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WOMEN VIETNAM VETERANS HEALTH STUDY

PROTOCOL DEVELOPMENT

CONTRACT NO. V101(93)P-1138

STUDY DESIGN AND PROTOCOL

DELIVERABLE D

SUBMITTED BY NEW ENGLAND RESEARCH INSTITUTE

PRINCIPAL INVESTIGATOR

SONJA M. MCKINLAY, PH.D

NEW ENGLAND RESEARCH INSTITUTE, INC.

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

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INTRODUCTION

This document describes and justifies a proposed design and protocol for the study of women Vietnam veterans. Following a brief overview of the background to this study (Section 1), the general approach is outlined and justified (Section 2). Section 3 then presents the major variables for exposure, outcome and confounding effects, including a discussion of measurement approaches. The hypotheses relating these variables are specified in Section 4, while Section 5 describes and justifies the populations and sample sizes selected for the study. Section 6 then documents the adequacy of the proposed sample sizes to detect and estimate the smallest Relative Risks corresponding to each hypothesis. Section 7 outlines the proposed data collection strategy, including quality control and data management requirements. Section 8 outlines the analytic approaches required to address the hypotheses specified in Section 4, while Section 9 presents human subjects protection requirements, in terms of informed consent and confidentiality. Section 10 proposes a schedule for implementing the study, including set up of data management systems, staff recruitment and training, data collection, processing and analysis as well as estimated effort and project organization. A final Section 11 outlines some unresolved issues as of June, 1987 which may affect aspects of this design and protocol.

1. BACKGROUND

A comprehensive literature review, conducted in preparation for this study, has indicated clearly that there is a need for this congressionally mandated investigation of the impact of the Vietnam Experience (VE) for women in the military. Women have served in other wars this century, primarily as nurses. In this role they have been wounded and killed by enemy fire, lived under similar conditions to combat troops and have been held as prisoners of war. Yet no study of the impact of this experience on these women has yet been conducted. The Vietnam Experience was similar to prior war experiences for nurses with respect to: risk of injury or death; exposure to tropical diseases and the prophylactics or preventatives to combat them (drugs, repellent sprays, insecticides); difficult, primitive living and working conditions; and the lack of public acceptance of the valid contribution of such women to the war effort. The Vietnam Experience was (at least potentially) different from prior war situations in: the use of phenoxy herbicides as defoliants; lack of a definable front-line and constant presence of the Viet Cong in or near U.S. installations; lack of a clearly articulated rationale for the presence of U.S. troops in Vietnam and the concommitant lack of public support in the U.S.; and the fact that this largely guerilla action fought over several years, was never officially declared a war, which was won or lost.

Exposure to any of these aspects of the Vietnam conflict (singly or in combination) constitutes a unique "Vietnam Experience," the effects of which, in terms of subsequent physical and mental health are to be assessed in this study.

2. STUDY APPROACH

2.1 DESCRIPTION OF THE STUDY DESIGN

Four components are proposed for the study design. They are:

- Historical Cohort Study;
- Case/Control Study of Reproductive Outcomes;
- Sub-study of Post Traumatic Stress Disorder (PTSD); and
- Validation Sub-studies.

Each of these is described in the following subsections.

2.1.1 Historical Cohort Study

The proposed study has a basic historical cohort design with two cohorts, one exposed to the Vietnam Experience (Cohort A) and one not exposed (Cohort B). This design is similar to a prospective observational study, in that comparison groups are defined on exposure, but both exposure and outcome occur before the point of data collection. For each cohort, several outcomes will be included, in the areas of general health, reproductive function (normal cyclic function in the absence of conception) and reproductive outcomes. The exact variables proposed (exposure, outcome

and potential confounding factors) are described in detail in the following section.

Included in Cohort A will be all women in the Armed Services (Army, Air Force, Navy and Marines) who served in Vietnam (See Section 5 below for a definition). This group consisted primarily of nurses (approximately 85%), other line officers and some enlisted personnel (about 15%, combined). An equivalent sample of women in the Armed Services who did not serve in Vietnam, frequency matched on service, and occupation with Cohort A will constitute Cohort B. These Vietnam-era veterans were eligible for Vietnam service but did not actually serve in Vietnam.

Variations to this basic cohort study are also proposed, defined by the inclusion or exclusion of selected cohort members. These variations will produce four primary data sets for analysis as described below.

Data Set 1 (Entire Cohort).

This will comprise all eligible members of Cohorts A and B, including those who died subsequent to the exposure period of service on which eligibility is defined. Deceased participants (approximately 100 expected in each cohort) are included in this data set for analyses of outcomes which could result in death (e.g., heart disease, selected cancers, attempted suicide, alcohol consumption). Because key exposure and confounding information may not be obtainable from proxy interviews for deceased participants, it is recognized that this data set will be used for a limited range of analyses.

Data Set 2 (Entire Live Cohort)

This data set is equivalent to Data Set 1, but excludes deceased members. Because information is expected to be complete for this set, this is the data set on which the majority of analyses addressing the overall impact of VE on military women will be based.

Data Set 3 (Nurses Sub-Study)

Although this is a study assessing the effects of VE in women veterans the cohorts are very skewed in terms of VE exposure, both by service and by occupation. Approximately 80% of all women in Cohort A served in the Army and about 85% of these were nurses of officer rank. In other words, about 70% of all women Vietnam veterans were Army nurses.

Other line officers and enlisted personnel, in all the Services, were few in number and primarily in support occupations in or near Ho Chi Minh City (formerly Saigon). Their exposure to the various elements of VE was, therefore different from nurses in field hospitals.

Nurses in the Air Force and Navy were distinct from Army nurses in at least the following major respects:

- These nurses were more likely to be career military and therefore older and more likely to remain in active service for several years after the war;
- Unlike Army nurses, these women had to serve a full tour of duty (one year) before overseas assignment;
- Navy nurses worked in stable teams and were not exposed to phenoxy herbicides or combat, except at

the on-shore base at Da Nang, relatively late in the period;

- Air Force nurses were minimally exposed to phenoxy herbicides and to the trauma of dealing with major wounds, as they were on evacuation flights, but worked essentially alone with considerable responsibility.

Army nurses were assigned individually to hospital units on an as needed basis, were typically within one year of graduation from nursing school (except for the relatively few senior officers, mostly veterans of World War II or the Korean Conflict), were least likely to remain in a military career, and were most exposed to "in country" combat areas and other related trauma. This is, therefore, a relatively homogeneous group with respect to age, education and VE exposure and comprises the majority of Cohort A.

The equivalent group in Cohort B was variably exposed to the trauma of nursing wounded veterans, who were evacuated from Vietnam, usually within a few days. In contrast to their Vietnam veteran counterparts, they were exposed to the extraordinary nursing demands of major sepsis of all wounds and to the emotional problems of readjustment experienced by the wounded veterans. It is important to note that this unique nursing exposure was also experienced by many Vietnam veteran nurses from Cohort A, either before or after their Vietnam tour of duty and is therefore not unique to Cohort B members.

Because of the varying degrees of exposure to nursing of the wounded veterans experienced by nurses in Cohort B, it is therefore proposed to include a third cohort of nurses not exposed to <u>either</u> VE <u>or</u> the nursing of recovering

wounded veterans. The cohort proposed is the subset of Air Force nurses included in Cohort B, who did not nurse wounded veterans and were not Flight nurses. This sub-group will include almost all Air Force nurses in the cohort as comparatively few Air Force personnel were wounded and returned to CONUS Air Force hospitals. Moreover, any wounded Air Force veterans were nursed separately in Casualty Staging Units, primarily by corpsmen. Nurses had little contact with these patients in the Air Force CONUS hospitals until they were relatively recovered.

This data set will therefore consist of three comparison cohorts (including subsequently deceased members):

1. Vietnam veteran Army Nurses only from Cohort A
2. Vietnam-era Army Nurses from Cohort B
3. Vietnam-era Air Force Nurses (excluding those who nursed wounded veterans), from Cohort B.

Some age and/or nursing service adjustments in either sampling for the third cohort or analysis will be required to reduce any age and nursing service differences between Army and Air Force personnel.

Data Set 4 (Live Nurses Sub-Study)

This data set is equivalent to Data Set 3 but excludes those nurses who died after the exposure period (as in Data Set 2).

This data set will be the basis for most of the analyses addressing the effects of combat-related stress.

The Air Force nurses will serve as a control group, subject to the routine stresses of a military nurse. The Cohort B Army nurses will serve as an intermediate group variably exposed to additional stresses of caring for wounded veterans during recovery. The Cohort A Army nurses were all exposed to VE and variably to the caring of wounded veterans during recovery.

2.1.2 Case/Control Study of Reproductive Outcomes

An increased rate of adverse reproductive outcomes (including congenital abnormality and spontaneous abortion) has been associated with exposure to the dioxin TCDD in animals, and with exposure to phenoxy herbicides and/or to TCDD (the highly toxic contaminant in the production of the phenoxy herbicide 2,4,5-T and hexachlorophene) in humans (see Literature Review). Less than one percent of live births in a general population will produce a major diagnosed congenital abnormality, while multiple spontaneous abortions are likely to occur in less than 3% of fertile women given a 15% rate for a single conception (Kline et al, 1981). Spontaneous abortion is defined here as loss in less than 20 weeks gestation. These reproductive outcomes are, therefore, relatively rare.

This sub-study will investigate the set of hypotheses relating TCDD exposure to subsequent adverse reproductive outcomes: that rates of major congenital malformation and multiple spontaneous abortion will be higher in the exposed cohort (H_{PF}, H_{PL} in Table 1, Section 4, below).

Cases will be defined as all women (from Cohort A) who are alive at the time of study and either report at least one pregnancy resulting in a congenital abnormality; or

report two or more spontaneous abortions not clearly attributable to an identified cause. Excluded causes are:

- Unequivocal karyotypic abnormality;
- Uterine abnormality (fibroid tumors; other intra-uterine pathology; congenital, Mullerian anomalies).

All remaining causes of repeat spontaneous abortion will be included as cases. Possible causes included in this group are: Lupus anticoagulant, immunologic abnormalities, luteal phase insufficiency, hypothyroid abnormality, DES exposure, maternal diabetes, and recurrent infection.

Controls also from Cohort A, will be pair-matched on the following variables:

- maternal age at birth for the index pregnancy resulting in abnormality (or for the first such pregnancy in the case of multiple abnormalities) or maternal age at first spontaneous abortion; and

- order of the index birth/pregnancy (first or subsequent);

For example, if a participant has a major abnormality in her second child, born when she was 28, then an ideally matched control will have at least two live children, with the second child born when she was also 28.

In practice, an age match within five year age ranges will be adequate for women aged < 35 years at the time of the index birth or fetal loss. For women aged ≥ 35 at the event, matches will be sought within 2 year ranges to accommodate the rapidly escalating risk of a fetal

abnormality beyond this age (NCHS, 1978). Age ranges within which a match will be defined are:

15 - 19 years at last birthday
20 - 24
25 - 29
30 - 34
35 - 36
37 - 38
39 - 40
41 - 42
43 - 44 etc.

Birth order is included as the other variable known to affect the rate of abnormality (NCHS, 1978). The major difference in rates is between first and subsequent live births. Matching will be on first or subsequent birth with exact matching on birth order only if the pool of potential matches is sufficient. There will be no additional matching for cases of spontaneous abortion.

Matching on parity, gravidity or any other potential confounder, such as paternal exposure to TCDD is not considered, to avoid over-matching and the problems of unmatchables (McKinlay, 1974; Schlesselman, 1982).

Measurements will include blood (serum) TCDD determinations on all cases and controls. Currently, the half life of TCDD in human tissue is being investigated on the Ranch Hand II Study. Depending on the results of this investigation, it may be possible to extrapolate from current TCDD body burdens to the TCDD level at the date of the index pregnancy to provide an estimate of TCDD exposure at the time of conception.

