Item ID Number	01852
Author	McKinlay, Sonja M.
Corporate Author	New England Research Institute, Inc., Watertown, Mass
Report/Article Title	Women's Vietnam Veterans Health Study Protocol Development, Summary Report of Expert Panel Review, Deliverable E
Journal/Book Title	
Year	0000
Month/Day	
Color	☐
Number of Images	25
Description Notes	Contract No. V101(93)P-1138

WOMEN'S VIETNAM VETERANS HEALTH STUDY

PROTOCOL DEVELOPMENT

CONTRACT NO. V101(93)P-1138

SUMMARY REPORT OF EXPERT PANEL REVIEW

DELIVERABLE E

SUBMITTED BY NEW ENGLAND RESEARCH INSTITUTE, INC.

PRINCIPAL INVESTIGATOR

SONJA M. MCKINLAY, Ph.D.

NEW ENGLAND RESEARCH INSTITUTE, INC.

42 Pleasant Street
Watertown, Massachusetts 02172
(617) 923-7747

TABLE OF CONTENTS

INTRODUCTION

A key task under the current contract was the formation of an Expert Panel of Consultants who would review the following final products:

- Literature Review;
- Study Design; and
- Questionnaire

As proposed, NERI expanded this mandated function to include review of preliminary drafts and participation in a one day discussion including prepared written comments on specific assignments. Finally, the Technical Representative (Dr. H. Kang) requested written affidavits indicating acceptance, by panel members, of the final products.

The following sections include a summary of input on the Literature Review (Section 1), a summary of input on the Study Design (Section 2) and on the Questionnaire (Section 3). A final section lists the panel members and their areas of expertise, includes copies of the panel assignments for the one day review and affidavits accepting the Study Design and Questionnaire submitted to the VA as final products.

1. LITERATURE REVIEW

A draft of the Literature Review was sent to panel members for review and verbal or written comments in January, 1987.

Apart from clarification of some ambiguous statements, the primary input was in the form of additional key references which were very recently published or in press.

This input was exactly what was desired. Panel members were clearly at the forefront of important areas of research, including phenoxy herbicides, nursing exposures and reproductive toxicology in particular.

Interestingly, one important occupational exposure not included in the original review and not raised by the panel was hexachlorophene - a major occupational exposure for nurses in the study period, which also has TCDD as a contaminant in its manufacture. This exposure was identified through two sources: a senior staff member at CDC (personal communication) and the updated report of the NIOSH Occupational Dioxin Registry (Fingerhut et al, 1985). A review of this potentially confounding occupational exposure is included in the final products as an Addendum to the Literature Review.

2. STUDY DESIGN

Substantial input was obtained from panel members in the following forms:

- written comments submitted for the one day meeting;
- verbal comments at the meeting; and
- verbal or written comments on a subsequently revised document.

For clarity, comments and decisions will be summarized under the following sub-headings:

- Basic cohort design and sub-studies;
- VE exposure components;
- Population definintion and sample size;
- General health outcomes; and
- Reproductive outcomes.

2.1 COHORT DESIGN AND SUB-STUDIES

(a) Cancer Case/Control Study

The originally proposed case/control study of cancers was deleted from the study design after the following comments and issues were reviewed and discussed:

1. The inclusion of all cancers was considered insensitive to TCDD exposure. Reference was made to the SEER (NCI) data which included better incidence data with which to estimate expected numbers of relevant cancers (Soft Tissue Sarcoma, Hodgkin's Disease and Non-Hodgkin's Lymphoma).

2. Risk factors (confounders) would differ for each cancer site.

3. The inclusion of cancer cases and controls from Cohort B, which will not have been exposed to TCDD (at least to the same degree) was considered non-informational, given the aim of this substudy to investigate associations between cancer and TCDD exposure.

4. Debilitation and therapy in cancer cases will affect both immune status (one of the intervening variables to be measured) and body fat available for TCDD determinations.

As suggested by panel members, the expected number of STS, HD and NHL cancer cases combined was subsequently estimated as 30 for both cohorts combined, using SEER data (NCI, 1987). These numbers were too small for a case/control study to be feasible.

(b) Congenital Abnormality Case/Control Study

The case/control study of congenital abnormalities was generally well-received as an important sub-study. The following issues were raised in its design:

1. The study should be restricted to Cohort A (VE-exposed subjects).

2. The detection of abnormality in aborted fetuses was considered problematic - not all hospital records would include sufficient details. Rather, panel members recommended including only abnormalities detected in live born offspring.

3. The suggestion was made during discussion to include spontaneous abortions as the other adverse reproductive outcome for this case/control study. This last suggestion was further modified to include only multiple abortions (2+) with no clear cause, as otherwise numbers for this sub-study would have been too large.

