CSP# 585 Pilot Project:

Gulf War Era Cohort and Biorepository

Study Chair:

Dawn Provenzale, MD, MS

Protocol Submitted to VA Central IRB

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Contents

Department of Veterans Affairs

DEPARTMENT OF VETERANS AFFAIRS
Medical Center
508 Fulton Street (152)
Durham, NC 27705

May 8, 2013

«V_FULL_NAME»
«V_MAIL_ADDR»
«V_C_S_Z»

Dear «V_SALUT» «V_LNAME»,

It has been more than 20 years since the first Gulf War began in 1990. As a Veteran of the Gulf War Era (1990-91), we are inviting your participation in a new project sponsored by the Department of Veterans Affairs. The project is called, "Gulf War Era Cohort and Biorepository," and its aim is to develop a resource for future research studies that will be focused on expanding our knowledge of the conditions that are affecting Gulf War Era Veterans like you. The project is open to all Gulf War Era Veterans, whether or not you were deployed to the Persian Gulf area, or whether or not you receive health care services from the VA.

The project mainly involves collecting information from a survey, national VA resources, and prior studies of Gulf War era Veterans, as well as collecting blood specimens. However, before we begin our full recruitment into the study, we would like to pilot test the survey with veterans. We want to be sure that the questions make sense and see how long it takes people to complete the survey. The pilot test should take about an hour and a half and you will receive a $50 gift card for your time and effort.

The pilot test will take place at the offices of SRA International in Durham, near the intersection of Highway 55 and Interstate 40. I have included a map and directions to the office for your convenience.

If you have any questions or are interested in participating in the pilot test, please call Kathy Hampton at 919-313-7579.

If we do not hear from you soon, we will call to see if you are interested in participating in the pilot test.

Thank you very much for considering our invitation to help us with this important project. We hope you accept our invitation, and we look forward to talking with you.

Sincerely,

Dawn Provenzale

Study Chair and Director
Epidemiologic Research & Information Center

PID «PID»
Doc CTL 201303-2.0 (03/22/2012)

Appendix E.

Figures

I. Summary

To date, the Department of Veterans Affairs (VA), the Department of Defense (DoD), and the Department of Health and Human Services have funded over 360 research projects pertaining to the health consequences of military service in the 1990-1991 Gulf War. This past research represents a tremendous investment into understanding the medical conditions of these Veterans. However, many important questions remain to be answered about conditions affecting Gulf War Veterans. In addition, the Gulf War Veteran population is entering the age range at which the incidence of chronic diseases increases rapidly, and other questions regarding the health and medical care of this important cohort will be raised in the next few years. For these reasons, we proposed to develop a research cohort of Gulf War Era Veterans and a biorepository to be made available for future research studies.

We planned to establish a large-scale longitudinal research database that would integrate epidemiological, survey, clinical, and environmental exposure data of the Gulf War Era cohort. Blood specimens were used to establish the biorepository. Our goal was to enable the availability of blood specimens and the research database for a wide range of future genomic and genetic studies, biologic and immunologic research, and epidemiological, clinical, and health services research. Phase one of this pilot project represented the initial implementation of the cohort and biorepository. We targeted an enrollment of 3,000 Veterans. During the pilot project, the recruitment response rate and other operational and logistical aspects were assessed.

Veterans of the Gulf War Era were identified largely through existing VA and Department of Defense registries and databases. We aimed to recruit 3,000 Veterans. These included both users and non-users of the VA healthcare system. A Veteran was eligible if s/he served in the military in 1990-91 without regard to actual deployment to Southwest Asia. Initially, the Gulf War Era Research Database has been populated with data collected from a survey of participating Veterans. The database and biorepository may be supplemented by data and blood collected from national VA resources and from future or prior studies of Gulf War Era Veterans. Completing the survey and providing blood specimens were required for enrollment in the pilot project.

Recruitment for phase one of the pilot project ended in May 2016. Although active recruitment has ended, the CSP 585 project team may continue to receive participant materials, because this was a mailed recruitment process. As such, Veterans may continue to be enrolled if they send back signed informed consent forms. If this happens, Veterans will be mailed a letter notifying them that phase one of the project has ended. We now plan to engage in analysis of the data collected to better understand the health and health conditions of participants (Veterans with signed consent forms, survey information, and a blood sample) in this project.

During phase two of the pilot project, we assessed operational and logistical aspects of this project and projects like it through a qualitative research component. During phase one of this pilot study, we developed a number of processes to support our project protocol, many of which

have not been widely used within VA research. Typically, VA-sponsored studies do not target non-users, nor work with contractors to manage data systems and blood collection processes. It was important to assess whether Gulf War Era (GWE) Veterans, especially non-users, would participate in a project like this, and to identify ways in which current and future processes in this and other projects may be refined to better meet the needs of this population and more effectively accomplish project aims. Gulf War Era research remains a high priority within the VA, and the findings from the qualitative component can inform improvements to research projects recruiting Gulf War Era Veterans.

Through the qualitative component, we gained a better understanding of GWE Veterans' (VHA users and non-users) perspectives regarding enrollment in CSP 585 and other projects like it, specifically around barriers and facilitators to participation and effective recruitment strategies. Findings from this activity provided valuable Veteran-reported perspectives on participation in research that will support the development of more effective enrollment strategies for this population.

By learning more about Veterans' perspectives and experiences, we were able to better understand issues related to recruitment and retention in CSP 585, and can offer valuable recommendations that can be applied throughout VA research as a whole.

II. Specific Aims

This was a minimal risk observational pilot project to test the processes needed to establish a research cohort and biorepository of Gulf War Era Veterans to be used for future research studies. The pilot project had two specific aims:

1. Assess the feasibility and efficacy of the planned recruitment, consenting, and blood drawing and shipping processes, and of modifications to the processes (if necessary), including assessing Veterans' perspectives on this project and others like it and

2. Develop, test, and implement the database structures required for subject enrollment tracking, blood sample tracking, and data storage.