2.1.3 Sub-Study of Post Traumatic Stress Disorder

The extent to which PTSD may be related to other neurobehavioral problems and/or phenoxy herbicide exposure is not clear from research to date, although PTSD has been related to war stress among male veterans of the Vietnam conflict as well as of prior wars, albeit under other labels (see Literature Review). A sub-study is therefore proposed, within Data Set 4, of live Army nurses, to investigate these relationships. Equal samples of Army nurses will be randomly selected from the following five groups:

1. Cohort A, classified with acute PTSD from the quesionnaire;
2. Cohort A, classified with delayed PTSD from the questionnaire;
3. Cohort A, classified with chronic PTSD from the questionnaire;
4. Cohort A, with no evidence of PTSD from the questionnaire; and
5. Cohort B, with no evidence of PTSD from the questionnaire;

Each will be eligible for an extensive battery of memory and related neurobehavioral tests as well as TCDD determinations.

NO justification

Army nurses are proposed as subjects from Cohorts A and B because of their uniformly high level of educational attainment (required for several tests) as well as for their relative homogeneity of socio-economic background. This group is also, a priori, more likely to be exposed to phenoxy herbicides, hexachlorophene and/or war-related stressors than other women veterans.

2.1.4 Validation Sub-Studies

Because the majority of the data collected will be by interview (or self-administered questionnaire), and therefore self-reported, several key items will require independent validation. This is particularly true of items relating to the index service period (up to 24 years earlier, assuming data collection in 1988-89). The following validation studies are proposed, based on currently available knowledge. One or more may be deleted or replaced, depending on the results of on-going research. Six such studies are briefly described below.

(a) Reproductive Outcomes

Both reported congenital abnormalities and reported multiple spontaneous abortions will be verified, wherever possible, by independent (blind) abstraction of medical records and pathology reports. Participants will be asked to identify hospital or physician records most likely to document the abnormality, diagnosis or spontaneous abortion, and written releases will be obtained for future acquisition of the record.

This will be attempted for all cases in the case/control study of reproductive outcomes. It is recognized that access may be refused by some participants, while others may not remember where records exist. For still other cases, the records may no longer be available (a hospital may have closed or may no longer retain records; a physician may have died, moved or destroyed old records).

Additionally, for all live, accessible offspring, a pediatric examination is proposed, following the protocol used on the Ranch Hand Study, for both cases and controls in the case/control study of reproductive outcomes (see

Appendix). This examination will be performed by a single pediatric neurologist or physician qualified in an equivalent specialty and trained to perform the examination blind to the participant's self-reported status. This is considered feasible, given the relatively small number of families involved, over a two year period.

If there is 90% agreement or better between the participant's self-report and the examination or medical record documentation (where available), then all cases will be included based on self-report. If the agreement is less than 90%, then only those cases verified by at least one independent data source will be included as cases.

(b) Validation of Selected Disease Diagnoses

The following diagnoses will be verified by independent (blind) abstraction of appropriate medical records:

- soft-tissue sarcomas (STS), liver cancers, non-Hodgkin's lymphoma, Hodgkin's Disease and any other cancer of an internal organ likely to be misclassified when it is actually STS (Percy et al, 1981). For each of these cancers, copies of the hospital record, pathology report and the slides themselves will be requested for validation, following protocols already developed (See Appendix). Only verified cases will be included.

- myocardial infarction, sudden death, cerebrovascular accident. For these outcomes, medical records will be requested, including ECG tracings, CK (and CK-MB) enzyme determinations. In the case of sudden death (which generally occurs out of hospital) an interview with next-of-kin may be required. Protocols for this validation have already been well

developed by projects funded by the National Heart, Lung, and Blood Institute (see Appendix). Only verified cases will be included.

- randomly-selected sample of reported cases of breast cancer, benign breast tumors or cysts, cervical or endometrial uterine cancer, endometriosis, fibroids or ovarian tumor (benign, malignant or other cyst). Agreement between self-report and medical record in this sample of 90% or better will result in acceptance of all self-reported cases. If a lower rate of agreement is obtained, then the possibility will be considered, funds permitting, of verifying all cases and including only verified cases in analysis. Surgical notes will also be used to verify endometriosis, where available.

- randomly selected sample of reported cases of depression or related psychiatric diagnoses (including PTSD). For a sample of these self-reported cases, records will be obtained from a hospital, physician or psychologist making the diagnosis. As above, if agreement is 90% or better, all self-reports will be included. If less than 90%, all cases may require validation for inclusion in analysis.

Even for those diagnoses to be sampled for verification, it is proposed that written release (and possibly a copy of the record itself) be obtained for all reported diagnoses, in anticipation of possible further study. Also, where regular hospital records may no longer be available, key laboratory reports (pathology, ECG, enzymes, etc.) may be accessible in the original, which is usually independently filed by the department or laboratory responsible, and retained over longer periods.

(c) Validation of Other Health Events

Apart from key diagnoses, certain events and surgical procedures will also require validation.

- Hysterectomy/Oopherectomy: medical records and (where available) pathology reports will be reviewed for a sample of surgeries reported to involve removal of the uterus, with or without removal of at least one ovary. As above, the 90% agreement criterion will be used to determine inclusion of cases.
- Prolonged amenorrhea (12 consecutive months) with no obvious cause (e.g., pregnancy and/or lactation) in women under 40 years will result in a check of hormone levels for all cases, especially gonadotropins from two venous blood samples of at least 5 ml of whole blood each, drawn 20-30 minutes apart, using a standardized kit, and obtained between 7:00 am and 10:00 am. Elevation of FSH in particular ($\geq$ 30 mIU) is an indicator of permanent ovarian failure (as in natural menopause).

- Attempted Suicide will be verified from hospital records, where available.

- Tropical Diseases will be verified for a sample of nurses in Cohort A by comparing with the Chief Nurse's Monthly Report (where available). The 90% criterion for inclusion of all self-reports will be used.

(d) Validation of Phenoxy Herbicide Exposure

Based on the pending results of the CDC validation studies, an index of exposure may be constructed on the basis of the "Service Herbs" tapes for all Vietnam veterans in Cohort A. Minimally exposed groups include Navy and Air Force Nurses as well as line officers and enlisted personnel who were based primarily in or near Ho Chi Minh City. Most vulnerable to exposure were Army nurses. If an index is constructed for potential analysis, then the subgroups on which TCDD body burden is determined will provide validation of that index. The criterion for determining validity (magnitude of correlation) will be determined using CDC results.

(e) Validation of VA Lists for Cohorts A and B (Data Set 1)

The completeness of these lists to be used as the sample list for the proposed study (see Section 5 below), will be determined by asking each participant to name one other woman serving with them:

- For Cohort A, during their (longest) Vietnam tour; and

- For Cohort B, during a sampled tour of duty in the exposure period.

This name will then be checked against the Cohort A list (for Cohort A) or against the appropriate morning report (for the Army), computerized personnel files (Air Force, Navy and Marines), and/or the Cohort B listing (for Cohort B).

This approach is a simple capture-recapture experiment, with the list of names reported by participants as the initial "marked" sample, and the lists within which these names should appear as the second "mixed" sample. List completeness will be estimated directly as the proportion of the "marked" names successfully matched (see, for example, Seber, 1973). The success of this estimation method will of course depend on the memories of participants, completeness of existing lists (such as morning reports) and the availability of sufficient information on each "marked" sample name to ensure an accurate match. Only one name will be solicited to reduce the impact of recall bias among subjects on the probability of name selection.

This important validation study is proposed as a substitute for the originally specified Pilot Study in the Planning Contract No. V101(93)P-1138. This task was deleted from the initial contract because of problems of feasibility and overlap with activities in the concurrent mortality study being conducted by the VA.

2.2 RATIONALE FOR THE PROPOSED DESIGN

This section reviews the issues considered in selecting the four components of the study design described above.

2.2.1 Historical Cohort Design

This design has already been used in CDC's major VE exposure study which is on-going (CDC, 1987). It is the most appropriate design for a study of women veterans as VE (the primary exposure) is clearly defined but the important

outcomes are uncertain. It is this uncertainty of several health and reproductive outcomes in women which has been a major motivation for the study. An alternative case/control design would only be appropriate if a single, salient outcome had been identified for specific study.

2.2.2 Case/Control Study of Reproductive Outcomes

This small case/control study is included because the potential impact of phenoxy herbicide/dioxin exposure on women has not yet been investigated using reliable methodologies (as documented in the Literature Review). At the same time, there is suggestive evidence that increased incidence of these major outcomes may be related to such exposure in women (See Table 3, p.60 of the Literature Review). The expected number of cases (see Section 6 below) is sufficiently small and the exposure measurement (TCDD blood sample determination) sufficiently expensive to obtain, that such a case/control study is clearly the design of choice for this limited set of hypotheses.

2.2.3 Case/Control Study of Cancers

An equivalent case/control study of selected cancers was also considered and rejected for at least the following reasons:

- the number of cases of clearly relevant cancers (STS, Hodgkin's Disease, Non-Hodgkin's Lymphoma) would be marginally sufficient for study as less than two cases of STS are expected across both cohorts and less than 30 cases of HD or NHL are expected, based on SEER registry rates (NCI, 1987) - see Table 4 below;

- there is no clear rationale for including other cancers as potential outcomes of VE exposure;

- even if sufficient numbers of cases were available, several may be deceased or too ill for further study;

- exposure to chemotherapy and/or radiation therapy in many cases will have compromised the immune system; and

- cancer treatment and/or the disease itself may have resulted in such a depletion of adipose tissue in some cases that TCDD determinations will not be feasible (even if the subject was well enough for the sampling of a unit of blood).

2.2.4 Sub-Study of PTSD

This is proposed for a sub-group of women in Cohort A (and B) who are not included in the case/control study of reproductive outcomes. The motivation for this study is to investigate whether or not PTSD (as diagnosed from interview) is related to neuro-behavioral function and/or to phenoxy herbicide/dioxin exposure.

2.2.5 Cell-Mediated Immune Function Sub-Study

Following the suggestive findings of Hoffman et al., (1986) on residents of a trailer park on TCDD contaminated ground, and animal study results, (see Literature Review) inclusion of immune function tests in the cancer case/control study was proposed. The hypothesis was that cell-mediated immune function would be compromised in those

highly exposed to TCDD and would increase the risk of subsequent cancer development.

With deletion of the cancer case/control study, this hypothesis could no longer be tested in the proposed study design. However, if the TCDD values obtained in the two proposed sub-studies of reproductive outcomes and PTSD are sufficiently varied to indicate a relatively wide range of exposures, the possibility of performing appropriate immune function tests on these women may be considered later in the study, time and funds permitting. There is insufficient evidence of a strong association to justify a costly sub-study of immune function at this point.

2.2.6 Validation Sub-Studies

As a general principle in any study, given heavy reliance on self-report, validation sub-studies should always be included. Such studies are particularly important for the proposed investigation because:

- recall is required over the entire period of adult life and in particular the period since Vietnam exposure (up to 24 years);

- the political climate in which this study will be conducted makes it particularly vulnerable to reporting bias (subjects will over- or under-emphasize certain symptoms, behaviors, events); and

- the fact that this is the first such study of women veterans, and the cohorts will consist of entire populations of certain groups or relatively large samples of others, implies a need to complete as comprehensive and thorough a study as possible at this time.

3. VARIABLES

This section describes the major (groups of) variables to be included in study hypotheses. The two primary groups of variables are: exposure and outcome. A third group of potential confounding variables will also be considered briefly.

3.1 EXPOSURE VARIABLES

As specified in the original RFP for the current planning and development contract, the primary exposure of interest in this study is:

exposure to the "Vietnam Experience"

This general exposure includes variable exposure to any of the following elements for women veterans;

- phenoxy herbicides;
- insecticides;
- prophylactic drugs, repellents etc. to combat tropical diseases;
- combat (confrontation with the enemy);
- pervasively vulnerable and primitive living conditions associated with serving in Vietnam; and
- difficult demobilization in an (increasingly) hostile political climate in which this action was fought.

Clearly, not all women military serving in Vietnam will have been exposed to all of the above elements. At the same time, some of these elements will have been different enough from prior or subsequent experience to qualify as "unique".

Apart from considering this total experience as a single, invariant exposure, some limited measurement of individual elements of this exposure are proposed.

