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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control

Memorandum

Date September 10, 1987

From Director
Center for Environmental Health and Injury Control

Subject Protocol for Women's Vietnam Veterans Health Study

To Ronald W. Hart, Ph.D.,
Chairman, Science Panel
Agent Orange Working Group

We have reviewed the Women's Vietnam Veterans Health Study Protocol submitted by the New England Research Institute, Inc. We have serious concerns about this submission which we have listed below. Until these concerns are adequately addressed, I cannot support conduct of the proposed study. Detailed below are comments on the protocol for the Women's Veteran Health Study.

A. Cohort Selection

1. Unlike the Vietnam Experience Study, there are differences between the exposed group and the comparison groups in variables other than experience in Vietnam. The presence of such differences increases potential confounding and complicates the analyses. Would it be more satisfactory to limit the scope of the study and the selection of a comparison group (e.g., limit the study to army cases and controls) to address the most important hypotheses rather than try to do too much?

2. It is not clear how the VA developed its list of 5000 Army Vietnam veterans--how complete is this list? How complete are the lists of Vietnam veterans in the other services?

3. The sampling frame for the non-Vietnam veterans is not clearly described.

4. How valid is their proposed capture-recapture method as a method of documenting the completeness of the cohorts.

5. What duty stations will women veterans for Cohort B come from? Will the Air Force sample of nurses be large enough for separate comparisons?

6. pages 2-3: What does matched on occupation mean and how will this be possible?

7. Consideration might be given to increasing the number of controls (per case) in the overall study, especially in some of the proposed substudies (e.g., reproductive health).

B. Reproductive Health

1. The expectation is to find major birth defects in 1% of offspring; a more appropriate expectation is 2-3%. It would be wise to compile a list of specific defects which are to be considered "major" before the study begins.

2. Cases are defined as women who have had a baby with a defect or "two or more spontaneous abortions not clearly attributable to an identified cause." They propose excluding those with an "unequivocal karyotypic abnormality", and those with a uterine abnormality. Exclusion of women who themselves have a karyotypic abnormality seems reasonable, but it is unlikely that any will be found in the sample. If the reference implies that aborted fetuses that have a karyotypic abnormality will be excluded, this is not reasonable. An abortion associated with a chromosomal anomaly is a health outcome worth considering in the study. In general, more details are needed on why certain diseases/conditions are being excluded.

3. Spontaneous abortions will be difficult to validate since they are frequently not medically documented.

4. It is stated that women with diethylstilbesterol (DES) exposure would be kept in the sample. We would suggest exclusion since they are excluding spontaneous abortions associated with uterine abnormality, and DES exposed women have a higher rate of abortion, usually from uterine abnormality.

5. We would suggest matching controls on age at the last abnormal pregnancy, rather than the first. Spontaneous abortion is strongly related to age and a woman's pregnancies may be separated by many years.

6. At the time this study will be done, most women Vietnam veterans will be 40 or more years of age. Therefore the evaluation of prolonged amenorrhea should probably be deleted from the study.

7. A definition of fertility/infertility is needed.

C. Psychological/Neuropsychological Testing

1. The proposal to use the CDC Vietnam Experience Study (VES) neuropsychological battery is inappropriate. That battery was designed to assess primarily neuropsychological deficits which might be expected from exposure to a toxin (e.g. TCDD). The battery also included some assessment of psychological and neuropsychological problems that might be related to stress.

This latter component is not included (as far as we can tell) in the present protocol. Since TCDD exposure is unlikely to have been a major problem for most nurses in Vietnam, it would probably be better to give greater emphasis to long-term psychological stress faced by these veterans while in Vietnam. This would mean that the proposed battery should include some measures of stress which have been well validated and accepted in psychological research.

In addition, greater emphasis should be given to depression, anxiety, and alcohol and drug use, which are possible sequelae of stress. Also, consideration should be given to including the Minnesota Multiphasic Personality Inventory (MMPI), and more of the Diagnostic Interview Schedule (DIS) than just the Post Traumatic Stress Disorder (PTSD) section.

2. Another concern in the psychological area is the testing in the home of the participant. The VES battery was designed to be administered in a standard testing environment by trained technicians under close supervision. Quality control and standardization will be difficult in the proposed setting.

3. The rationale for measurement of TCDD levels in the PTSD substudy needs further clarification/justification.

4. With respect to the psychological area in general, we suggest that advice be sought from experts in psychology/psychiatry to evaluate the proposed psychological test battery. In addition, staffing for the study should include a qualified psychologist or psychiatrist.

D. <u>Serum Dioxin (TCDD) Measurement</u>

1. The whole issue of Agent Orange exposure assessment/TCDD testing becomes questionable now that the results of CDC's Validation Study are known. If TCDD testing is to be done, is a whole unit of blood necessary--if willing to accept some cut-off level (e.g. 20 ppt) less blood may be required. Also, if TCDD testing is to be done, consideration should be given to using a sample of Vietnam and non-Vietnam veterans--based on the results of a sample, a decision could be made about testing other participants.

2. Serum TCDD measurements are to be used as the measure of exposure for both the Reproductive Outcomes Study and the Post Traumatic Stress Disorder Study. Apparently about 550 serum analyses will be needed for these two studies combined. The current proposal does not involve flying the participants to a centralized collection center but rather using local Red Cross Centers on contract. These approximately 550 women will be located all over

the United States and the Red Cross is not even present in every state, so obtaining the samples solely in this manner will not be possible. A very large number (>100) of Red Cross contracts will be involved to obtain blood on persons near a Red Cross Center under the current plan. The use of at least regional Red Cross Centers would be a marked improvement and the quality of sample acquisition would be significantly higher if only a few (even one) Red Cross Center(s) were used.

3. The cost of the serum 2,3,7,8-TCDD measurement should be noted to be $1000 apiece. Currently the protocol states that EHLS is the only lab in the U.S. that can perform the measurements, but clearance for such measurements at EHLS has not been obtained. Similarly, has the American Red Cross been approached as to their willingness to participate in this study?

E. Operational and Other Issues

1. The protocol anticipates a fair amount of dependence on both interviews and military records. What are the limitations of these data in terms of the questions addressed (e.g., ascertainment of spontaneous abortions by history)?.

2. The authors do not provide information on how they propose to address the issue of name changes in female veterans and the difficulties this might cause in locating these veterans.

3. The operational aspects of the pediatric examination component are not clearly described. Has the Ranch Hand Study been successful in this area? What end points will be looked at and analyzed?

4. The choice of conditions to be validated might be expanded to include some conditions which have been suggested to be associated with TCDD exposure--e.g. skin conditions (chloracne, hyperpigmentation, etc.), liver disorders including prophyria, peripheral neuropathy, immunologic deficits.

5. Quality control of the physical and routine laboratory examinations must be assured.

6. Has adequate effort been made to insure that the medical records and pathology slides will be reviewed in a blinded manner?

7. What efforts are being made to insure quality assurance and quality control of hormone blood testing?

Vernon N. Houk, M.D.
Assistant Surgeon General