III. Importance

There has been substantial research into the health care needs of Gulf War Era Veterans, but the incidence of chronic diseases that should be expected as this population ages is uncertain. Data from the cohort described in this protocol and the integration of blood-dependent methodologies such as genome-wide association studies (GWAS) will provide valuable resources for identifying risk factors and potential treatment pathways for conditions affecting Gulf War Era Veterans, including chronic and aging related diseases. These data can then be used to identify the current and future health care needs of Gulf War Era Veterans to more effectively target programs towards them. The intended users of the Gulf War Era Research Database and Biorepository are

the project staff, VA and non-VA researchers who are specifically interested in conditions affecting Gulf War Era Veterans, and VA and non-VA researchers interested in the physical and mental health concerns that affect a population of this age group. The availability of a research cohort with the particular demographics and the documented experiences of Gulf War Era service will enable more detailed analyses regarding diagnosis and treatment of conditions affecting an aging population than is possible with administrative databases alone. With insights that analyses of data and blood specimens will provide, VA will be better able to focus interventions that will improve diagnosis, treatment, and outcomes of care for all Veterans.

Additionally, Gulf War Era research remains a priority in the VA. Many research projects aim to recruit Gulf War Era Veterans. The knowledge gained through assessing Gulf War Era Veterans' perspectives on this and other research projects has the potential to inform improvements to other research projects recruiting Gulf War Era Veterans.

IV. Project Infrastructure

Cooperative Studies Program: The project is funded by the Department of Veterans Affairs Cooperative Studies Program (CSP) and is being conducted by Dr. Dawn Provenzale at the CSP Epidemiology Center (CSPEC) – Durham and CSP research staff. All information collected over the course of this project will be stored in the Gulf War Era Research Database within the CSPEC-Durham Data and Specimen Repository and maintained by CSP. All blood specimens collected for this project were shipped to and stored at the CSP Central Biorepository, currently in Boston MA, and will be maintained by CSP. A genome-wide association study (GWAS) of DNA from the blood samples will be performed at the Pharmacogenomics Analysis Laboratory (PAL) within CSP. Additional genomic analyses (e.g. methylation, etc.) may also be performed. Specimens collected for this project may also be stored at the CSP backup repository at the CSP Pharmacy in Albuquerque, NM, or another CSP approved repository in the future. The data and blood will be stored and maintained according to CSP policies.

Collaborators: This pilot project to establish the cohort and research database and biorepository employed standard methods for identifying, recruiting, and enrolling project participants and collecting blood specimens. This initiative represents collaboration between CSPEC-Durham and the VA Post-deployment Health Epidemiology Program (PDHEP).

- As Study Chair, **Dawn Provenzale, MD, MS** will oversee all protocol activities. The Gulf War Era Research Database will reside on a secure VA server and will incorporate all data collected under this protocol.
- **Erin Dursa, PhD**, **MPH**, Epidemiologist at PDHEP, will provide Gulf War epidemiology expertise as well as access to relevant VA databases.

Executive Committee: An Executive Committee has been convened and meets regularly to monitor project progress, address IRB, protocol and all other issues and activities related to the project, keep records, maintain the privacy of subjects and the confidentiality of their data, and ensure data are stored and secured according to VA requirements.

Project Meetings: Project meetings consisting of key project staff (local site investigators, site coordinators, project coordinators, statisticians, and others as appropriate) occur on a regular schedule. Regular agenda items will include site progress reports, special events such as site visits by the Study PI or designee (for monitoring purposes), interim results, and IRB and other regulatory issues.

Requests for Data and Samples: Data and specimens collected through this project have become part of the CSPEC-Durham Data and Specimen Repository. All requests for samples and data will be reviewed according to this repository protocol and current VA/CSP policies. This review will include approvals by the Data and Specimen Repository Administrator, in consultation with the repository's Scientific and Ethical Oversight Committee. Criteria will include a detailed proposal and proof of appropriate IRB approvals. Fully executed Material Transfer Agreements and/or Data Use/Transfer Agreements will be required before specimens and data are released.

SMART: The CSP Site Monitoring and Review Team (SMART) will share responsibility for monitoring the project with the Study Chair, Local Site Investigator, and Executive Committee. SMART conducted GCP and Tools training for all project team members at the project kick-off meeting; did an on-line audit of consent forms; reviewed the draft of the project operations manual; and conducted an initial 2-day on-site audit at the Enrollment Coordinating Center. This on-site audit was scheduled shortly after the recruitment and enrollment process was initiated and included monitoring of those activities as they were being performed.

The GCP and Tools Training placed added emphasis on VA-specific guidelines and procedures for the Enrollment Coordinating Center, who attended, in particular, trainings on the informed consent process, non-compliance reporting, adverse event reporting, data security, and confidentiality. SMART assisted the project manager with developing a "central documents binder" and instructions for its use. The binder is organized to meet VA, IRB, and other federal requirements.

As of March 23, 2012, all VA employees will obtain their VA privacy and security training on the VA Talent Management System (TMS). Training for all project team members will be updated per VA requirements.

Local Research Compliance Officers (RCOs): As required by VA, local RCOs have been conducting regulatory audits on the prescribed annual and tri-annual schedule. These audits are conducted independently of other project monitoring procedures and committees. The RCO audit requires a review of documents, most notably the informed consent forms and HIPAA Authorizations. Key project documents are stored at CSPEC- Durham, where they are available for auditing. A copy of routine audit findings is submitted to the VA Central IRB on an ongoing

basis. VA Central IRB will be notified by the RCO of audit findings of serious or continuing non-compliance within five days.