(a) Phenoxy Herbicide Exposure

Based on the on-going Agent Orange study being conducted by CDC, an index of probable exposure could be constructed, using information on assignments and movements of women from such sources as morning reports, Chief Nurses' Monthly Reports and self-reported recall in combination with, primarily, Service Herbs tapes of perimeter and other ground spraying operations. Because of wide-spread, incomplete or missing data, primarily in reports of perimeter sprayings (Report of the Agent Orange Working Group Science Subpanel on Exposure Assessment, 6/3/86), construction of such an index is not proposed for this study, at this time.

Alternatively, as a validation of exposure, TCDD body burdens will be measured on sub-samples of Vietnam veterans, as this is a contaminant of concern in the production of the phenoxy acid 2,4,5-T, the most widely used phenoxy herbicide in Vietnam. These measurements will be made in the two sub-studies proposed (of reproductive outcomes and PTSD).

(b) Insecticides

Although the exposure to insecticide spraying is insufficiently documented for reliable inclusion in this study, participants will be asked to recall the use of skin repellents during their Vietnam tour. Details on type of repellent or frequency of use will not be obtained as recall of this information is unreliable up to 25 years later.

(c) Tropical Diseases

Illness due to such diseases among nurses was documented in the Chief Nurses' Monthly Reports which will provide a validation of participant recall for nurses.

(d) Prophylactic Drugs

Anti-malarials (Chloraquine-Primaquine and Dapsone) were routinely prescribed but not generally taken because of the frequently severe side effects of gastric upset (stomach cramps, diarrhea). Self-report of use will be the measurement included.

(e) Combat/Contact with the Enemy

This measure will include care of Viet Cong and North Vietnamese casualties, exposure to direct rocket/mortar fire or other enemy attack and service before/after the TET offensive. To the extent available, the first two exposures will be validated from the Chief Nurses' Monthly Report, which is likely to include such information. This exposure applies primarily to nurses.

(f) Workload (nurses only)

The volume of casualties per day, divided by the number of nursing staff (including corpsmen) per shift will be used to construct an index of (potentially stressful) workload for veteran nurses. Such data are provided in the Chief Nurses' Monthly Report, which will be used directly with Data Sets 3 and 4 (described above) for Vietnam veterans. Reports from CONUS hospitals will be used for nurses in Cohort B.

3.2 OUTCOME VARIABLES

The original RFP specified the following categories of health outcomes:

- general physical health;
- general mental health;
- reproductive function; and
- specific reproductive outcomes.

Each of these categories is addressed below.

(a) General Physical Health will be assessed primarily by considering all major disease diagnoses including cancers and hospitalizations or other institutionalizations (e.g., rehabilitation facility) for physical complaints in the study period. Excluded here are elective hospitalizations for procedures such as elective abortions, tubal ligation or

tooth removal which are not the direct result of an acute health problem. Selected diagnoses and other events will be validated as described in Section 2 above. Women with births resulting in congenital abnormality may be more likely to have tubal ligation and likely to have it earlier than other women. However, as an elective procedure for contraceptive purposes, this surgery, as well as elective abortions, would not be included as a major health outcome.

Additionally, current health and prescription drug use will be assessed.

(b) General Mental Health is similarly defined as all major psychiatric diagnoses, (including PTSD) hospitalizations and institutionalizations for mental health problems in the study period. Aspects of status to be assessed from the questionnaire will include presence of (delayed/chronic) post-traumatic stress disorder (PTSD), history of acute/delayed PTSD, depression and general mood state. Neurobehavioral assessments of mental functioning will be conducted in the PTSD sub-study.

Indirect measures of mental health (adjustment) will also be assessed from the questionnaire, including: alcohol and other drug consumption; arrests for driving under the influence of alcohol; family problems; job history; and marital history.

(c) Reproductive Functioning includes menstrual history (menarche, menopause, regularity, flow, fertility, and prolonged amenorrhea). These aspects of health will be assessed from the onset of menarche.

(d) Reproductive Outcomes will be assessed from a complete pregnancy history, including all recognized fetal loss (spontaneous and induced), still births, reasons for fetal loss or still births (including fetal abnormality), and live births. For all live births, major congenital abnormalities will be documented.

It is important here to distinquish between aspects of health related to reproductive function (reproductive health) and outcomes of reproduction which are, by definition, outcomes of conception (pregnancies). Reproductive outcomes may have an impact on maternal health, but are themselves not health outcomes.

3.3 CONFOUNDING VARIABLES

In planning an observational study, all known risk factors for specific outcomes should be considered potential confounders, with actual confounding status to be determined in the analysis.

The potential confounders included here are not an exhaustive list of candidate variables, but rather indicate the types of variables to be considered. For example, personal lifestyle characteristics will include such key variables as: smoking, alcohol use, other recreational drug use (including marijuana, cocaine), and other drugs not for specific medical indication (including oral contraceptives in particular). This category could also include such dietary supplements as vitamins.

Environmental characteristics will include residential or occupational toxic exposures, other occupational exposure (to stress, for example) and (for reproductive outcomes)

paternal toxic exposures. This category will also include exposure to the medical care system (in terms of the frequency of utilization of medical services). This last variable is of particular importance in interview studies relying heavily on self-reported data for aspects of health. Those who use the medical care system more frequently are more likely to have conditions diagnosed and treated (McKinlay and McKinlay, 1986; Roos, 1983). Moreover, it is plausible that utilization rates will vary by exposure to service in Vietnam (especially given the increasing public interest in the health consequences of this experience). For nurses, this category will also include important chemical exposures, particularly hexachlorophene which was widely used until the late 1970's and anesthetic gas exposure.

The third important set of potential confounding variables are socio-demographic. For example, date of birth, which is probably associated with exposure severity (in terms of pre- or post- TET offensive service), also determines risks to certain outcomes (such as number of pregnancies, or certain cancers). Similarly race, educational attainment and related socio-economic indicators may be associated with differing exposure and/or outcome.

Because some of these factors pre-date military service, they may not be confounders as defined above. Rather they may be external variables which determine (are causally related to) exposure variables and thence to outcomes, but have no direct association with outcomes. It is appropriate to include these variables as potential confounders in the proposed study design.

4. HYPOTHESES

The following can be stated as the basic hypothesis of the proposed study (in the null form):

General Hypothesis (H_o):

> That exposure to the Vietnam Experience (VE) has no subsequent effect on physical or mental health, reproductive function or reproductive outcomes in women veterans, followed for up to 24 years after exposure.

Specific hypotheses can then be considered in two groups:

- those hypotheses relating VE to specific outcomes; and
- those hypotheses relating elements of VE to specific outcomes - to be considered in sub-studies only.

These hypotheses are summarized in Table 1. Each column of this table represents an exposure element, with the first column representing the total VE exposure. Each row then corresponds to a specific set of outcomes. Each cell entry corresponds to the hypothesis so formed with the exposure subscript listed first. For example H_{VM} can be specified as:

H_{VM}: That exposure to VE has not resulted in an increased rate of menstrual disorders.

It is anticipated that the proposed study design will allow testing of all hypotheses relating to the general VE exposure (all with subscript V).

The power to detect small relative risks of certain outcomes (e.g., specific cancers) may not be adequate. This is discussed further in Section 6 below.

The hypotheses relating to Phenoxy Herbicide exposure (P) will only be tested in the Case/Control Study of Reproductive Outcomes (H_{PF} and $H_{PL)}$ and in the sub-study of PTSD (H_{PN} and H_{PS}).

Finally, hypotheses relating exposure to the wounded veterans (W) to health outcomes will only be considered for Data Sets 3 and 4. Moreover, it should be noted that Army nurses in Cohort B were also exposed to this element to varying degrees. Therefore, a third comparison group of no exposure, consisting of comparable Air Force nurses in Cohort B is included. Hypotheses in this column will compare all three groups in two stages as follows:

Stage 1:

Army nurses exposed to wounded veterans, regardless of Vietnam service, will be no different in outcome from Air Force nurses not exposed to war wounded.

Stage 2:

Among Army nurses exposed to wounded veterans, differences in outcome are related (if at all) to degree of exposure, independently of Vietnam service.

TABLE 1 SUMMARY OF SPECIFIC HYPOTHESES[a]

OUTCOMES	EXPOSURES		
	VIETNAM EXPERIENCE (V)	PHENOXY[b] HERBICIDES/TCDD (P)	EXPOSURE TO[c] WAR WOUNDED (W)
GENERAL HEALTH			
• Cancers (C)	H_{VC}	--	H_{WC}
• Cardio-vascular Disease (H)	H_{VH}	--	H_{WH}
• PTSD (acute/chronic/ delayed) (S)	H_{VS}	H_{PS}	H_{WS}
• Neuro-behavioral function (N)	--	H_{PN}	--
• Accident/Suicide (attempted) (A)	H_{VA}	--	H_{WA}
REPRODUCTIVE FUNCTION			
• Infertility (I)	H_{VI}	--	H_{WI}
• Menstrual Disorder (M)	H_{VM}	--	H_{WM}
REPRODUCTIVE OUTCOME			
• Fetal Loss (F)	H_{VF}	H_{PF}	H_{WF}
• Congenital Abnormality in Live Born (L)	H_{VL}	H_{PL}	H_{WL}

(a) Assigned subscripts are indicated in parentheses for each variable.

(b) This set of hypotheses will be addressed only for the sub-samples measured for TCDD body burden depending on the pending CDC results.

(c) This set of hypotheses will be addressed in Data Sets 3 and 4 (Nurses only, three comparison groups in Nurses Sub -study).

(d) Measured in sub-study of PTSD only.

5. ELIGIBLE POPULATION AND SAMPLING FRAMES

5.1 POPULATION DEFINITION

This study involves the comparison of two basic groups of women military personnel:

- the Exposed Group - those who served in Vietnam (Vietnam Veterans); and
- the Non-Exposed Group - those who were eligible to serve in Vietnam at the same time but who did not (Vietnam-era veterans).

Because service in Vietnam was acknowledged by the Armed Forces through the award of a special Vietnam ribbon, and eligibility for this award is specified on all military records (whether or not the ribbon was actually requested by the veteran), this award is used to define Vietnam veterans unambiguously. All those who served in Vietnam, its water, airspace, or in neighboring Thailand, Laos or Cambodia between July 3, 1965 and March 28, 1973 were eligible for this award.

Apart from service "in country" in Vietnam, on evacuation flights, or on hospital ships (the U.S.S. Sanctuary and U.S.S. Repose), the only other women military eligible for the award were a small number of primarily Air Force support personnel stationed in Thailand (estimated at approximately 100). This small group would be included in Data Sets 1 and 2 only.

Another group, inclusion of which is also questionable, includes all women military personnel stationed in Guam, the Philippines and Japan. These women, as Vietnam-era veterans,

are eligible for inclusion in the non-exposed group but were exposed to tropical diseases in these South West Pacific islands. The nurses in these stations were exposed to war wounded in first-line evacuation hospitals. After discussion, it was decided to include these women in the study as, apart from the tropical living conditions, their experience is not different from nurses in other hospitals on the evacuation routes from Vietnam and their living and working conditions were comparable to state-side assignments. Even if excluded for analysis from Data Sets 1 and 2, they certainly should be included in Data Sets 3 and 4.

Finally, the few women military "advisors" - primarily nurses- serving in Vietnam before July 3, 1965 are excluded from the study. Their numbers were very small (estimated at less than 100 - see Holm, 1982), they were much less likely to be exposed to herbicide spraying or risks of rocket or mortar fire, and they were not exposed to the nursing work conditions experienced once the fighting began.

Eligibility for service in Vietnam generally required that basic training and an initial tour of duty in the United States had been completed, although there were exceptions. Those who had not completed this in time to complete a minimum tour of duty in Vietnam to qualify for the Vietnam service award before March 28, 1973, are not eligible for the study. Table 2 summarizes these criteria.

