Review of a Protocol for a Study of Reproductive Health Outcomes Among Women Vietnam Veterans

December 1991

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OTA Background Paper

Review of a Protocol for "A Study of Reproductive Health Outcomes Among Women Vietnam Veterans" (dated July 1991)

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OTA Health Program
U.S. Congress
Washington, DC

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OTA REVIEW OF A PROTOCOL FOR

"A STUDY OF REPRODUCTIVE HEALTH OUTCOMES AMONG WOMEN VIETNAM VETERANS" (dated July 1991)

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INTRODUCTION

OTA's Veterans Studies Advisory Panel met on November 21, 1991 to review the protocol for "A Study of Reproductive Health Outcomes Among Women Vietnam Veterans." The study has been proposed as a partial response to the mandate of Public Law 99-272; that law also requires approval from the Director of OTA before any such studies are undertaken, which is the reason for this review. Dr. Kang, the principal investigator from the Department of Veterans' Affairs (VA), joined the meeting for the morning.

This study is one of three that make up the full VA response to the mandate to look into the health of women Vietnam veterans. The first was a study of the patterns of mortality among women Vietnam veterans after leaving the service, which has been published in the November 1991 issue of the *American Journal of Epidemiology.* The second piece is an in-depth analysis of psychological health data collected in the National Vietnam Veterans Readjustment Study (NVVRS). The NVVRS was carried out under contract to VA by Research Triangle Institute; VA itself plans to carry out the additional analysis of data from interviews of women Vietnam veterans.

OVERVIEW OF STUDY

This protocol describes a study of the reproductive history of women who served in the military in Vietnam. The study would compare women Vietnam veterans with other women who served in the military during the Vietnam era, but remained largely within the continental United States. This "control"

group would be selected to achieve similarity with the Vietnam cohort in the proportion of women from each service; and within each service, of rank and military occupation. Most of the women (80 percent) who served in Vietnam were nurses.

VA has identified about 4600 women of the estimated 5,000-7,000 who served in Vietnam; as many as possible of those identified will be included in the study. Assuming that it is possible to locate 90 percent of them, and that 95 percent of those located agree to be interviewed, about 3600 will participate; an equal number of controls will be sought. The first hurdle will be to obtain current addresses for the full Vietnam and control cohorts, and to contact them by mail about the study. Each willing participant will be interviewed by telephone. During the interview, women will be asked to identify doctors from whom care was received for reproductive events and the hospitals where events took place, and to obtain permission for the records to be released to the researchers. Appropriate records would then be sought to verify interview data and to gather additional information.

The VA has, with the assistance of the services, identified the cohorts, which were assembled for the mortality study. That study did not require direct contact with the women, however. When the protocol is final, VA will issue a Request for Proposals from researchers who would collect the data; this includes tracing and contacting potential participants, carrying out interviews, and obtaining medical records. The data analysis will be carried out by VA.

A pilot study will test the feasibility of the proposed procedures and gather some baseline information about the women in the Vietnam and control cohorts. VA will determine whether the procedures are working sufficiently

well at that time, and will propose either to proceed with the study (with or without adjustments) or to halt it in the event there are serious and insurmountable problems. OTA will review the pilot study results at that time, review the VA's plan for proceeding, and then report to the Congress and the Secretary of Veteran's Affairs on the outlook for the study.

An oversight committee, consisting of "no more than 5 nationally recognized experts" in relevant fields, is specified in the protocol. The committee will be involved throughout the study guiding the process and reviewing progress; however, it has not yet been recruited. VA has estimated the total time for the study at three years.

CRITIQUE

The question of reproductive health is important to women Vietnam veterans, and addressing it responds to the legal mandate. The protocol displays a thoughtful approach to the study question, and one that is of an appropriate and practical scale. It was the sense of the OTA Advisory Panel that the study should be allowed to proceed without further OTA intervention, on the condition that the aims of the study be clarified and prioritized, that more explicit consideration be given to potential problems in the comparability of the Vietnam and control cohorts, and that further development of the questionnaire take place before it is implemented. These concerns are discussed below.

It is also suggested that thought be given to criteria against which to measure the results of the pilot study for the final decision on whether to proceed with the full study, both for participation and for comparability of

the cohorts. An additional point that was raised concerns the potential to link individual data from the NVVRS with data collected in the current study, for those women in the NVVRS sample. According to Dr. Kang, hurdles still remain in working this out with Research Triangle Institute. We urge resolution of the problems so that this linkage can be made.

A final point deals with the proposed letter of invitation to participants, which identifies the study as a "health study of women Vietnam era veterans." It is possible that linking the study to Vietnam in the minds of participants could introduce a bias in the way the study is perceived, and therefore, in some women's responses. It would be honest and correct to identify the study as simply a health study of women veterans, and avoid this possibility.

Aims of the Study

The stated aims of the study relate to reproductive history and history of cancers of the reproductive system. This includes studying birth defects in children born to the women in the study. It is clear from the questionnaire, however, that additional information is being sought, particularly concerning current lifestyle and past experiences as a military nurse. Dr. Kang explained that the VA knows relatively little about women veterans, and this study is seen as an opportunity to fill in some gaps. The questionnaire is generally not too burdensome, and, if it is restructured, the additional questions should not interfere with gathering data essential to the reproductive health issues (see below). The desire to collect additional data should be made explicit, particularly as the questionnaire must undergo OMB review. The various aims should be clarified and highest priority should be

given to answering the central study questions. A question not currently addressed that should be added concerns childhood cancers in the children. This addition should not require a great deal more effort.