Reporting Requirements to the VA Central IRB: The study chair, local site investigator, and all other project team members will receive the Table of Reporting Requirements developed by the VA Central IRB. Adverse events, serious unanticipated problems, protocol deviations and violations, complaints, and suspension or termination of the research were addressed by SMART to all project team members at the kick-off meeting. These situations required reporting to VA Central IRB (on applicable forms) no later than 5 days after occurrence or having been made aware of their occurrence. Non-routine events and information requiring a report to VA Central IRB will be submitted on the applicable forms (if available) and within the time frame designated by VA Central IRB Handout on Reporting and in VA Handbook 1058.01. These forms are transmitted to VA Central IRB via a secure SharePoint site.

As a minimal risk project with limited in-person contact (for blood collection and/or focus group participation), it is not likely that we will become aware of participants who may become incarcerated or that new information will indicate a change in risks or potential benefits. If these situations do arise, we will notify the VA Central IRB, as required.

When in doubt about any reporting requirements, the study chair will contact the VA Central IRB. The local site will be instructed to notify the study chair of all serious adverse events or unanticipated problems involving risks to participants or others that they have reported to VA Central IRB.

V. Project Design

The basic research methods used in this project were/will be a survey, chart reviews (including VA and non-VA medical records), and the analysis of existing VA and other databases as well as data from relevant research studies. The methods used in the qualitative component were a demographic survey, focus group discussions, and interviews. The blood and DNA samples are stored in a VA biorepository and will be used for genomic analyses (e.g., GWAS, methylation, etc.) as well as future research not yet planned. This project does not involve international research.

A. Cohort Identification

Gulf War Era Veterans were identified from existing VA and Department of Defense (DoD) Manpower Data Center (DMDC) resources and similar resources such as the Gulf War Registry. As Gulf War Era Veterans were identified by DMDC and other resources, the name, social security number, date of birth, and contact information of each were added to a master recruitment roster. CSPEC-Durham then ascertained VA health system user status and vital

status for everyone on the roster. The Enrollment Coordinating Center also updated contact information for users and non-users of the VA health system. In the future, information – including social security number, date of birth, and contact information - on self-nominated, Path C participants may be confirmed by DMDC data.

B. Inclusion/Exclusion Criteria

To enroll in the cohort and biorepository, a potential participant must have been a member of the uniformed services during the 1990-91 Gulf War Era. A Veteran was eligible without regard to deployment to or combat status in Southwest Asia and without regard to current or past user status in the Veterans Health Administration. Veterans currently living in the 48 contiguous United States (excludes Alaska and Hawaii) were eligible. Veterans who were unable to sign their name or make their own mark on consent forms (including with an 'X'), and who required a Legally Authorized Representative to sign, were not eligible to participate. We included deceased Veterans meeting these criteria, as their health histories will be useful to future researchers. A Decedent's Research Form was submitted to the VA Central IRB.

Inclusion/Exclusion Criteria for the qualitative component are listed in the qualitative component section on page 33.

C. Estimated Number of Participants

For this pilot project, we expected to enroll approximately 3,000 participants. The enrollment rate was one aspect of the project that was tested in this pilot phase.