5.2 SAMPLING FRAMES

The obvious sampling frame for the population defined above would be a list of all women on active duty in the Armed Forces and eligible to serve in Vietnam in the period

TABLE 2. ELIGIBILITY FOR VIETNAM SERVICE RIBBON

Branch	Personnel	Basic Training Length	Location	Latest Service Entry Date for Eligibility
Army	Enlisted	12 weeks	Various centers depending upon MOS	1/2/73
	Medical Officer	5 weeks	Fort Sam Houston Academy of Health Services	2/20/73
	Officer Candidate School	16 weeks	Fort Benjamin Harrison, Ind.	12/5/72
* Air Force	Enlisted	6 weeks	Lackland A.F.B.	2/13/72
	Medical Officer	3 weeks	Sheppard A.F.B. Wichita Falls Texas	3/6/72
	Officer Candidate School	12 weeks	Lackland A.F.B.	1/2/72
* U.S. Navy	Enlisted	8 weeks	Orlando, FL.	1/30/72
	Medical Officer	4 weeks	Newport, R.I.	3/13/72
	Officer Candidate School	16 weeks	Newport, R.I.	12/5/71

* Dates reflect necessity to do one year CONUS tour of duty before overseas assignment by Air Force and Navy.

7/3/65 - 3/28/73. Such lists, however, only exist in accessible, computerized form for the Air Force, Navy and Marines, which together comprise a relatively small proportion (less than one third) of all women military personnel (Holm, 1982). No readily available listing of women serving in the Army is available. Rather, morning reports of the various units on active duty during the appropriate period must be screened for women assigned to them, and personnel records abstracted at the National Personnel Records Center in St. Louis, Missouri. Even then, current name, address and vital status (as of January 1987, say) will not be available from these sources.

Alternative listings considered include: available lists of those completing training at the few training centers for women; and lists of those claiming a variety of veteran's benefits (educational, medical, pension) and current Reserve lists. The first type of list has the following major disadvantages:

- these lists do not exist sufficiently far back in time to include all women seeing their first war-time service in the period 1965-1972;
- they do not include women who were on the Reserve lists from World War II and Korea;
- they do not include current (or recent) name and address; and
- they are not computerized.

The second type of lists will not include those still on active duty as of the start of the study (projected for 1988 - 1989). This proportion may be as high as 15%, although it

is almost certainly decreasing rapidly up to 24 years after Vietnam-era service, as career military personnel reach retirement. Some advantages of these lists are:

- computerization;
- recent or current name and address; and
- vital status.

The primary disadvantage, however, which outweighs these advantages, is their lack of completeness (not all discharged veterans will have claimed educational or medical benefits). Finally, current reserve lists, although complete, may not be up-to-date with respect to vital status, current name and address.

The labor required to obtain complete listings with current name, address and vital status is such that constructing a complete sampling frame is not feasible.

Currently, the VA is conducting a mortality study of women Vietnam veterans for which they have nearly completed construction of a list of the approximately 5000 women Vietnam veterans, with current name, address and vital status, at least as of January 1, 1986. Work is just beginning on the sampling of computerized personnel lists and Army morning reports to construct an equivalent sample of Vietnam-era veterans. Given the costs of producing these lists, it is reasonable to use them to provide the basis for the proposed study sample. Because nurses were disproportionately assigned to Vietnam service, the sampling of Vietnam-era veterans is being frequency matched by service and personnel category to corresponding numbers of Vietnam veterans. Sampling fractions are therefore being adjusted to provide a Vietnam-era sample as similar to the Vietnam cohort as possible in terms of occupation and

TABLE 3: CONTROL SAMPLE NUMBERS FOR THE VA MORTALITY STUDY

ESTIMATED JUNE, 1986

BRANCH OF SERVICE	TARGET SAMPLE OF ELIGIBLE CONTROLS	INITIAL SAMPLE OF POTENTIAL CONTROLS
ARMY		
Nurses	3800	4940
Other Officers	210	273
Enlisted Personnel	750	975
AIR FORCE		
Nurses	450 (500)	585 (1,000)
Other Officers	250	325
Enlisted Personnel	100	130
NAVY		
Nurses	450	585
Other Officers	20	26
MARINES		
Officers (no nurses)	25	33
Enlisted Personnel	20	26
TOTAL	6,075 (6,575)	7,898 (8,898)

service distribution. In particular, almost all Vietnam-era Army Nurses will be sampled for the Mortality Study Comparison group and, therefore, for Cohort B of the proposed study.

Estimates of eligible women required, in each service, as of June, 1986, are provided in Table 3, based on then available estimates of Vietnam veterans. Currently (June, 1987) the number of Vietnam veterans is approximately 5000, after removal of ineligibles (by year, gender) and duplicates (by name or from different branches of the service). The large initial sample of potential controls is inflated to compensate for losses from ineligibility, duplicates and untracables.

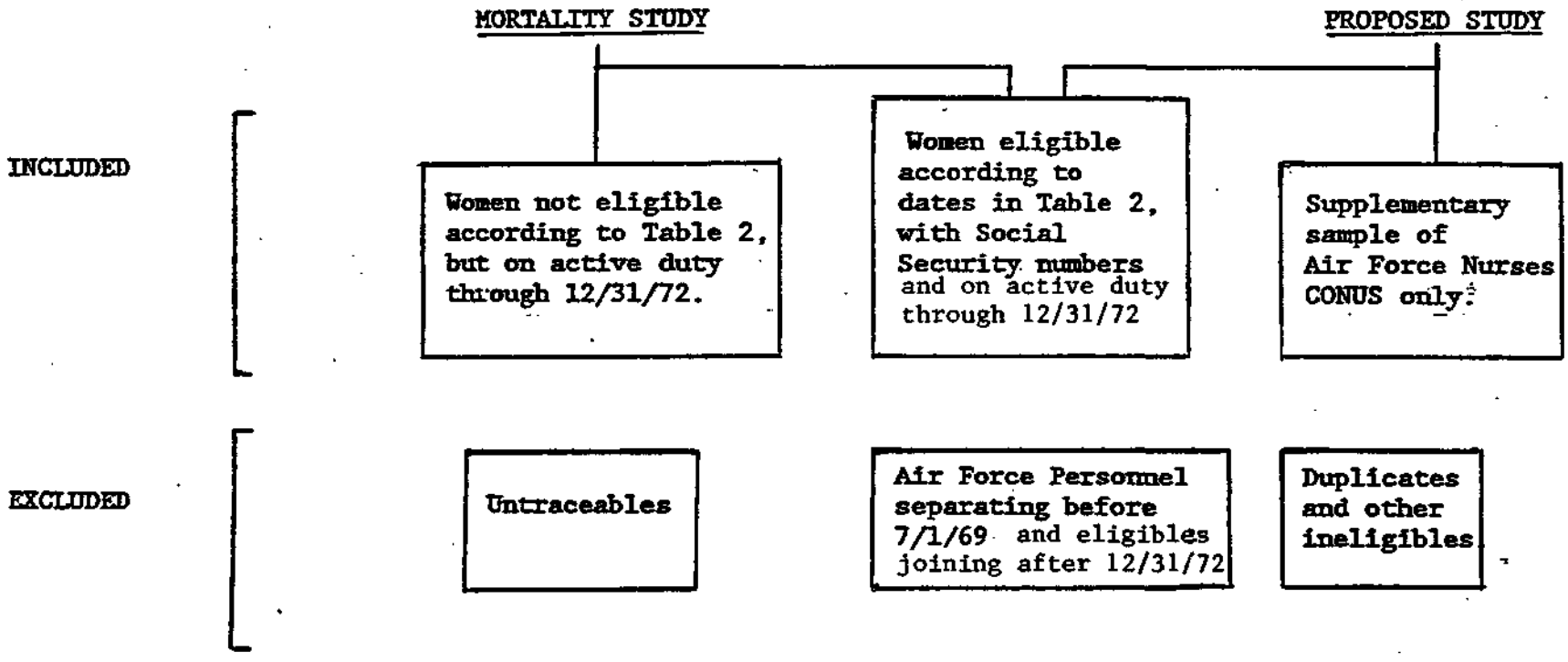
Two points should be made concerning the sampling of the control group for the Mortality study.

- The sampling period is 1964-1972 inclusive for the initial sample, with application of the dates 7/4/65 - 3/28/73 for period of service to define final eligibility. Personnel joining after 12/31/72 will not be eligible for inclusion.

- Women who separated from the Air Force before July 1, 1969 were not sampled as their social security numbers were not available in the record. This item was required for tracing purposes. Approximately 34% of officer and 53% of enlisted records were not sampled for the three years 1966-1968 as a result. This will introduce a bias towards longer service in those sampled in years 1966-1968, as they had to be on active service as of July 1, 1969.

Figure 1 diagrammatically represents overlap between those included in the Mortality Study and those eligible for

FIGURE 1. OVERLAP OF MORTALITY STUDY AND PROPOSED STUDY SAMPLES
(VIETNAM AND VIETNAM-ERA)



the proposed study. Given the dates in Table 2, it is clear that all those eligible for the proposed study will be included in the Mortality Study sample, with the exception of the supplementary sample of Air Force Nurses for the third comparison group in the Nurses Sub-Study and a very few Army enlisted and nursing officer personnel.

Not depicted in Figure 1 is the potential identification of women in the Mortality Study control group who are eligible as Vietnam veterans according to the proposed criteria even though they did not serve a full tour of duty in Vietnam. Crossover between Mortality Study cohorts is expected for a few subjects, in defining cohorts for the proposed study.

Current estimates of eligible women in each service, for the Vietnam and Vietnam-era groups in the Mortality Study are provided in Table 3. The sample of Vietnam-era Air Force nurses will be augmented by the number in parentheses for the proposed study (Cohort B), although they are not required for the Mortality study.

Figure 1 provides a diagrammatic representation of how the defined Cohorts A and B for the proposed study overlap with the Mortality Study lists.

6. SAMPLE SIZES

6.1. ASSUMPTIONS

In calculating expected sample sizes and assessing their adequacy to detect relative risks and/or differences, the following assumptions are made:

1. The expected total number of Vietnam veterans (Cohort A) eligible for study is 5000.

2. The expected total number of Vietnam veteran Army nurses (Cohort A) eligible for study is 5000 x .7 = 3,500.

3. The expected numbers of Vietnam-era veterans (Cohort B) eligible for study is as in Table 3 above.

4. Response rate to initial telephone survey for all subjects (or proxies) is 85%.

5. Response rates to any in-person protocol is 90% of those responding to the initial interview.

The numbers expected for the overall study and the Nurses Sub-Study (Army nurses only) are provided in Table 5, based on the above assumptions.

6.2 RESPONSE RATES

Two response rates must be considered:

(a) Response to the initial telephone interview; and

TABLE 4. ESTIMATED RATES FOR SELECTED HEALTH AND REPRODUCTIVE OUTCOMES

OUTCOME	YEAR	BASE POPULATION	RATE (per 100)
A. GENERAL HEALTH			
• Malignant Neoplasm Incidence[a] (white women, age adj.)	1983	Civilian pop., U.S.	0.31
• Malignant Neoplasm Mortality[a] (white women, 35-54 yrs, age adj.)	1984	"	0.14
• Incidence of Hodgkin's Disease[a] and Non-Hodgkin's Lymphema (white women, age adj.)	1984	"	0.013
• Incidence of Soft tissue Sarcomas[a] (incl. Head)(all women, age adj.)	1980-84	"	0.002
• Heart Disease Prevalence[c] (all women, < 45 yrs)	1985	"	3.71
• Heart Disease Mortality[b] (white women, 35-54 yrs, age adj.)	1984	"	0.08
• Cerebrovascular Disease Prevalence[c] (all women, < 45 yrs)	1985	"	0.14
• Cerebrovascular Disease Mortality[b] (white women, 35-54 yrs, age adj.)	1984	"	0.02
• PTSD (chronic and/or delayed)[d]	1980+	U.S. Veteran pop.	3.0+
B. REPRODUCTIVE FUNCTION			
• Infertility Rate[d] (30-39 yrs)	1982	Currently married women, U.S.	10.0

TABLE 4. Continued

OUTCOME	YEAR	BASE POPULATION	RATE (per 100)
C. REPRODUCTIVE OUTCOME			
• Major Congenital Malformation[f]	1973-74	Live births, U.S.	0.82
• Multiple Spontaneous Abortion[g] (< 20 wks gestation)	1980 (approx)	Pregnancies	3.00
• Fetal Mortality[b] (≥ 20 wks gestation)	1984	Live births to fetal deaths, U.S.	0.81
• Infant Mortality[b] (< 1 yr)	1984	Live births, U.S.	1.10

Sources:

(a) NCI: 1986 Annual Cancer Statistics Review. NIH Pub. No. 87-2789.