Comparabilitv of the Vietnam and Control Cohorts

The most basic assumption underlying a cohort study such as the one proposed by VA is that the two cohorts are similar except for the “exposure” of interest, in this case, having served in Vietnam. Differences in the outcomes of interest (in this case reproductive events) other than those caused by random variations between the two groups, can be confidently associated with the exposure (whether actually caused by it or associated through intermediate steps) only when this assumption is met. Various techniques can be used to improve this comparability- -e.g. , in this study by matching the frequency of ranks and military occupations within each service-- but there may be differences between the groups that no amount of manipulation can erase, and which may invalidate the results. It is important that, to the extent possible, the potential for such differences be investigated before the study begins and during the pilot phase. The particular concerns raised by the Advisory Panel have to do with how women in the military were chosen to go to Vietnam and what happened to them if they became pregnant or gave birth while in the military.

During the Vietnam era, women were not drafted, so all those in the military had volunteered. But no information was provided in the protocol to explain the criteria used to determine which servicewomen would go to Vietnam and when, and the concern is that fertility status, or marital status, might have influenced those decisions. In the extreme case, for instance, if all

women who were married or had children stayed in the United States and only those without those ties were sent to Vietnam, then by definition, the Vietnam cohort would have started out infertile relative to the stateside cohort. It is also possible that treatment of women who gave birth might have been different for those serving in Vietnam and those in the United States. It is important to determine the service policy relating to marriage and pregnancy not only during the Vietnam era, but after Vietnam as well. A difference in career nursing patterns after Vietnam could also introduce a substantial bias.

The Advisory Panel suggested two approaches to this issue. First, VA researchers should find out from each service the criteria used for assigning women to Vietnam or United States posts, and the official rules for handling pregnancies and childbirths among military women. Second, specific analyses " should be carried out on the pilot study data to test the hypothesis that the fertility status of a woman might have influenced her assignment and that variations in handling childbirth might have also created differences between the two cohorts. If major differences are found, serious consideration should be given to halting the study.

It should also be noted that post-Vietnam experiences and exposures to agents that cause infertility or birth defects are equally or more likely to be related to differences in outcome between Vietnam and non-Vietnam exposed nurses than are their Vietnam-era experiences. This makes subsequent occupational and social history very important.

Further Development of the Questionnaire

Some restructuring and development of the questionnaire will be needed before the pilot study can begin. The Advisory Panel agreed that VA should

use its oversight committee to assist with this task, and to seek out questionnaires used in other studies for components that might be superior to those in the current draft. The strongest recommendation concerning the structure of the questionnaire is that the primary aims--those related to reproductive system events--be preeminent. This would require moving all lifestyle questions (except those with direct relevance to pregnancies) to the end of the questionnaire (the brief general health questions could remain at the beginning as an introduction) , and possibly eliminating some of the existing redundancy in the draft questionnaire.

There are a number of acceptable approaches to eliciting a reproductive history, and VA should explore some of these alternatives. In particular, interest was expressed in a chronological approach that incorporates marital and sexual history, reproductive history, pregnancy history (including relevant exposures and illnesses), and menstrual history, all of which are separate sections in the draft that we reviewed.

Many details of the questionnaire were discussed with Dr. Kang at the meeting and will not be included in this review. But it should be noted that there are currently problems with logic in some places, and that lists of diseases (i.e., those affecting fertility) and exposures (i.e., potentially genotoxic exposures) are incomplete and in some cases, misplaced (e.g. , history of sexually transmitted diseases is elicited for pregnant women only, when they are major causes of infertility) . It was’ felt that review by experts in the relevant fields would be sufficient to correct these deficiencies and that this was a necessary step before the pilot study could begin.

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The Honorable Alan Cranston
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DEC 271991

Dear Alan:

Enclosed is OTA's review of the protocol for "A Study of Reproductive Health Outcomes Among Women Vietnam Veterans , " prepared by the Department of Veterans Affairs (VA) in partial response to the mandate of Public Law 99-272, which requires study of potential health effects of Vietnam service on women veterans. The study complements two other components) which together make up the full VA response to the mandate. The first was a study of the patterns of mortality among women Vietnam veterans after leaving the service, which has been published in the November 1991 issue of the American **Journal of** *Epidemiology. The* second piece is an in-depth **analysis** of psychological health data collected on women Vietnam veterans in the National Vietnam Veterans Readjustment Study (NVVRS). The NVVRS was carried out under contract to VA by Research Triangle Institute; VA itself plans to carry out the additional analysis of data from interviews of women Vietnam veterans.

The protocol describes a reasonable and workable approach to studying the reproductive health of women Vietnam veterans. As is required in PL 99-272, I hereby approve the protocol, but do so with the following condition. OTA believes that significant, though not extensive, reworking of the proposed questionnaire is necessary before the pilot study begins. The issues of concern are described in the enclosed review, and a suggestion for making **the** improvements through the oversight committee for the study is made. It is OTA's judgment that the reworking is best left to the VA and its advisors, and that no additional actions by OTA will be necessary until the results of the pilot study are ready for review. At that time, OTA will examine the results and VA's recommendations for proceeding, and get back to the Committee with our assessment. According to the schedule in the protocol, that will be about 16 months after the study begins.

It is gratifying to be able to approve this protocol after a disappointing experience with the first protocol attempt. If all goes according to plan with this study, it will provide important information for women Vietnam veterans and for the Congress. Please do not hesitate to call on me if you have questions about this, or to contact Hellen Gelband in the OTA Health Program, who is responsible for this review.

Sincerely,

(signed) Jack

John H. Gibbons

Enclosure