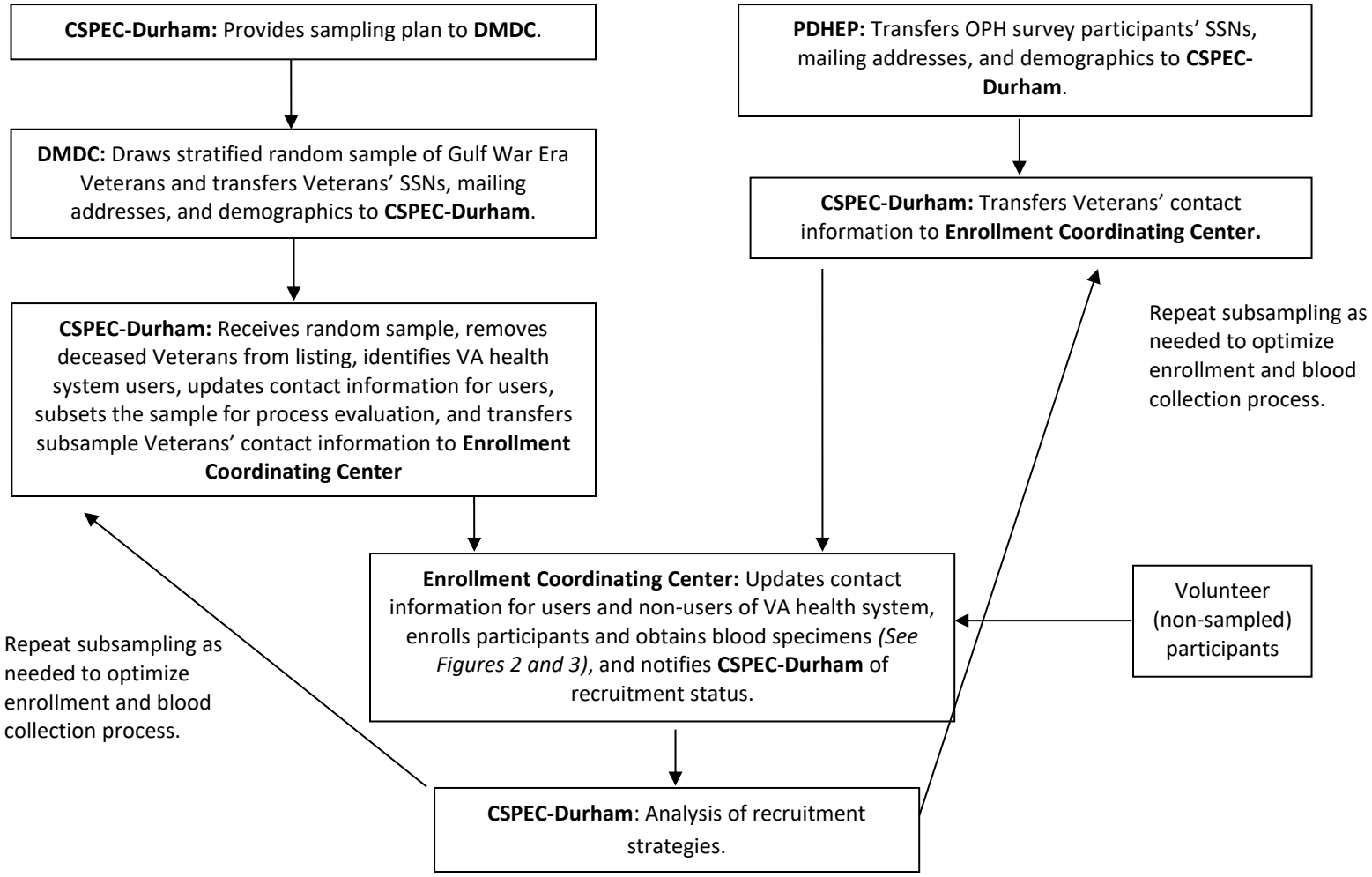
D. Sample Size and Statistical Power

The primary objective of this pilot project was to assess the feasibility and efficacy of the planned recruitment, consenting, and blood draw processes.

In each mailing, a minimum of 50 letters were mailed, for a maximum total project-wide sample size of 10,045 letters sent. Frequent mailings to relatively few Veterans allowed formal and rapid evaluation of project process logistics and refinements, identification of potential challenges, and responsive implementation of approved process changes. Thus, this approach provided a moderately sensitive environment to evaluate the feasibility and efficacy of the planned logistical processes.

A graphical summary of the cohort identification and sampling process, a previous phase of this project that ended in May 2016, is provided in **Figure 1**.

Figure 1. Participant identification



VI. Description of Historical Cohort and Biorepository Recruitment and Enrollment Activities

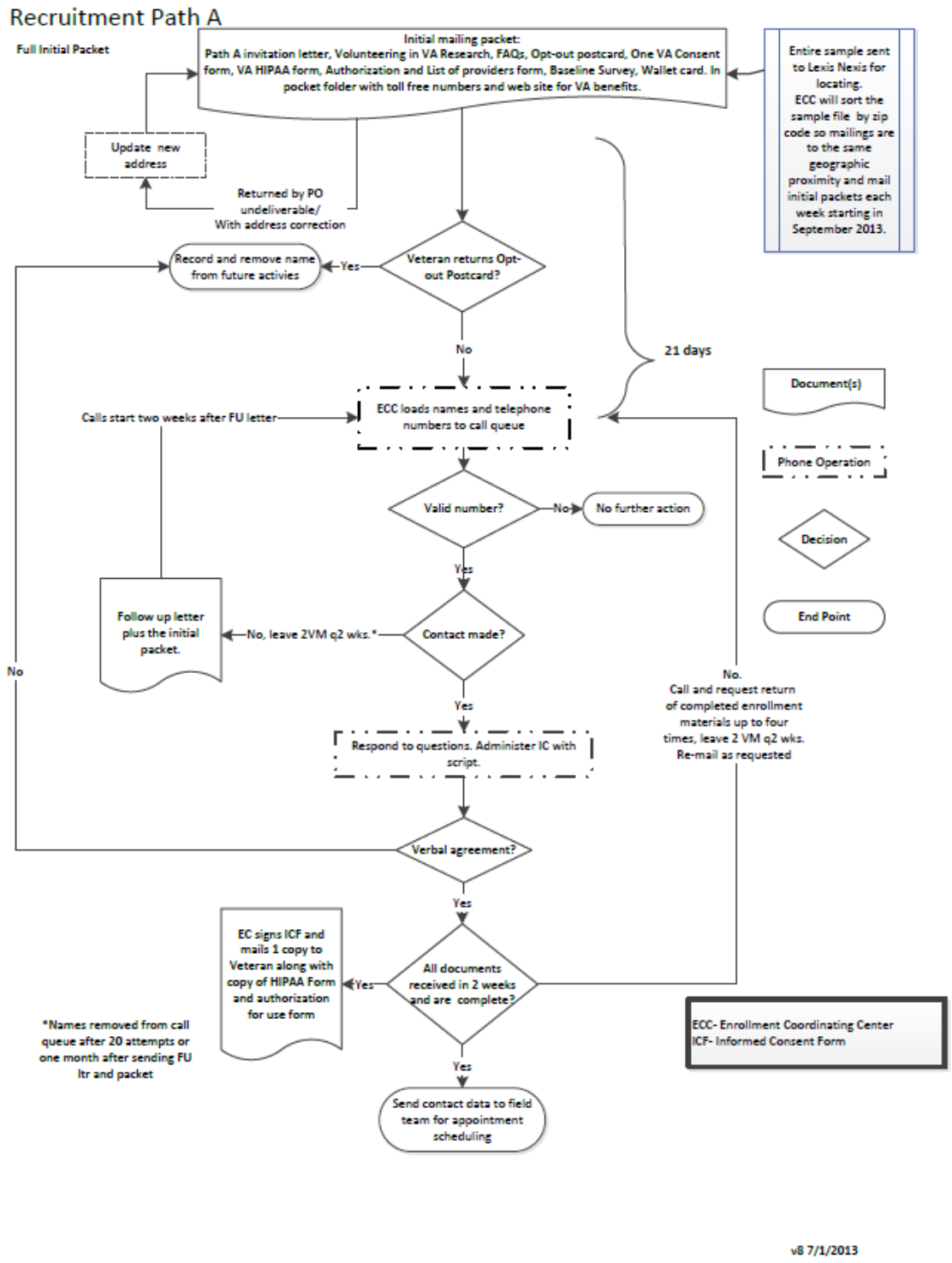
Recruitment, enrollment, and blood collection were contracted to the Enrollment Coordinating Center. The Enrollment Coordinating Center was responsible for obtaining informed consent from the participants for this project. We obtained a waiver to VHA Handbook 1200.05 which granted the Enrollment Coordinating Center the same status as other VA investigators. The Enrollment Coordinating Center was engaged in human subjects research and had the project reviewed and approved by its IRB of record. The IRB approval was a condition of the contract. The FWA and IRB registration number for the Enrollment Coordinating Center's IRB was forwarded to the VA Central IRB.