(b) NCHS: Health, United States, 1986. DHHS Pub. No. (PHS) 87-1232, PHS, Washington, D.C., U.S. Govt. Printing Office, Dec. 1986.

(c) NCHS: Current Estimates form the National Health Interview Survey, U.S. 1985 Vital & Health Statistics Series 10, No. 160 DHHS Pub. No. (PHS) 86-1588, PHS Washington, D.C., U.S. Govt. Printing Office, Sept. 1986.

(d) Literature Review, VA Contract V107 (93) P-1138, 1987.

(e) Mosher, W.D. Reproductive Impairments in the U.S., 1965-82, Demography (1985) 22:415-430.

(f) NCHS: Congenital Anomalies and Birth Injuries among Live Births: U.S., 1973-74 Vital & Health Statistics Series 21, No.31 DHHS Pub. No. 79-1909, PHS, Washington, D.C., U.S. Govt. Printing Office, Nov. 1978.

(g) This is estimated using a basic rate of 15% spontaneous abortion/pregnancy quoted by Kline et al., 1981.

(b) Response to in-person measurement.

The response to the initial interview, given interest in the study and prior experience with similar studies (including CDC's VE study), is expected to be 85% of eligible subjects. Maintenance of this response rate will depend on attention to some of the special issues mentioned below (Section 7.1.6).

Response to in-person protocols, conditional on response to the telephone interview, is expected to be at least 90%, provided the participant burden is minimized and protocols are completed locally, at the participant's convenience (wherever possible in the participant's home). This projection is based on the contractor's own experience with other on-going research.

Because the response rates are expected to be relatively high, no major bias from non-response is anticipated. Some data from service records will be available on non-respondents, from the Mortality Study, with which to check evidence of potential bias. These data include: date of birth, length of service, veteran status (Vietnam or Vietnam-era), highest rank attained, branch of service and occupation.

6.3. OUTCOME RATES

Table 4 presents rates for key study outcomes for female populations. These rates are used to approximate outcome rates for Cohort B subjects (control population).

Wherever possible, rates are presented for the most recent year for which data are available. It is clear from this table that, except for some death rates and cancer

incidence rates, outcome rates are generally near or greater than 0.1%. Moreover, for congenital malformation rates, calculated on a base of live births, conservatively twice the number of births are expected in the cohort for the number of women (NCHS, 1986), effectively doubling the available sample size. Age ranges approximating that of the cohort were used for rates where large age differences are observed. Assuming the minimum age at potential VE exposure was 20 years in 1973 and the maximum age in 1965 was 40, the age range of the cohort in 1989 will be approximatley 35-64 years, with the majority in the range 35-49 years.

6.4 SUB-STUDY SAMPLE SIZES

This section provides estimates of expected numbers for the sub-studies.

6.4.1 Reproductive Outcome Study

As noted in Section 2 above and Table 4, the rate of major congenital abnormalities is approximately 1/100 live births, while the rate of two or more spontaneous abortions per woman is estimated at no more than 3%. An average of two live births per woman is assumed, using live births, by age of mother (NCHS, 1986), averaged and deflated slightly to yield a rate of 2.0 live births/woman. This lower rate is used on the assumption that veterans were less likely to marry (or marry early) than other women of the same age. (This trend was suggested from pre-testing and focus group experience during the planning of this study. No data are presently available to confirm it.) Certainly, use of a conservative rate of live births will result in a conservative lower bound for expected sample size.

The rate of congenital abnormality (assuming two live births/woman) is therefore:

TABLE 5. EXPECTED SAMPLE SIZES [a]
FOR THE ENTIRE STUDY AND NURSES SUB-STUDY
(ARMY NURSES ONLY)

COMPONENT STUDY	COHORT A	COHORT B
Entire Study	4,250	5,164
Entire Study (Alive Only [b])	4,165	5,062
Army Nurses Sub-Study	2,975	3,230

(a) Total eligible x 0.85

(b) Assuming a death rate of .02 in both cohorts (based on 100/5000 deaths identified in Cohort A for the Mortality Study), 100 deaths in Cohort A and 120 expected deaths in Cohort B are deducted from eligible numbers before multiplication by Response Rate (0.85).

.07 x 4,165 x 2 = 83,

using live Cohort A subjects only (Table 5).

Assuming a 3% rate of repeat spontaneous abortions/woman and that 50% (conservatively) have no obvious cause (Dr. A. Haney, personal communication), the number of women with unexplained habitual abortion is estimated as:

.03 x .5 x 4,165 = 62.

Provided no woman reports both adverse reproductive outcomes, the expected number of cases in Cohort A is:

83 + 62 = 145.

An equal number of controls will be selected from the remaining 4020 subjects in Cohort A (a ratio of 28:1 of available: required matches). With a 90% in-person response rate, approximately 260 subjects (and offspring) will be available for this study.

6.4.2 PTSD Sub-Study

The numbers required for this sub-study involved additional assumptions. From Lezak (1983) (see Appendix) it appears that the outcomes of the neurobehavioral tests are either scores (which can be considered continuous) or consist of proportions (numbers) of successes/failures.

For the tests producing scores, the ratio of S.D. to mean,

TABLE 6. Coefficients of variation (CV) for selected values of α and β, assuming a two-sided test

β	α		
	0.05	0.01	0.001
0.30	0.40	0.32	0.26
0.20	0.36	0.29	0.24
0.10	0.31	0.26	0.22

S.D./mean $\leq$ 0.25,

in all cases. Assuming a mean μ, in the control group, a minimum meaningful difference in scores $\Delta = 0.1\mu$ and population S.D. $= \sigma$, the required sample size (n), assuming equal sample sizes, is:

$$n = 2\sigma^2/[.01\mu^2 \times CV^{-2}(D)],$$

$$= 2(.25^2)/[.01 \times CV^2(D)],$$

where $CV(D) = S.E.(D)/\Delta$ and is pre-specified. Table 6 demonstrates the relationship between CV(D) and the power for detecting pre-specified differences, which indicates that $CV(D) \leq .30$ is sufficient to provide adequate power. Solving for n with CV(D) = .3 yields a minimum sample size of 139.

Assuming a 90% in-person response rate for the neurobehavioral tests, an initial sample of 155 subjects, identified from the telephone interview, will be required for each of five groups (a total of 775 subjects) to yield 698 completed responses. An alternative sample selection design which will retain equivalent power for <u>combined</u> comparisons but use fewer subjects is as follows:

Acute PTSD	= 52	PTSD Combined = 156
Delayed PTSD	= 52	
Chronic PTSD	= 52	
Control (Cohort A)	= 78	Controls Combined = 156
Control (Cohort B)	= 78	
Total Sample		= 312

This alternative uses 45% of the subjects (312/698) and reduces cost accordingly. Comparisons between sub-groups of PTSD and controls will have reduced power in this design. However, it should be noted that, for many of the tests, $\sigma/\mu \leq .15$. For these tests, $n \leq 50$ is sufficient to maintain $CV(D) \leq .30$.

The alternative design (total sample selected = 312) is therefore proposed.

6.4.3 Nurses Sub-Study

All available Army nurses will be included in this sub-study (Table 5). It remains to determine the number of Air Force nurses from Cohort B for the third comparison group.

From Table 3, 450 eligible Air Force nurses will be available for use in Cohort B. This subgroup will be available as the third comparison group in the Nurses Sub-Study and is restricted to Air Force nurses who are:

- not on flight status at any time during the entire exposure period; and

- not exposed to any measurable extent to care of wounded Vietnam veterans during the entire exposure period.

Assuming an 85% response rate, 382 will be available, of whom an estimated 75% will meet the above criteria (this is a conservative guess, as statistics are not readily available for these factors). In other words, only 287 (estimated) will be available for the third comparison

group. This small number is further compromised by the bias towards longer service in the early years of the exposure period.

In order to increase this number by 500 (to approximately 790), an additional 500 ÷ 0.75 ÷ 0.85 = 785 eligible Air Force nurses will be required. As in the Mortality Study, this is increased by 30% to ensure enough potential subjects in the initial sampling. In other words, approximately an additional 1000 Air Force nurses will need to be selected from the computerized Air Force listings for this study (over and above those selected for the Mortality Study).

6.4.4 Validation Sub-Studies

The criterion for acceptance of self-reports, based on verification of a sample, is 10% discrepancy or less. Reliable estimation of the proportion (p) of discrepant reports is defined by (Cochran, 1977):

$$CV(\hat{p}) = (1-p)/np.$$

Assuming a maximum $CV(\hat{p})$ of .3, as above, and solving for n,

$$n = 100$$

In other words, random samples of 100 self-reported cases should be sufficient to provide precise estimates of the proportion validated.

TABLE 7. SMALLEST DETECTABLE RELATIVE RISK (>1) FOR α = .05 (TWO-SIDED), VARYING SAMPLE SIZE[a], β AND p[b]

		SAMPLE SIZE			
	p	5000	3000	780	130
β = 0.20					
	0.001	3.72	4.95	12.79	68.37
	0.01	1.65	1.87	3.03	8.56
	0.05	1.28	1.36	1.78	3.38
	0.10	1.20	1.26	1.54	2.60
β = 0.10					
	0.001	4.35	5.93	16.26	81.14
	0.01	1.77	2.04	3.48	10.67
	0.05	1.32	1.43	1.92	3.93
	0.10	1.23	1.30	1.64	2.94

(a) Sample size is the size of the control sample (see Schlesselman, 1982)

(b) p is the outcome rate in the control population

6.5 SAMPLE SIZE ADEQUACY

Table 7 presents the smallest detectable Relative Risks for various pertinent sample sizes, outcome rates and two values of β (0.10, 0.20). The significance level (α) is assumed constant at 0.05, for two-tailed tests.

The entire sample will detect relative risks less than 4.0 with 80% power, for outcome proportions as small as 0.001. These numbers are clearly adequate to detect meaningful risks for major health outcomes except rare cancers (STS in particular - see Table 4).

The Nurses Sub-Study will detect risks of less than 3.0 with adequate power for proportions of .01 or higher, assuming that the Air Force control group contains at least 780 subjects. For comparisons involving Army nurses only, the minimum detectable risks are less than 2.0, for $p \geq .01$.

For the Reproductive Outcome Case/Control Study, odds-ratios (relative risks) of 3.5 or less will be detectable for exposure rates of .05 or higher (assuming TCDD exposure can be meaningfully dichotomized).

7. DATA COLLECTION

This section outlines the major data collection strategies proposed, with rationale, and a discussion of special issues (7.1), followed by quality control and data management requirements (7.2).

7.1 STRATEGIES

The various data collection strategies are described here for each study component.

7.1.1. Full Cohort Study

This study involves collection of data by telephone interview with each subject (or with a next-of-kin for deceased subjects).

(a) Telephone Interview

Because participants will be scattered throughout the U.S. and other countries, the primary mode of data collection must be feasible, cost efficient and produce data of acceptable quality.

Telephone interviews were chosen over mailed self-administered questionnaires (SAQ's) for the following primary reasons:

- Respondent Burden (SAQ's take longer to complete.)
- Data Quality (Even short, simple SAQ's result in skipped questions and/or missing or ambiguous items which are not random but are related to educational level and, independently, to health status.)

- Bias (Respondents have less opportunity in a telephone interview to discuss the questions and their responses with others, compared to a SAQ which can be shared with colleagues, family or friends, before or after completion.)

- Response Rate (The considerably lower perceived burden and direct interaction with an interviewer will increase response rates - especially among those with less education.)

- Accurate Completion (Assurance is obtained that the correct person provides the information, without prompting or consultation.)

Given the complexity of the interview, which includes occupational, contraceptive and reproductive histories and requires 1.75 - 2.0 hours to administer, the use of computer-assisted telephone interviewing (CATI) was not considered feasible. Once a respondent's memory is activated in one area, responses may be corrected in another area, many pages and skip patterns earlier. Moreover, CATI discourages interviewer comments which will be most valuable in this unique study.