4. The suggestion was made to use information on the half-life of TCDD in adipose tissue (if available) to estimate TCDD body burden at conception.

(c) Nurses Sub-Study

Because nurses are expected to comprise at least 85% of the Cohorts, this sub-study was seen by panel members as perhaps the main study. A lively discussion developed out of which a consensus was obtained that emphasis should be on as homogeneous a group as possible.

The decision was therefore made to restrict this sub-study to Army nurses from both cohorts.

Further discussion centered on the desirability of a civilian control group in order to unconfound, as much as possible, the basic nursing occupational exposures. This was a major concern given that nurses in Cohort B were also exposed to unique stresses of caring for wounded Vietnam veterans. Subsequent discussions with Dr. Kang on this issue of a third control group produced the alternative proposal from Dr. Kang to include Air Force nurses in Cohort B as a third, relatively unexposed group. This suggestion was also incorporated in the final design.

(d) PTSD Sub-Study

There was discussion at the one day meeting concerning the possibility of investigating PTSD, its relation to neuro-behavioral functioning and TCDD exposure. The final PTSD sub-study resulted from this discussion.

(e) Validation Sub-Studies

The following recommendations were made concerning validation of key outcomes:

- It was strongly recommended that pathology slides be obtained to validate at least the following cancers - STS, HD, NHL.

- Early amenorrhea (< 40 years) should be verified with FSH levels.

- Records should be obtained (or at least releases to obtain them) for all major diagnoses, even if all are not verified immediately. Members of the panel also felt that pediatric examination of all congenital abnormalities may not be necessary. Rather record verification with examination of a small sub-sample may be sufficient.

- The operative note is the most important source for verifying endometrial pathology, rather than the pathology report and should be obtained, if possible. Results of pelvic examination were inadequate validation evidence for endometriosis.

- Pathology reports should be obtained for all induced abortions.

(f) Mortality Study

An originally proposed analytic study of deaths in both cohorts was considered not very informative as outlined and somewhat duplicative of the VA Mortality Study in progress. At the same time, it was generally considered essential to include deaths as outcomes in as many analyses as possible, to minimize bias. The final approach proposed involves analysis of primary data sets with and without deceased cohort members included.

2.2 VIETNAM EXPERIENCE (VE) EXPOSURE COMPONENTS

There was protracted discussion of VE exposure components and the following points were made (and incorporated in revisions):

- Exposure to TCDD and to phenoxy herbicides should be kept distinct, conceptually as there are no satisfactory direct measures of phenoxy herbicide exposure;

- Emphasis should be on VE as a whole and exposure to phenoxy herbicides (TCDD);

- An attempt should be made to obtain some data on use of insect repellents, even if detailed insecticide exposure is not available; and

- The panel members were intrigued with the availability of workload data in the Chief Nurses' Reports and encouraged the extraction and use of such information for the final study.

All of these recommendations were incorporated into the final Study Design.

2.3 POPULATION DEFINITION AND SAMPLE SIZES

The panel considered that, given the difficulties in obtaining lists with current contact information, use of the VA Mortality Study lists was an acceptable compromise. At the same time the panel members urged that:

1. The sampling design used in compiling the lists be documented;

2. The adequacy (coverage) of the lists (especially for Cohort B) be verified during the Phase II study.

Both of these recommendations were incorporated into the final design.

With respect to sample size, there was some discussion concerning whether Cohort A constituted a sample or a population. If the emphasis is on generalization to women Vietnam veterans only, then Cohort A is a population and no sampling variation is estimable for this cohort. If the emphasis is on women Vietnam veterans as a sample of women potentially exposed to VE (or its equivalent) then Cohort A is a sample. The consensus was that Cohort A should be considered as a sample and smallest detectable relative risks calculated on this assumption. This consensus is reflected in the final study design.

2.4 GENERAL HEALTH OUTCOMES

All the proposed health outcomes were reviewed by the panel and the following recommendations made:

- Those cancers likely to be misclassified as organ-specific when they are, in fact, STS should be included for record review; and

- There should be emphasis on Post Traumatic Shock Disorder (PTSD) and selected other health outcomes.

These were incorporated into the final design.

2.5 REPRODUCTIVE OUTCOMES

Following panel recommendations this class of outcomes was sub-divided as follows:

1. Reproductive Function: menstrual (ovulatory) function without conception, including measures of infertility, risk factors for anovulatory or irregular cycles, presence of pelvic infection (including sexually transmitted disesases - STD's - Tuberculosis of the Pelvis and other Pelvic Inflammatory Disease) and prolonged periods of amenorrhea.