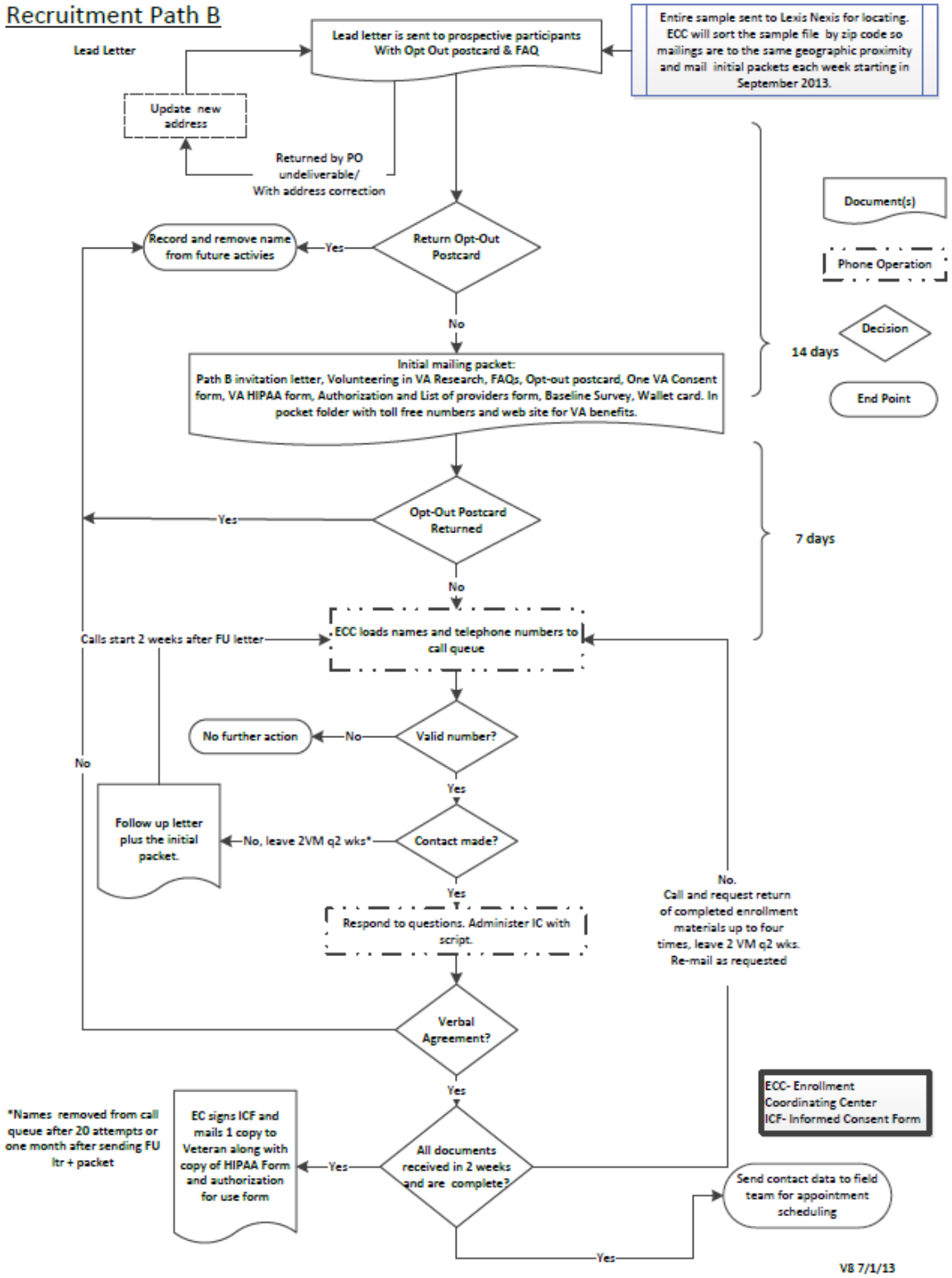
A Business Associate Agreement (BAA) was established with the Enrollment Coordinating Center to further ensure the protection of participants' data and privacy.