It is expected, on the basis of pre-test experience, that the majority of interviews will be completed in one call. Interrupted interviews (because of family or other intrusions into respondents' time) must be completed as soon as possible (generally within 24 hours).

Given the nature of the study and the sensitivity of the topics, the use of professional interviewers with considerable experience is required. Data from the open-ended questions will be post-coded to standardized

categories, thus eliminating the potential for interviewer error and delay, when presented with the long answer lists required for certain close-ended questions. Much of the coding of medical data will require professionals trained in the use of ICD-9 codes and surgical procedures.

In-person interviews for those without telephones or with unlisted numbers will be conducted - estimated at 10% of the sample.

(b) Proxy Interview

For already identified deceased subjects, the next-of-kin listed on the death certificate will be contacted in order to identify the best person(s) with whom to complete a proxy interview. For subects dying after list compilation, the informant providing this information will be the initial contact.

The best proxy will meet the following criteria:

(a) knew subject immediately prior to the death; and

(b) of those meeting criterion (a), knew her the longest.

It is expected that in most cases the informant will be a parent, sibling, offspring or spouse in that order, unless living with the spouse for at least 10 years. For the veterans under study, lower rates of marriage and/or less stable marriages than average may require heavy reliance on parents or siblings for proxy interviews.

As for subjects, in-person interviews with proxies will be conducted in the absence of an accessible telephone.

7.1.2 Reproductive Outcome Study

This study will involve in-person measurement of the subject (blood sampling for TCDD determination) and of the approximately 170 offspring of women reporting a major congenital abnormality. Hospital record review will be required to validate the 60+ habitual abortion histories. Each of these strategies is discussed below.

(a) Blood Sampling for TCDD Determinations

Because a unit (450 mls) of whole blood is required (see Appendix), to be obtained under strictly sterile, controlled conditions, it is proposed that this collection be completed by regional Red Cross offices under sub-contract. Individual collection kits which are free of chemical contaminants will be required. These will be delivered to the designated Red Cross office, and Red Cross staff will be trained in their use by project staff.

The assays must be completed in a laboratory with the capacity already established as the assay is highly complex to set up successfully (Patterson et al, 1987 - see Appendix). Currently only CDC has this capability in the U.S.

For this sub-study, a maximum of 260 assays will be required. This number may be reduced if a subject is too sick or has an unacceptably low hematocrit for sampling of a unit of blood (see Section 9). Data regarding deferrals for low hematocrits are not consistently tabulated by the Red Cross. However, the national office estimates that approximately 4% of women donors are deferred for hematocrit

levels less than 38 (personal communication, Red Cross, Blood Operations Support, 1987).

(b) Pediatric Examination

It is proposed to follow closely the protocol developed for the Ranch Hand Study, with all examinations to be completed by a single, trained physician. This should be feasible as approximately 80 families will be eligible (170 children) to be examined over 24 months. This is equivalent to 7 examinations (3 - 4 families) per month. The protocol for this examination, following closely that used on the Ranch Hand Study being conducted by the Air Force, is in the Appendix.

(c) Medical Record Verification

In those cases for which a pediatric examination is not possible (the offspring is deceased, ill or living in another country), the physician performing the examinations will review available hospital and medical records to verify the abnormality.

All repeat abortions will have records reviewed to rule out the excluding causes listed above. A panel of three physicians specializing in reproductive medicine will independently review these records and determine eligibility for inclusion. A majority (2/3) determination will be sufficient for a decision.

7.1.3 PTSD Sub-Study

(a) Neuro-behavioral Testing

All 312 women consenting to participate in this sub-study will complete a battery of tests as presented in the

Appendix, following closely the test protocol used on the CDC VE study.

This battery will be completed by one of a small number of trained project staff with appropriate backgrounds in psychological testing. Depending on the availability of a quiet room, without interruption in the participant's home, the testing will be completed either in the subject's home or in an appropriate room (for example hotel conference room) rented nearby.

(b) TCDD Determination

All 312 subjects will also be eligible for blood sampling for TCDD determinations. These will be collected as proposed in Section 7.1.2 above.

7.1.4 Validation Studies

Apart from the validation of cases described in Section 7.1.2 above, three types of validation are proposed:

- medical record review;
- review of pathology slides; and
- blood testing.

Each is described briefly below.

(a) Medical Record Review

For each case (including fatal and non-fatal diagnoses) a panel of three physicians, including at least one internist and at least one specialist in the appropriate area, will independently review each case and determine the

diagnosis. A majority (2/3) will be sufficient for a decision.

The major exception to this procedure will be suspected cases of myocardial infarction, sudden death and stroke, for which an established diagnostic algorithm is available (Gillum et al, 1984) and a protocol developed and tested (see Appendix).

(b) Pathology Slide Review

To verify oopherectomy, slides will be independently reviewed by a panel of three gynecologists (reproductive specialists). A majority (2/3) will be sufficient to confirm the surgery.

To verify cancer type, a panel of three oncologists/pathologists including specialists in Hodgkins Disease and Non-Hodgkins Lymphoma will independently review pathology slides (if available) or records.

In the case of STS, suspected cases will be reviewed using the WHO criteria (Enzinger et al, 1969) (see Appendix).

(c) Hormone Blood Testing

To confirm premature menopause (12 months of consecutive amenorrhea without obvious cause in a woman under age 40), FSH and LH levels will be checked using two venous blood samples, of at least 5 ml whole blood each, drawn 20-30 minutes apart, between 7:00-10:00am. Blood specimens will be collected in the subject's home. Samples will be centrifuged and serum shipped to a well-established

endocrine laboratory for analysis. Standardized "kits" are available for these assays.

7.1.5 Rationale for Individual In-Person Measurement

It is proposed to collect all blood samples and complete all in-person measurement individually, either in the subject's home or at a locally convenient site, rather than at a nationally central site (as in the CDC VE study) for the following primary reasons:

- respondents are likely to have family responsibilities making travel to a pre-determined location difficult;
- requiring travel of a respondent increases perceived burden, increases broken appointments, and decreases response; and
- it is more cost-efficient to complete protocols in the home, in terms of project staff time and required travel costs especially given the relatively small number (less than 600 subjects) involved.

7.1.6 Special Issues in Data Collection

The following concerns will require special consideration in the conduct of the study:

- the impact of publicity external to and prior to the study;
- the most effective publicity (especially sponsorship) to enhance response rates on the study;

- the maintenance of interviewer/examiner blindness to veteran status (Vietnam veteran or Vietnam-era veteran); and

- participant networking which may increasingly affect response rate and/or response bias among subjects interviewed later during the study.

These and related issues must be addressed in data collection and/or analysis.

7.2 QUALITY CONTROL AND DATA MANAGEMENT

To the extent possible, as few project staff as possible should be involved in data collection. This is a particular concern for in-person protocols, for which direct supervision may not be possible. The following sub-sections address minimum quality control requirements for telephone interviewing and in-person measurement as well as minimum requirements for a data management system.

(a) Telephone Interviewing Quality Control

Telephone interviewing quality control should consist of at least the following:

- regular monitoring of interviews by a supervisor;

- call-back and edit checks, by a supervisor, of 10% of all final dispositions (including ineligibles, refusals, and completed interviews); and

- regular review of refusal and production rates of all interviewers.

(b) In-Person Protocol Qualtiy Control

Because specialists and subcontractors will be employed for most of the in-person protocols, random visits by the Project Director (or other senior project staff) during scheduled data collection should be completed (on at least 5% of all scheduled appointments). Another 10% of subjects/ subcontractors should be called after the scheduled data collection to ensure timely accurate completion of protocols.

(c) Data Management Requirements

A responsive, automated data management system is required to complete the following tasks:

- produce regular (weekly) production reports;
- provide for immediate entry, verification and editing of all data within 2 weeks of acquisition;
- assist in efficient scheduling of project staff/subcontractors and subjects for in-person protocols;
- provide range and logic checks for data entry/editing;
- monitor protocol completion (including integration of laboratory results, multiple physician diagnoses, etc. into the data base);

- produce automated form letters and record release requests;

- produce automated reports on in-person measurements for subjects and (optionally) for their physicians; and

- produce periodic summary reports of aspects of data collection, including production statistics and quality control check statistics.

8. ANALYSIS

The analytical approach for this study will vary depending on the hypotheses and sub-study of interest. The recommended analytic strategies are outlined in this section for each of the component studies and with reference to the hypotheses presented in Section 4 above.

8.1 FULL COHORT STUDY OF VE EXPOSURE

The overall investigation of the effect of VE on various health related outcomes will be completed on Data Sets 1 and 2 of the two cohorts (A and B). Hypotheses addressed include all those in the far left-hand column of Table 1 above.

As is clear from Section 3 and Table 4, all of the major health or reproductive outcomes can be considered as dichotomies (present/absent). It will therefore be possible to derive, directly, estimates of relative risks of these outcomes by exposure from the historical cohort design.

The primary issue in deriving these estimates will be effective adjustment for potential confounding variables (age, length of service, smoking, alcohol consumption, etc.). It is recommended that a logistic approach be employed to estimate the contribution of potential confounding variables and that the final estimates of relative risk be adjusted for those effects which contribute significantly and consistently. In other words, for an outcome proportion p_i,

$$\log[p_i/(1-p_i)] = \text{logit}(p_i) = \alpha_i + \sum_j \beta_j x_{ij} ,$$

where x_{ij} is the jth covariate (potential confounding variable) associated with the ith outcome.

Given the estimation of multiple equations from the data set, the following restrictions on the analysis are recommended:

- the significance level for inclusion of a variable in the logistic model should be set, strictly, at 0.01;

- interaction terms should only be considered if all lower order terms involving these variables are included in the model;

- consistency of models with biological mechanisms and findings from other relevant studies (on veterans, nurses, etc.) should be checked; and

- the stability of models should be investigated by some form of jack-knifing (using, say, several random samples of 50% of each cohort for repeat estimation).

References for this type of analysis include Bishop et al (1974) and Kleinbaum and Kupper (1978).

8.2 REPRODUCTIVE OUTCOME CASE/CONTROL STUDY

Because the outcome variable (TCDD body burden) is essentially continuous, mean differences may be considered. Assuming that pair-matching is effective, differences in TCDD levels between pairs will be observed and the mean of these differences calculated.

The effectiveness of the pair-matching should be checked by comparing the variance of the mean of paired differences ($\sigma_{\bar{d}}^2$) with the variance of the difference of two means calculated from the observations as if from independent samples ($\sigma_{\bar{x}_1 - \bar{x}_2}^2$). If these two variances are equivalent and produce the same test statistic, then pair-matching was ineffective.

Mean differences can be adjusted for continuous covariates using analysis of covariance (Snedecor and Cochran, 1972). For dichotomous or other categorical confounders, post-stratified estimates of mean paired differences can be estimated. Such adjustment methods are described further by Schlesselmann (1982).

8.3 PTSD SUB-STUDY

This study will be relating TCDD levels and results of neuro-behavioral tests to PTSD, diagnosed from a version of the Diagnostic Interview Schedule (DIS - see Appendix). The hypotheses addressed are those specifically relating PTSD and neuro-behavioral functioning to TCDD exposure (see Table 1).

As is clear from the Appendix, most of the neuro-behavioral tests have scores, which can be treated as essentially continuous data. The remaining tests use number or percent of "successes" or "failures" as the primary outcome (approximating Poisson-distributed "count" variables).

As noted above, TCDD is also measured continuously in parts per quadrillion.

For continuous outcomes, therefore, using the initial PTSD groupings as blocks or strata, analysis of variance

(covariance) techniques can be employed to investigate differences in test results, adjusting for TCDD levels. See Snedecor and Cochran (1972) for further discussion of covariance adjustment. For "count" data, a square root transformation can be used (see, for example, Tukey, 1977) and analysis of covariance performed on the transformed data.

