year, mostly for new or revised forms. The principal investigator is requesting the addition of Christie Barker-Cummings to the protocol and deletion of key research personnel from the study with this submission. In addition, Michael Jones, PhD (University of Iowa) and Eric Postel, MD (Duke University) have been removed as Asociate Investigators.

Significant new findings:

There have been no new findings that would affect the IRB's evaluation of the study or the subject's willingness to continue participation in the research.

Protocol recruitment:

Since the last review by the NIEHS IRB a total of 314 subjects have been enrolled in the Parkinson's Disease Validation effort conducted under this protocol. The annual inclusion report provides the demographics of these subjects. The accrual numbers also include subject recruitement to the Autoimmune Validation and PD Validation sub-studies. The accrual information provided with the original submission was incorrect; however, the information was updated prior to the IRB's review. Subject selection remains equitable.

Summary of Adverse Events, Protocol Violations, Serious or Continuing Non-compliance and Unanticipated Problems:

There had been some issues in the previous reporting period but none in the present one.

Scientific design:

No changes in research have affected the scientific design.

Informed consent process is adequate and is appropriately documented (45 CFR 46.111(a)(4), 46.116 and 46.117):

Consent procedures continue to be adequate.

Additional safeguards for vulnerable subjects (45 CFR 46.111(a)(1)):

There are no vulnerable subjects in this study. Children are excluded.

Monitoring of data to ensure safety of subjects (45 CFR 46.111(a)(6)):

The study does not require a data safety and monitoring board. Subject safety is monitored by the PI.

Privacy & confidentiality (45 CFR 46.111(a)(7)):

There have been no changes in privacy and confidentiality which continue to be adequate.

Risks are reasonable in relationship to anticipated benefits/benefits, if any(45 CFR 46.111(a)(2):

There have been no changes in risk, and nothing has appeared in the literature that would change the IRB's assessment of the risks in relationship to benefit.

Period of Approval:

One year.

Additional considerations:

Approvals are included for off-site studies folded into this protocol as well as the approval from the Copernicus Group IRB.

From:	Maria DiCaprio
To:	Bost, Patricia; O"Connell, Elizabeth; O"Connell, Elizabeth; Bost, Patricia
Subject:	Study Closure Notification for Protocol 11-E-N196 (SSS1-11-220)
Date:	Tuesday, April 21, 2015 1:58:21 PM

This protocol is now considered closed. If this is incorrect please contact Jason Garrett

Maria DiCaprio
Study Status Analyst I
Client Services

Copernicus Group IRB
One Triangle Drive, Suite 100
Research Triangle Park NC 27709
Direct: 919-287-6620

Toll Free: 888.303.2224

Fax number: 919-654-7197

http://www.cgirb.com

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Immediate Response Required

Principal Investigator Site Closeout Report

DO NOT submit this form unless you intend for your site to be closed with Copernicus Group IRB

Submit this form directly to CGIRB via Connexus

Blank & Incomplete Answers Will Result in Delayed Reviews

- Please complete this Principal Investigator Site Closeout Report if your study is closed or otherwise terminated and submit to CGIRB for review. Upon closure, acknowledgement will be sent.
  - Do **not** use this form for principal investigator (PI) transfers. Complete the ***Principal Investigator Transfer Form***, located on the CGIRB website (http://www.cgirb.com).
- If you have additional sites participating in this CGIRB-approved study, you should not submit this form until all of the sites have completed all study-related activities.
- Note: CGIRB processes all events that are reportable under CGIRB's promptly reportable information policy for up to 6 months after study/site closure.
- Refer to the ***CGIRB Investigator Guidebook*** for additional information about study closure at a PI site.

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

Principal Investigator (PI):	Dale Sandler, Ph.D.	
Site/Center Name:	NIEHS	
PI Phone # 919-541-4668		**PI Fax #** 919-541-2511
PI E-mail: sandler@niehs.nih.gov		

SECTION 1:

This research study is: **Please select one:**

☐	**Closed**	NO subjects were screened or enrolled. **Complete and date section 3 and submit. (Do NOT complete section 2.**
☐	**Closed**	Subjects were enrolled and have completed all applicable study visits; No Active subjects remain in the study (including subjects being followed for any reason, e.g. safety follow-up) **Complete sections 2 and 3.**
☒	**Closed**	**Other *(specify)*** OHSRP approved reliance agreement with NIH as the IRB of record, no longer requiring review and approval by CGIRB **Complete sections 2 and 3. Attach additional documentation as necessary.**

If enrollment is closed but you expect subjects to remain active in the study (eg, completing remaining study visits) you MAY NOT close your site.

Principal Investigator Site Closeout Report

SECTION 2:

	Since the START of the study or most recent continuing review:	YES	NO
2A.	Have any **unanticipated problems involving risks to research subjects or** others occurred at your site that have ***not*** previously been reported to CGIRB? NOTE: To determine which events are reportable under CGIRB's promptly reportable information policy and how to submit them, refer to the ***CGIRB Investigator Guidebook***. **If *YES*, attach documentation to this report**	☐	☒
2B.	Have any changes/modifications to the research taken place that have not yet been reported to CGIRB (including changes made without prior IRB approval in order to avoid an apparent, immediate hazard to human subjects)? **If *YES* ensure these are submitted as attachments to this report.**	☐	☒
2C.	Has there been any complaint by a subject or other, where the complaint indicates an unexpected risk or cannot be resolved by the research staff, which has not been previously reported to CGIRB? **If *YES* attach an explanation**	☐	☒
2D.	Has any subject sought compensation for injury associated with this study at your site? **If *YES* attach an explanation**	☐	☒
2E.	Has the Food and Drug Administration (FDA), or Office of Human Research Protection (OHRP), or other regulatory agency inspected/evaluated your site since the start of the study or the most recent continuing review?	☐	☒
	If 2E is checked ***YES***: was a Form FDA 483 or list of objectionable observations issued? **If *YES*, attach the observations and your response letter**	☐	☐
2F.	Has your state medical license been revoked, sanctioned, or suspended? **If *YES*, attach an explanation**	☐	☒
2G.	Are there any new findings or relevant information that may affect the risk/benefit ratio of this study? **If *YES*, attach an explanation**	☐	☒

SECTION 3:

By submitting this form, I am confirming that I am the Principal Investigator (PI) or the PI's designee authorized to submit on behalf of the PI. The information within this form is accurate and complete with the PI's full awareness of the information submitted.

eoconnell@s-3.com

Submitter's e-mail address

Elizabeth O'Connell	Study Manager	21Apr2015
Name of Individual at Site Completing Form	**Title of Individual at Site Completing Form**	**Date**