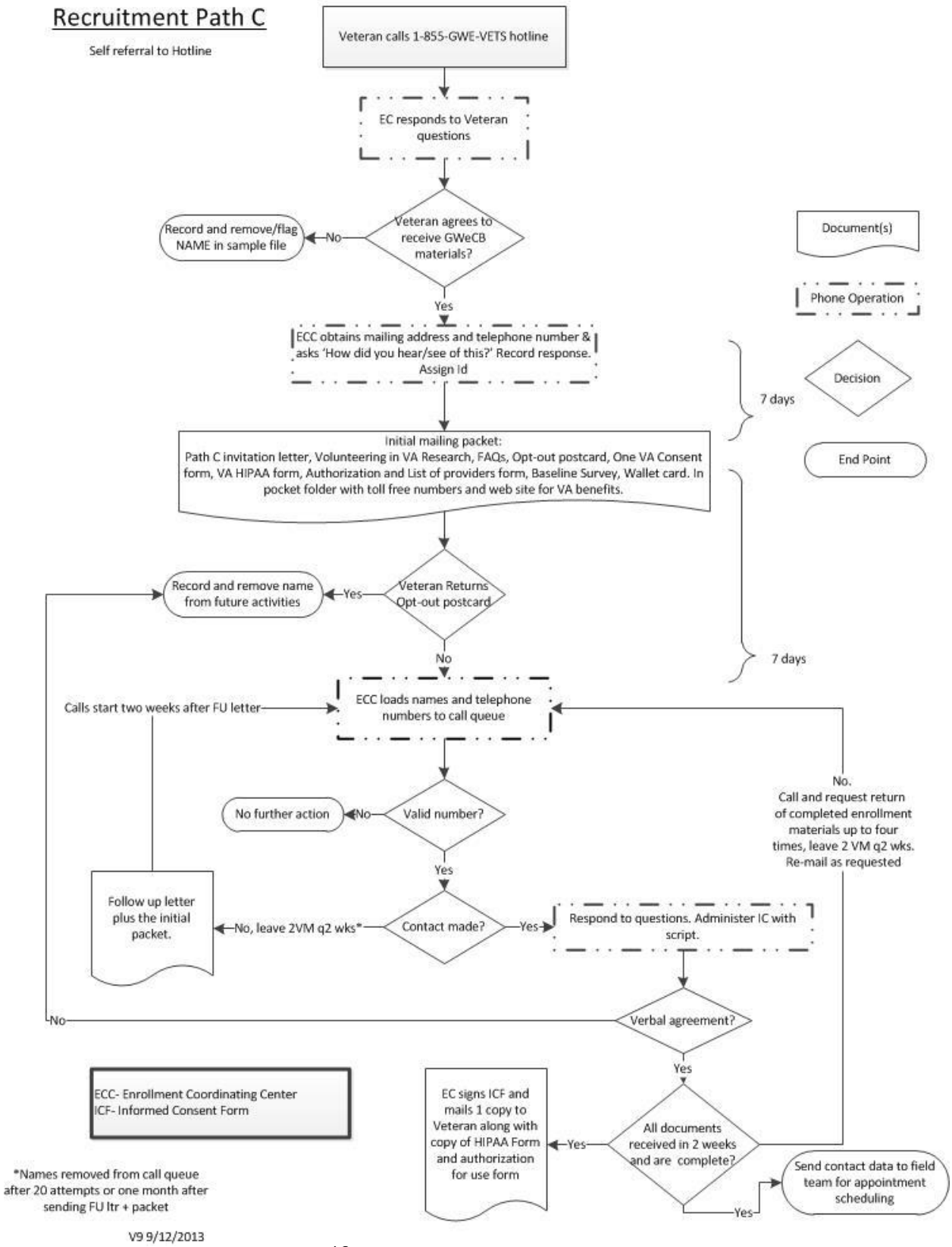
The Enrollment Coordinating Center's employees received training in Good Clinical Practice, including informed consent procedures, by SMART at the project's kick-off meeting. The Enrollment Coordinating Center received their required VA privacy and security training through the TMS and was required to maintain updated training credentials per VA requirements. They were instructed to verify this training before any contact with potential project participants was made. (See Section IV for other SMART activities.)

The historical process of recruitment and enrollment into the cohort and biorepository is summarized in Figure 2. We did not request assent for participants unable to give consent.

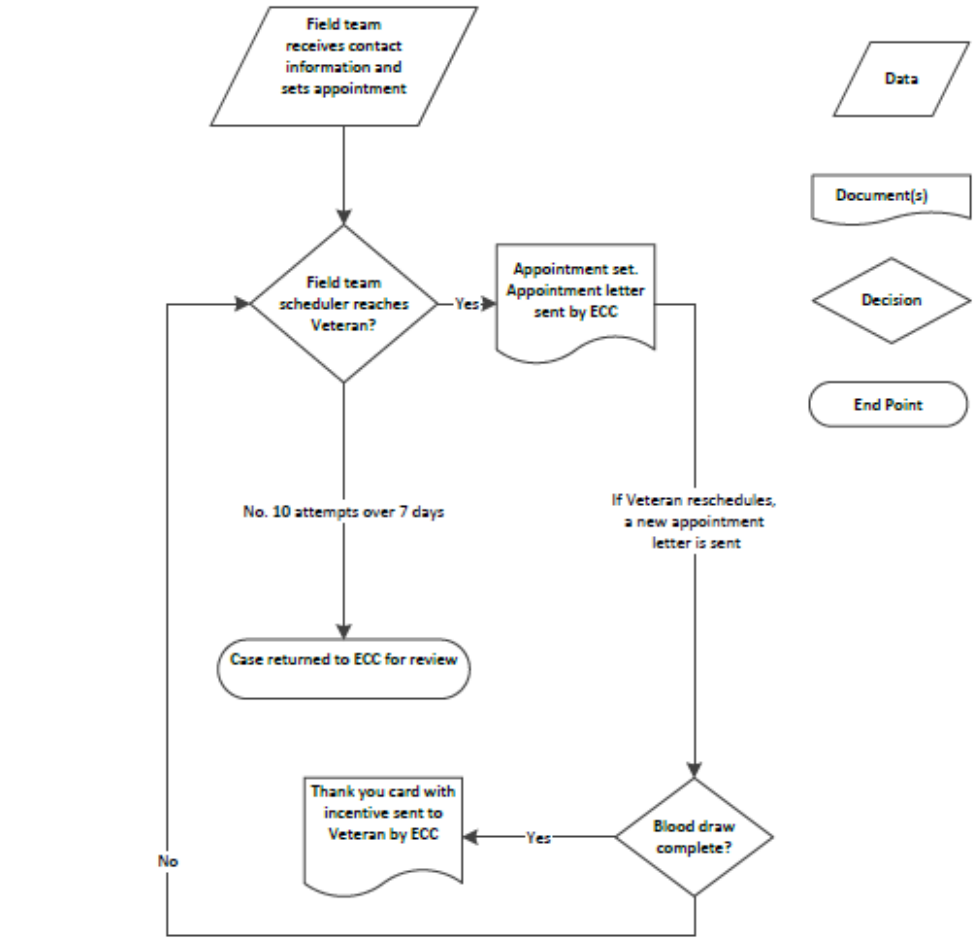
Figure 2. Enrollment Process - HISTORICAL