For dichotomized results of neuro-behavioral tests, the equivalent approach is logistic regression, comparing PTSD groups pair-wise. If this approach is used, the following set of comparisons should be made:

PTSD Groups:

1. Acute PTSD
2. Delayed PTSD
3. Chronic PTSD
4. Cohort A control
5. Cohort B control

Comparisons:

(a) 1 + 2 + 3 v. 4 + 5 (PTSD v. no PTSD)

(b) 1 v. 2 + 3 (Acute v. delayed or chronic PTSD)

(c) 1 + 2 v. 3 (Acute or delayed v. chronic PTSD)

(d) 4 v. 5 (Cohort A v. Cohort B controls or VE v. no VE exposure)

Finally, using experience from the CDC VE study, principal components analysis or other equivalent multivariate techniques may be used to construct one or more composite indices from the neuro-behavioral tests (Cureton and D'Agostino, 1983). These indices may then be used in place of individual test scores in analyses of variance.

8.4 NURSES SUB-STUDY

The analytic approach to this sub-study will be similar to that for the entire cohort and will address hypotheses in the right-hand column of Table 1.

Two distinct features of this study are:

1. An index of exposure to wounded veterans can be constructed based on nursing workload, proportion of veterans treated, and department or ward assigned.

2. Three comparison groups are available representing a continuum of exposure to nursing of wounded veterans.

With respect to the first feature, an index of exposure must first be constructed. The variables from each tour of duty to be included in the index are:

- workload (average hours worked per day x average number of patients/average number of nurses);
- average proportion of patients who were Vietnam veterans; and
- ward, department or type of hospital unit assigned for all or most of the tour.

Index values will then be summed across all tours of nursing duty during the exposure period. Clearly the Air Force control group from Cohort B will have uniformly low values, based primarily on a regular workload and no nursing care of Vietnam veterans, while Army nurses serving at least one full tour in Vietnam and additional tours in CONUS hospitals will have the highest scores.

Logistic models will then be constructed for health outcomes, using this index and other covariates (including age and length of service prior to exposure) and ignoring comparison group designation.

Apart from this comprehensive analysis, the following group comparisons should be investigated:

Comparison Group:

1. Army nurse, Cohort A

2. Army nurse, Cohort B

3. Air Force nurse, Cohort B

Comparisons:

(a) 1 + 2 v. 3

(b) 1 v. 2

8.5 VALIDATION SUB-STUDIES

This distinct set of studies involves relatively straight forward estimation of the proportion of self-reports not verified by other independent information sources.

The proportion will be estimated and a one-sided test of significance used as follows:

H_o: $p \leq 0.10$

H_1: $p > 0.10$

The significance level, because of multiple testing, will be set at 0.01 (one-sided), so that the test criterion will be 2.33 standard errors above 0.10. An estimate ($\hat{p}$) above the test criterion will result in rejection of unvalidated self-reported outcomes for inclusion in analysis.

8.6 COMPARISON WITH OTHER DATA SETS

Sections of the questionnaire (see Deliverable C) to be administered in the telephone interview have been deliberately designed for equivalence with data from the following national surveys:

- National Health Interview Survey (NCHS: on-going);
- National Health and Nutrition Examination Survey III (NCHS: Scheduled to begin the first 3-yr. sample, October, 1988);
- National Survey of Family Growth (NCHS: Cycle IV, 1987).

To the extent that data from these surveys will be available, comparisons on important health outcomes and major confounding variables will be feasible with national, civilian samples of women, surveyed approximately concurrently with this study.

9. HUMAN SUBJECTS

This section reviews requirements for informed consent (9.1) and confidentiality (9.2) in the proposed study, as well as reports to respondents (9.3).

9.1 INFORMED CONSENT

Four types of informed consent will be required from the subject (or next of kin). They are:

- verbal consent to a telephone interview;
- written consent to access medical records;
- written consent to in-person measurement; and
- written consent for examination of offspring.

The basic procedures to be followed in obtaining all of these consents include:

- providing full and accurate information, verbally and in writing;
- answering all subjects' questions; and
- providing subjects with sufficient written material and appropriate contact names and telephone numbers, so that remaining concerns can be adequately addressed even after informed consent is obtained.

Each of the types of consent is discussed below and consent forms are provided in the Appendix.

9.1.1 Verbal Consent

Subjects (proxies) should be mailed, immediately before telephone contact (wherever possible), a letter describing the study, its purpose and sponsorship, inviting participation and alerting the subject to a subsequent telephone call. The letter should contain local and/or toll-free telephone numbers which the subjects can call to verify the legitimacy of the study, as well as the telephone number for the contractor completing the study.

At initial telephone contact, the interviewer will describe, clearly, the following:

- the length of the interview (1.75-2.0 hours);
- the fact that refusal to participate or to answer specific questions will not jeopardize their status with respect to the VA or related services; and
- the complete confidentiality of the information given (even the VA will only have data by ID number, with no way to identify actual individuals by name).

Completion of part or all of the telephone interview will constitute implicit consent.

9.1.2 Access to Medical Records

A written consent form will be mailed, with an accompanying letter, to all subjects (proxies) volunteering the name and address of hospitals or physicians to verify

procedures or diagnoses. A consent form, specifying the name of the hospital/physician source, the name of the subject and the date (as accurately as possible) for the record will be sent to the subject for each procedure/diagnosis. The subject will check the accuracy of the form, sign and date it, and return each form to the contractor. The accompanying letter, to be retained by the subject (proxy), will list all requests made and describe how these requests will be used.

Copies of these written consents will then be sent by the contractor to the hospitals or physicians with covering letters requesting copies of the named record. Follow-up telephone calls to these sources may be required, as well as fees for pulling and copying records.

9.1.3 Consent to In-Person Measurement

For sub-studies requiring in-person measurement, the subject will be asked to read and sign an informed consent form which will be witnessed by a project staff member or subcontractor. The staff member will be trained to answer all questions concerning the procedure, including risks and benefits, before obtaining the subject's signature.

Such consent will be required as follows:

(a) TCDD Blood Sampling

The subject will be informed of her eligibility for this measurement by project staff (by telephone, confirmed by mail). Signed consent will be obtained and witnessed by a Red Cross staff person, who will be trained by the contractor for this study. The original of this consent will be sent to the contractor, a copy being retained by the Red Cross Regional Office.

The risks of giving a unit of blood will be fully explained. The benefits of the TCDD determination will be indirect, involving increased knowledge of the potential effects of this exposure. Blood will not be drawn from subjects with a low hematrocrit who are taking anticoagulants, who have a blood clotting disorder, who are too ill or have a chronic condition (e.g., diabetes) which increases risk of adverse effects from drawing this amount of blood.

(b) Hormone Blood Sampling

For the few women with suspected early natural menopause, a project staff member (or subcontractor) will, in the subject's home, draw two venous blood samples (5 mls each), 20-30 minutes apart, between 7:00am and 10:00am.

The purpose, risks and benefits will be explained, first on the telephone when the appointment is scheduled, and more fully in-person before informed consent is obtained and witnessed. Exclusions from this blood sampling are as in (a) above, except for hematocrit level and chronic condition.

(c) Neuro-Behavioral Testing

As in (a) and (b) above, initial telephone contact will be made by project staff to explain the procedure and schedule an appointment. This will be confirmed in a follow-up letter. The tester will provide, in-person, more detailed explanation and will obtain and witness informed consent.

There are no real risks from these tests (except some fatigue) and only indirect benefits in terms of knowledge accumulation.

9.1.4 Consent for Offspring Examination

For offspring who are legally minors (under 18 years of age), written consent must be obtained from a legal guardian (usually a parent). For children who are over 12 years of age, or who request it, direct written consent will also be obtained from them, if feasible. For offspring who are legally adults and able to give informed consent, written consent will be obtained directly. If an adult offspring is unable to give informed consent, it will be obtained from the legal guardian.

These procedures and the purpose of the examination will be explained to the subject (mother) by telephone and an appointment confirmed by mail, including the examining physician's name and contact telephone number.

At the appointment, the physician will provide a more detailed explanation, answer questions, and obtain and witness informed consent. In cases in which the subject (mother) is not the legal guardian, efforts will be made to obtain consent of the guardian by mail before the appointment is scheduled.

9.2 CONFIDENTIALITY

Minimum requirements for maintaining confidentiality of all data collected, include the following:

- clear separation of all personal identifiers from data collected: and
- strict file security with restricted access to master files which link personal identifiers with ID numbers.

All forms, including telephone contact records and informed consent forms, which include ID numbers and personal identifiers must be separately filed in a securely locked file, with access restricted to designated project staff. Similarly all such computerized files must be maintained under a secure password system.

If contact information is obtained for future follow-up of subjects, this information must be maintained independently and not made available for possible merging with the resulting data sets until such time as a contract is awarded for follow-up data collection.

9.3 REPORTS TO RESPONDENTS

The promise of a final report of findings has been found to be an important motivator to participate in such a study and effective in maintaining high response rates. If a follow-up of participants beyond this study is planned, such a report would have to be carefully prepared to avoid contaminating subsequent data collection. But further data collection should not be a sufficient reason not to send a report.

Finally, participants consenting to any test or measurement should have the option of receiving results of these tests and/or having them sent to a physician. While some tests may be difficult to interpret, most participants will value receiving results. A report should, therefore, at least describe what tests are completed, provide interpretable results wherever possible, and interpret them for the participant. If abnormal values indicate possible underlying pathology, this should be indicated with a recommendation to have a physician check these results.

In particular, two rare events require special attention. First, women with abnormally high TCDD levels, indicating high prior exposure, should be informed of this in a telephone call by project staff, followed by the report itself. The project staff should be prepared to answer respondent questions concerning this result and make appropriate referrals. Second, if an abnormality, not previously diagnosed, is identified in an offspring in the course of a pediatric examination, this information should be conveyed to the respondent by the examining physician verbally, before a report is sent. The examining physician should also be prepared to talk to the offspring's own physician concerning this diagnosis.

10. SCHEDULE AND WORKLOAD

This section outlines the schedule, tasks and workload for completing the proposed study, as well as required project organization.

10.1 TASKS

The following tasks and sub-tasks are identified:

- preparation (recruitment, training, printing of forms, set up of data-management and quality control procedures);
- sampling and tracing of 1000 additional Air Force nurse records;
- abstraction of Chief Nurse reports;
- data collection on cohorts (telephone interviews, in-person measurement, record abstraction, quality control);
- data entry, editing and analysis; and
- final report.

10.1.1 Preparation

This should not be a lengthy task, but provides time to recruit and train staff, set up any subcontracts, set up the data management system and quality control procedures and have all required forms printed.

Although instruments are already developed and tested, they will require formatting and printing by the contractor, in accordance with formatting conventions used by the contractor. Staff will require training in protocols and some staff may require recruitment.

10.1.2 Acquisition of Air Force Nurse Supplementary Sample

This task involves working closely with the VA and the Environmental Support Group (ESG) to sample 1000 records of non-Vietnam veteran Air Force nurses. The most recent name and address for each will then be traced using available record systems including the VA benefits records, active duty records, pension records and reserve listings.

10.1.3 Abstraction of Chief Nurse Reports

These are non-computerized paper reports which are archived in or near Washington D.C. They will require manual abstraction of information at the archive site for subsequent computerization. The maximum number of relevant reports for the exposure period is estimated at 92 months x 100 hospital units/facilities = 9200 reports. The actual number will be less, as not all hospital units operated for the entire 92 months (especially in Vietnam).

10.1.4 Data Collection on Cohorts

This includes obtaining final dispositions on approximately 11,700 names and addresses (including the Air Force supplement), resulting in approximately 9,900 completed interviews. It is estimated that 1000 interviews will be completed in-person, because of no telephones or unlisted numbers and the remainder will be completed by telephone. A 10% sample will be recontacted and dispositions reviewed for quality control.

Apart from the basic telephone interview, the following activities must also be completed:

- abstraction and diagnosis verification of approximately 1000 medical records, including review by three physicians of each of 700 of these records;

- pediatric examination to verify congenital anomalies in approximately 80 families (160 examinations);

- administration of a battery of neuro-behavioral tests to 312 subjects;

- sampling and processing of a unit of blood for TCDD determinations on approximately (260 + 312) x 0.95 = 540 subjects, assuming about 5% will not be eligible to have this amount of blood drawn.

- sampling and processing of blood samples for no more than 50 subjects requiring FSH/LH levels (approximately 1% of an estimated 3000 subjects under 40 years of age).