2. Adverse Reproductive Outcome: this includes selected adverse outcomes of conception (major congenital abnormality, multiple spontaneous abortion).

The panel also recommended that emphasis be given to adverse reproductive function and conception outcomes in the study.

3. QUESTIONNAIRE

The Expert Panel had several suggestions for question content and wording. Most of them were in the areas of reproductive function and outcome (Section 3.1) with some additional miscellaneous suggestions (Section 3.2).

3.1 REPRODUCTIVE FUNCTION/OUTCOME

The following specific suggestions were made:

(a) Emphasis was placed on obtaining menstrual histories from menarche onwards, to include an assessment of menstrual function (cycle length, regularity etc.) before the exposure period.

(b) Certain menstrual symptoms/events are good predictors of ovulatory cycles. In particular, ovulating women are more likely to experience cramps or other pre-menstrual symptoms, while clotting is associated with anovulatory cycles.

(c) Benign breast and uterine pathology are more likely in anovulatory women and should be recorded under diagnoses as another measure of probable reduced fertility.

(d) Because this is a retrospective longitudinal study, rather than cross-sectional, the definition of infertility used on the National Center for Health Statistics National Survey of Family Growth had to be carefully adapted, using a different set of questions. It was also recommended that subjects be asked directly if they had difficulty conceiving for

a period of at least twelve months of attempting to conceive.

(e) Pregnancy complications (toxemia etc.) could be omitted from the pregnancy history.

(f) Birth weight and length of gestation should be included as outcome variables.

(g) A standard list of occupational exposures for adverse reproductive outcomes should be included.

These suggestions were reviewed and revisions made to the questionnaire to accommodate them.

3.2 MISCELLANEOUS SUGGESTIONS

An excellent suggestion which was incorporated into the questionnaire was the addition of questions on knowledge of and access to VA services offered to women veterans. The motivation was to help diffuse the focus of the study and was in keeping with this being a Women Veterans Health Study.

A further suggestion which was considered carefully was the possibility of sending out to subjects a self-administered questionnaire (SAQ) on some of the standard histories (pregnancy, contraceptive, military, occcupational, marital) before the telephone interview. This would prepare the subject and give her a framework within which to refresh her memory.

After reviewing pre-testing experience, it was decided not to use a SAQ before the telephone interview for the following reasons:

1. subjects were able to remember and complete the histories in a timely fashion; and

2. there was concern that subjects would share this information with other veterans eligible for study, before they were interviewed, increasing the potential for either non-response and/or bias in prepared answers later in the study.

TABLE 3.3

EXPERT PANEL COMPOSITION

Name[a]	Affiliation	Areas of Expertise (Reference No.)[b]
R. Clapp, MPH*	Director, Massachusetts Cancer Registry Mass. Dept. Health Boston, MA	Agent Orange Exposure Vietnam Veterans (Mass.) Study Occupational/Environmental Exposure Studies
T. Colton, ScD	School of Public Health Boston University Boston, MA	Epidemiologic Methods and Statistical Analysis Agent Orange/Vietnam Veterans Studies
A. Haney, MD	Dept. Reproductive Medicine Duke University Durham, NC	Medical Management of Reproductive Health Problems Reproductive Epidemiology
M. Hatch, PhD	School of Public Health Columbia University New York, NY	Reproductive Epidemiology
D. Mattison, MD	Dept. of Ob/Gyn Div. Reproductive Pharm. and Toxicology University of Arkansas Little Rock, AK	Reproductive Toxicology
D. Ozonoff, MD, MPH	School of Public Health Boston University Boston, MA	Occupational/Environmental Epidemiology
Z. Stein, MA, MB, BCh	Director, Epidemiology of Brain Disorders Rsch NY State Psychiatric Inst Dept. Epidemiology Columbia University New York, NY	Psychiatric Epidemiology Agent Orange/Exposure Studies

WOMEN VIETNAM VETERANS HEALTH STUDY

PROTOCOL DEVELOPMENT

CONTRACT NO. V101(93)P-1138

EXPERT PANEL REVIEW

ASSIGNMENT REVIEW

Area for Review	Primary Reviewer	Secondary Reviewer
1. Phenoxy Herbicide Exposure (definition and measurement)	R. Clapp	D. Mattison D. Ozonoff
2. Other VE Exposure (definition and measurement)	M. Hatch	A. Haney D. Ozonoff
3. General (incl. Mental) Health Outcomes (definition and measurement)	Z. Stein	M. Hatch D. Ozonoff
4. Reproductive Health Outcomes (definition and measurement)	A. Haney	D. Mattison M. Hatch
5. Reproductive Outcomes (definition and measurement)	D. Mattison	A. Haney
6. Design Approach and Sample Size	T. Colton	D. Ozonoff R. Clapp
7. Population Definition	R. Clapp	T. Colton Z. Stein

EXPERT PANEL AFFIDAVITS

NEW ENGLAND RESEARCH INSTITUTE, INC.