Recruitment Path B
Lead Letter
Lead letter is sent to prospective participants With Opt Out postcard & FAQ
Entire sample sent to Lexis Nexis for locating. ECC will sort the sample file by zip code so mailings are to the same geographic proximity and mail initial packets each week starting in September 2013.
Update new address
Returned by PO undeliverable/ With address correction
Document(s)
Phone Operation
Decision
End Point
Record and remove name from future activies
Yes
Return Opt-Out Postcard
No
14 days
Initial mailing packet:
Path B invitation letter, Volunteering in VA Research, FAQs, Opt-out postcard, One VA Consent form, VA HIPAA form, Authorization and List of providers form, Baseline Survey, Wallet card. In pocket folder with toll free numbers and web site for VA benefits.
Yes
Opt-Out Postcard Returned
7 days
No
Calls start 2 weeks after FU letter
ECC loads names and telephone numbers to call queue
No further action
No
Valid number?
Yes
No
Follow up letter plus the initial packet.
No, leave 2VM q2 wks*
Contact made?
Yes
No.
Call and request return of completed enrollment materials up to four times, leave 2 VM q2 wks. Re-mail as requested
Respond to questions. Administer IC with script.
Verbal Agreement?
Yes
ECC- Enrollment Coordinating Center
ICF- Informed Consent Form
*Names removed from call queue after 20 attempts or one month after sending FU ltr + packet
EC signs ICF and mails 1 copy to Veteran along with copy of HIPAA Form and authorization for use form
Yes
All documents received in 2 weeks and are complete?
Send contact data to field team for appointment scheduling
Yes
VB 7/1/13


Recruitment Path C
Self referral to Hotline
Veteran calls 1-855-GWE-VETS hotline
EC responds to Veteran questions
Veteran agrees to receive GWeCB materials?
No
Record and remove/flag NAME in sample file
Yes
ECC obtains mailing address and telephone number & asks 'How did you hear/see of this?' Record response. Assign Id
Initial mailing packet:
Path C invitation letter, Volunteering in VA Research, FAQs, Opt-out postcard, One VA Consent form, VA HIPAA form, Authorization and List of providers form, Baseline Survey, Wallet card. In pocket folder with toll free numbers and web site for VA benefits.
Veteran Returns Opt-out postcard
Yes
Record and remove name from future activities
No
Calls start two weeks after FU letter
ECC loads names and telephone numbers to call queue
Valid number?
No
No further action
Yes
Contact made?
No, leave 2VM q2 wks*
Follow up letter plus the initial packet.
Yes
Respond to questions. Administer IC with script.
Verbal agreement?
No
Yes
All documents received in 2 weeks and are complete?
Yes
EC signs ICF and mails 1 copy to Veteran along with copy of HIPAA Form and authorization for use form
Yes
Send contact data to field team for appointment scheduling
No.
Call and request return of completed enrollment materials up to four times, leave 2 VM q2 wks. Re-mail as requested
7 days
7 days
Document(s)
Phone Operation
Decision
End Point
ECC- Enrollment Coordinating Center
ICF- Informed Consent Form
*Names removed from call queue after 20 attempts or one month after sending FU ltr + packet
V9 9/12/2013

Field Operations



ECC- Enrollment Coordinating Center

V3 7/1/13

A. Historical Recruitment into the Cohort and Biorepository

No VA sites were involved in recruitment or enrollment into the cohort and biorepository. Recruitment and enrollment were conducted centrally by mail, phone, print media (e.g. posters, postcards, table tents, project newsletter), and electronic media (e.g. website, web stories, social media).

We reached out in public venues through lectures, tables, and other in-person presentations to provide IRB-approved information about the project, including the phone number of the Enrollment Coordinating Center.

We displayed and provided VA Central IRB-approved informational print media (e.g. postcards, posters, table tents, project newsletters, and frequently asked questions sheet about the project) to individuals or organizations during meetings and conferences, or as a response to requests for information about the project. We referred interested participants to contact our Enrollment Coordinating Center at 1-855-493-8387.

When appropriate, we collected any contact information from interested parties via a VA encrypted laptop and provided their information to our Enrollment Coordinating Center for follow-up. The laptop was in possession of a VA approved project team member at all times. The laptop was used to capture names, phone numbers and/or addresses. This information resides on secure servers at the Durham VA Medical Center. OI&T personnel schedule and monitor daily backups of research data to OI&T servers or to backup tapes that are stored in a locked secure location.

Once the contact information was provided to the Enrollment Coordinating Center, the Enrollment Coordinating Center followed up with the Veteran to thank them for their interest in the project and relay any pertinent information such as start time, duration, and additional steps for participation. In the event that greater clarification or escalation was required, a member of the project team followed up with the Veteran as needed. If the Veteran asked not to be contacted further, the project team removed him/her from all calling lists.

If an interested party contacted the VA project team via phone or email, we answered his/her questions, collected contact information on a secure server at the Durham VAMC, and transferred him/her to the appropriate person or source (for example, study chair, project manager, or Enrollment Coordinating Center) for follow-up as appropriate. For example, if Veterans called the VA project team for more information about the project, we gave them an overview of the project, recorded their contact information, and put them in contact with the Enrollment Coordinating Center.

We contracted with Social & Scientific Systems, Inc. for the operations of an Enrollment Coordinating Center that was staffed by experienced enrollment coordinators and their supervisors. Before any direct contact with Veterans was permitted, the enrollment coordinators received training that included a telephone script and procedures manual developed specifically

for this project and a test of their knowledge of the project. A list of frequently asked questions (FAQs) and responses were collaboratively developed with the Enrollment Coordinating Center. If the enrollment coordinators were unable to address a Veteran's questions, they were instructed to call the project manager. A response to the Veteran was provided within 24 business hours.