10.1.5 Data Entry Editing and Analysis

This task will overlap with data collection and involves construction of clean, edited and documented data sets for analysis. The following data sets will be constructed for analysis:

- data sets 1, 2, 3 and 4 as described in Section 2 above for the main study and nurses sub-study;

- data sets for the Reproductive Outcome and PTSD sub-studies;

- validation data sets for all major outcome groupings as defined in Section 2 above, including self-reported data and equivalent data from all independent sources accessed, for each validated record;

- data set of Chief Nurses' Reports, to be linked by hospital code and dates to individual service records of subjects (data sets 1 - 4).

10.1.6 Final Report

It is assumed that a draft Final Report will be submitted for comment in time to allow reanalysis and other revisions before submission of a Final Report.

10.2 SCHEDULE

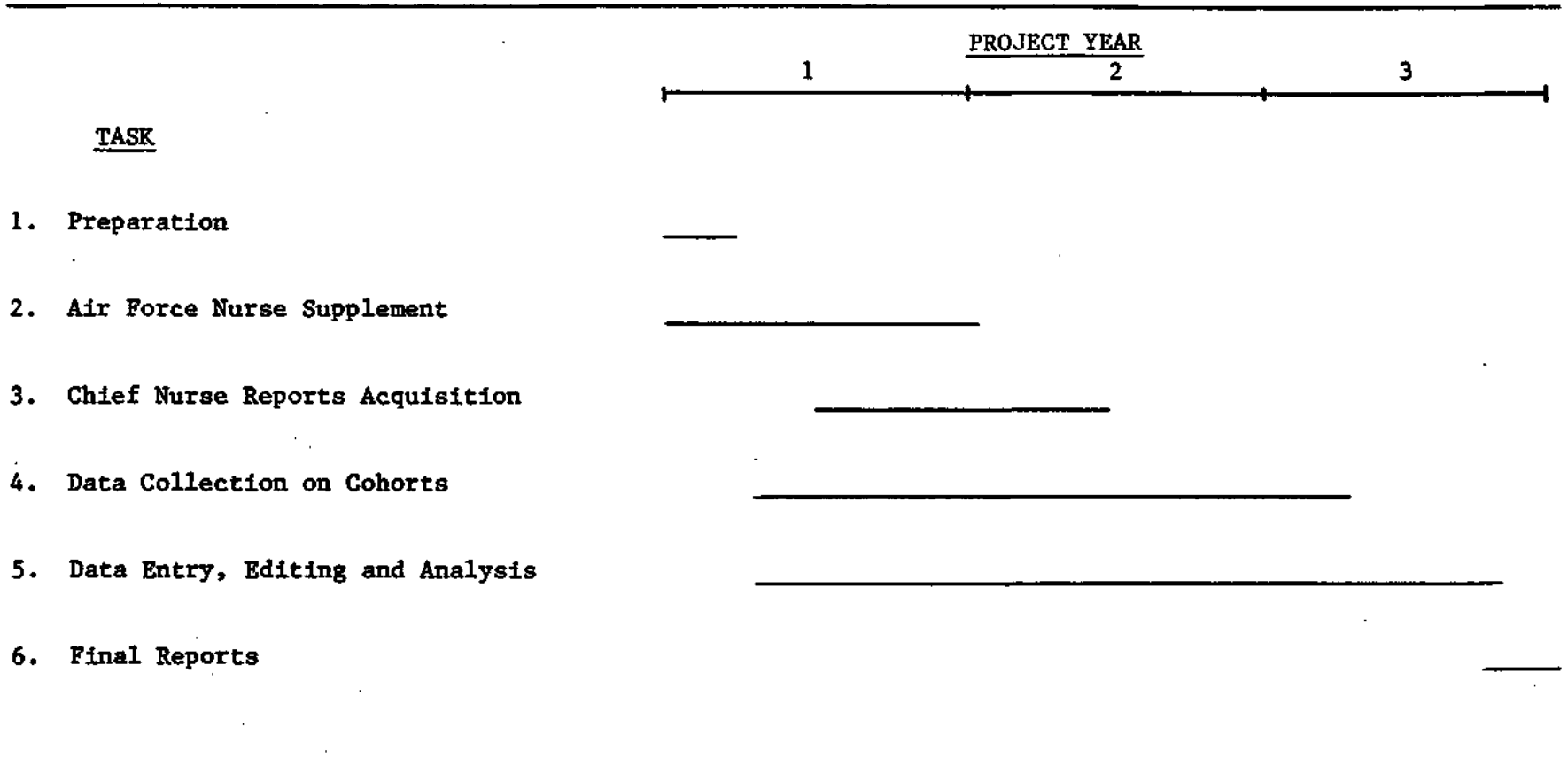
Assuming a three year study period, the schedule of tasks described in 10.1 above is summarized in Figure 2.

Only three months is provided for preparatory tasks as described above.

Sampling and tracing of the Air Force Nurse Supplement should be completed in one year, beginning in the first month, so that sufficient time is available (15 months) for data collection on this supplementary sample.

Abstraction and computerization of the Chief Nurse Reports can occur in parallel with data collection as it is an independent activity. Twelve months is allowed for this task so that the data set is available for pre-testing of linkages with a preliminary data set from telephone interviews with subjects.

FIGURE 2. SCHEDULE OF TASKS



All data collection is to be completed in 24 months. Collection activities will, of course, be staggered, with in-person measurement and record abstraction occurring up to three months after interview completion.

Data entry, editing and analysis is planned to occur in parallel with data collection. For the Reproductive Outcome, PTSD and validation substudies, data from the telephone interview must be computerized before eligibility is determined. This design constraint requires timely editing and computerization of all telephone interviews as they are completed.

10.3 WORKLOAD

Table 8 summarizes the volume of work required for all data collection tasks and indicates the level of effort required in full-time equivalents (FTE's) per month, based on 20 work days per month and the indicated completion rate per FTE per day. The completion rates include time for paperwork and travel as well as vacation and sick leave allowances. The rates are estimated from other, similar data collection tasks completed by the contractor.

10.4 ORGANIZATION

The project director or principal investigator should be an epidemiologist (Ph.D. or M.D.) with an appropriate background in reproductive, chronic disease and/or occupational epidemiology. Other senior project staff should provide complementary epidemiologic expertise. Project leadership will require at least 0.5 FTE (comprising one or more individuals).

TABLE 8. DATA COLLECTION WORKLOAD

Data Collection Task:	Volume	Completion/ FTE/day	No. FTE's per month
1. Interviewing			
(a) Telephone	10,530	4	5.5
(b) In person	1,170	1.5	1.5
2. Record Abstraction[a]			
(a) Acquisition/Abstraction	1,000	2	1.0
(b) Diagnosis verification	700	8	260 consultant physician days
3. Pediatric Examination	80	1 (family)	0.5 (physician)
4. Neuro-Behavioral Testing	312	1	1.0
5. TCDD Blood Sampling[b]	545	1	1.5 plus Red Cross
6. Chief Nurses' Reports	9,600 (max)	16	2.5
7. Air Force Nurses Supplement	1,000	--	2.0

continued next page

Table 8. continued

(a). Records will be abstracted as follows:

• Habitual Abortion	62	
• Selected Cancer Diagnoses	60	(30 cases STS, HD, NHC x2)
• Heart Disease and Stroke	380*	
• Other Cancer (sample)	100	
• Depression, PTSD (sample)	100	
• Hysterectomy and oopherectomy	100	
• Death certificates	200	
TOTAL	1002	

* Approximately 300 of these will not require physician review. Application of a standard algorithm will be sufficient.

(b). The total number required is calculated as follows:

• Reproductive Outcome Sub-Study	260	(130 each cases and controls)
• PTSD Sub-Study	314	
TOTAL	574	
5% eliminated	29	
	545	

Apart from project direction, the following supervision and technical effort is required:

- Interviewing: Supervision of 7 FTE interviewers;

- In-Person Measurement: Supervision of 4 FTE's for record abstraction, pediatric examination (physician), neuro-behavioral testing and training for TCDD blood sampling, as well as liaison with Red Cross Regional Offices and laboratories;

- Data Set Acquisition: Supervision of the acquisition of the Air Force Nurses Supplementary Sample and Chief Nurses' Reports;

- Data Management: Supervision of programmers and data entry personnel to ensure adequate support to the data collection effort and timely completion of data files for analysis;

- Data Analysis: Senior statistical expertise to direct statistical programmers in the analysis.

- Physician Panel: A panel of internists, oncologists, cardiologists, pathologists and reproductive specialists is to be retained for record review;

- Other Technical Consultants: Additional resources to be available to the project should include (but are not limited to) consultants on military and veteran issues, the Vietnam conflict, occupational risks in nursing, and phenoxy herbicide/TCDD effects.

11. UNRESOLVED ISSUES

As of June 30, 1987, some key issues remain unresolved, related to on-going research which may have an impact on study design, data collection and/or analysis. For most of these issues, data will be available later in 1987 or early in 1988, in time to inform the approach before data collection begins.

(a) Diagnostic and Statistical Manual Revision

A new version, with revised criteria for PTSD is currently being finalized. This will have a direct impact on the Diagnostic Interview Schedule (proposed to measure PTSD), which is also under revision to reflect these changes. The questionnaire should include questions to allow coding by either DSM-III or by the revised version in order to permit comparisons with other already completed studies which used the current version (DSM-III).

(b) Neuro-Behavioral Testing

A full-day, comprehensive battery of tests has been included in the VE study currently being conducted by CDC and is proposed for this study (see Appendix). The analysis of results on these tests should identify an optimal sub-set, which can be administered in a home setting to women veterans. Currently there are no appropriate data sets available on which to base such a determination. If possible, based on CDC VE study results, the battery of tests should be shortened to a subset which can be completed in 3 hours or less.

(c) Agent Orange Exposure Determination

The index constructed for use in CDC's current Agent Orange Pilot Study relied very heavily on the "Service Herbs" tapes documenting perimeter and other ground sprayings/contamination. Unfortunately, this data set is very incomplete as documented in the Report of the Agent Orange Working Group Science Subpanel on Exposure Assessment (June, 1986). Even though the movements of female personnel were much more restricted than combat troops and, therefore, more reliably documented, a preliminary review of available data indicates that the highly variable quality of spraying data makes construction of a valid, reliable index problematic.

It is, therefore, proposed that inclusion of an index of exposure to phenoxy herbicides/TCDD be contingent on the results of CDC's Agent Orange pilot study which validates the index against TCDD body burden. A report of these results is due July 31, 1987. The results of the pilot study may also modify the approach to analyzing TCDD data proposed for this study.

(d) Obtaining Medical Records

The contractors are unaware of any prior study which has successfully obtained medical (particularly hospital) records up to 25 years prior to contact with a respondent. Extensive follow-up of Framingham Study respondents over 20 years or more, to obtain hospital records, is currently underway. Preliminary results from this effort should be available early in 1988, with which to inform the feasibility of this proposed activity to validate health events and diagnoses.

Depending on the Framingham Study experience, validation studies proposed here, may require modification.

(e) PTSD Diagnosis

Dr. Lee Robins of University of Washington, St. Louis, Missouri, has recently developed a shorter version of the DIS used for diagnosing PTSD as well as other disorders. This instrument will be available by early fall, 1987, after thorough pre-testing and validation and is specifically designed for telephone administration. It is proposed that this instrument be considered to replace sections of the current questionnaire for the following reasons:

- it is relatively short (no more than 30 minutes);
- has been thoroughly tested and validated; and
- permits discrimination of acute, delayed and chronic PTSD.

(f) Future Follow-Up of Participants

It is proposed that comprehensive contact information be obtained from all study participants to facilitate possible further follow-up for both mortality as well as selected morbidity (including selected cancers and heart disease.) Given the cost of the NHANES I Follow-Up Study (NCHS), in which participants were traced at great expense after 10 years with no contact information available, it is strongly recommended that the same error not be made in this important study. The proposed study includes a follow-up since exposure of, at most, 24 years. The majority are still premenopausal, and have not reached the age at which cardiovascular events increase. Important cancers (STS, in particular) may have long latency periods of 30 years or

more. Funding for further follow-up is therefore recommended, and the collection of contact information is proposed with that in view.

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