I have reviewed the final study design and questionnaire for the proposed Women's Vietnam Veterans Health Study and my recommendation is as follows (check one option and add any comments):

__✓__ I approve the design and questionnaire as presented, with no further modifications. Any concerns have been clarified by telephone.

____ I do not approve the design and questionnaire as presented. It will require the following revisions to meet with my approval:

Richard W. Clapp — NAME
Richard W Clapp — SIGNATURE
7/2/87 — DATE

42 Pleasant Street
Watertown, Massachusetts 02172
(617) 923-7747

NEW ENGLAND RESEARCH INSTITUTE, INC.

I have reviewed the final study design and questionnaire for the proposed Women's Vietnam Veterans Health Study and my recommendation is as follows (check one option and add any comments):

✓ I approve the design and questionnaire as presented, with no further modifications. Any concerns have been clarified by telephone.

___ I do not approve the design and questionnaire as presented. It will require the following revisions to meet with my approval:

Although, in the limited time available I have not studied the protocol in detail, my scanning of it indicates that you have been most responsive to my comments on previous drafts.

THEODORE COLTON — Theodore Colton — 7/14/87

NAME SIGNATURE DATE

42 Pleasant Street
Watertown, Massachusetts 02172
(617) 923-7747

NEW ENGLAND RESEARCH INSTITUTE, INC.

I have reviewed the final study design and questionnaire for the proposed Women's Vietnam Veterans Health Study and my recommendation is as follows (check one option and add any comments):

_X_ I approve the design and questionnaire as presented, with no further modifications. Any concerns have been clarified by telephone.

____ I do not approve the design and questionnaire as presented. It will require the following revisions to meet with my approval:

A. F. HANEY
NAME

A Haney
SIGNATURE

6/26/87
DATE

42 Pleasant Street
Watertown, Massachusetts 02172
(617) 923-7747

NEW ENGLAND RESEARCH INSTITUTE, INC.

I have reviewed the final study design and questionnaire for the proposed Women's Vietnam Veterans Health Study and my recommendation is as follows (check one option and add any comments):

✓ I approve the design and questionnaire as presented, with no further modifications. Any concerns have been clarified by telephone.

____ I do not approve the design and questionnaire as presented. It will require the following revisions to meet with my approval:

Maureen Hatch — NAME

Maureen C. Hatch — SIGNATURE

6/23/87 — DATE

42 Pleasant Street
Watertown, Massachusetts 02172
(617) 923-7747

NEW ENGLAND RESEARCH INSTITUTE, INC.

I have reviewed the final study design and questionnaire for the proposed Women's Vietnam Veterans Health Study and my recommendation is as follows (check one option and add any comments):

✓ I approve the design and questionnaire as presented, with no further modifications. Any concerns have been clarified by telephone.

____ I do not approve the design and questionnaire as presented. It will require the following revisions to meet with my approval:

Dr. Donald Mattison	[signature]	7/20/89
NAME	SIGNATURE	DATE

42 Pleasant Street
Watertown, Massachusetts 02172
(617) 923-7747

NEW ENGLAND RESEARCH INSTITUTE, INC.

I have reviewed the final study design and questionnaire for the proposed Women's Vietnam Veterans Health Study and my recommendation is as follows (check one option and add any comments):

✓ I approve the design and questionnaire as presented, with no further modifications. Any concerns have been clarified by telephone.

____ I do not approve the design and questionnaire as presented. It will require the following revisions to meet with my approval:

David Cizonff	[signature]	7/16/87
NAME	SIGNATURE	DATE

42 Pleasant Street
Watertown, Massachusetts 02172
(617) 923-7747

NEW ENGLAND RESEARCH INSTITUTE, INC.

I have reviewed the final study design and questionnaire for the proposed Women's Vietnam Veterans Health Study and my recommendation is as follows (check one option and add any comments):

X I approve the design and questionnaire as presented, with no further modifications. Any concerns have been clarified by telephone.

___ I do not approve the design and questionnaire as presented. It will require the following revisions to meet with my approval:

Zena Stein, M.B., B.Ch.
NAME

SIGNATURE

24 June, 1987
DATE

42 Pleasant Street
Watertown, Massachusetts 02172
(617) 923-7747