Because there are little data on the efficacy of alternative recruitment mailing strategies, we implemented three recruitment strategies; i.e. sending a full recruitment packet including informational and consenting documents initially (Path A), compared to a modified Dillman approach in which a phased mailing strategy is employed (Path B), compared to self-referral (Path C).

In the first recruitment strategy (Path A), an invitation packet was sent to the Veteran.

The invitation packet contained:

- Path A invitation letter that described the purpose of the project, who was being recruited, what was expected of participants, and encouragement to call the project's toll-free number for additional information
- Frequently asked questions (FAQs)
- A postcard was provided if a Veteran wished to decline participation in this project. S/he could return a postcard provided for this purpose or call the toll-free number.
- Toll-free telephone number was included in the invitation letter and on all correspondence with prospective and enrolled participants. This phone number could be used by Veterans to obtain additional information, to agree or decline participation, and to schedule blood draw appointments
- Informed consent form (ICF)
- HIPAA Authorization for Release of Protected Health Information for Research Purposes
- Authorization for Use and/or Disclosure of Patient Health Information form, based on VA Form FL 10-212, authorizing non-VA providers to forward copies of medical records for purposes of this research project, and a sheet to list the contact information of providers that we may contact
- "Do not sign" sticky note attached to ICF, HIPAA, and Auth. for Use, forms to inform the Veteran that he or she should not sign the forms until h/she had spoken with an enrollment coordinator (Appendix A)
- Gulf War Era Veterans' survey
- VA brochure, *Volunteering in Research* (Appendix B)
- Pocket folder with the project's toll-free telephone number and toll-free numbers and website for VA benefits (Appendix C)
- Veteran's Crisis Wallet Card (Appendix E)

Veterans who did not opt out of the project within at least three weeks of the mailing date were contacted by phone by an enrollment coordinator.

The second recruitment strategy (Path B) differed slightly from recruitment Path A. This recruitment strategy used a modified Dillman approach (Dillman DA. Mail and Internet Surveys, 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc., 2007), which allows for a phased mailing of project documents. The invitation packet for Path B contained:

- Path B lead letter that described the purpose of the project, who was being recruited, what was expected of participants, and encouragement to call the project's toll-free number for additional information
- Frequently asked questions (FAQs)
- A postcard was provided if a Veteran wished to decline participation in this project. S/he could return a postcard provided for this purpose or call the toll-free number.

Veterans who did not opt out of the project within at least two weeks of the mailing date were sent an additional packet that included:

- Path B invitation letter that described the purpose of the project, who was being recruited, what was expected of participants, and encouragement to call the project's toll-free number for additional information
- Frequently asked questions (FAQs)
- A postcard was provided if a Veteran wished to decline participation in this project. S/he could return a postcard provided for this purpose or call the toll-free number.
- Informed consent form (ICF)
- HIPAA Authorization for Release of Protected Health Information for Research Purposes
- Authorization for Use and/or Disclosure of Patient Health Information, based on VA Form FL 10-212, authorizing non-VA providers to forward copies of medical records for purposes of this research project, and a sheet to list the contact information of providers that we may contact
- "Do not sign" sticky note attached to ICF, HIPAA, and Auth. For Use, forms to inform the Veteran that he or she should not sign the forms until h/she had spoken with an enrollment coordinator (Appendix A)
- Gulf War Era Veterans' survey
- VA brochure, *Volunteering in Research* (Appendix B)
- Pocket folder with the project's toll-free telephone number and toll-free numbers and website for VA benefits (Appendix C)
- Veterans Crisis Line Wallet Card (Appendix E)

If an opt-out card was not received by the Enrollment Coordinating Center within 7 days of the full packet mailing, the Veteran was contacted by phone by an enrollment coordinator.

The third recruitment strategy (Path C) allowed Veterans to self-refer to the project hotline. Veterans who called the hotline spoke with an enrollment coordinator who told them about the project. If the Veteran agreed to receive materials, the enrollment coordinator obtained mailing address and telephone number. The Veteran received a mailing packet that included:

- Path C invitation letter that described the purpose of the project, who was being recruited, what was expected of participants, and encouragement to call the project's toll-free number for additional information
- Frequently asked questions (FAQs)
- A postcard was provided if a Veteran wished to decline participation in this project. S/he could return a postcard provided for this purpose or call the toll-free number.
- Informed consent form (ICF)
- HIPAA Authorization for Release of Protected Health Information for Research Purposes
- Authorization for Use and/or Disclosure of Patient Health Information, based on VA Form FL 10-212, authorizing non-VA providers to forward copies of medical records for purposes of this research project, and a sheet to list the contact information of providers that we may contact
- "Do not sign" sticky note attached to ICF, Auth. For Use, and HIPAA forms to inform the Veteran that he or she should not sign the forms until h/she had spoken with an enrollment coordinator (Appendix A)
- Gulf War Era Veterans' survey
- VA brochure, *Volunteering in Research* (Appendix B)
- Pocket folder with the project's toll-free telephone number and toll-free numbers and website for VA benefits (Appendix C)
- Veterans Crisis Line Wallet Card (Appendix E)

If an opt-out card was not received by the Enrollment Coordinating Center within 7 days of the packet mailing, the Veteran was contacted by phone by an enrollment coordinator.

For all recruitment strategies, calls were placed Monday through Friday, not before 10 am local time or after 7 pm in the time zones of the contiguous United States (Eastern, Central, Mountain, and Pacific). If the Enrollment Center was unsuccessful in their attempts to reach the Veteran by telephone, then one follow-up mailing would be made, and the Veteran would be returned to the call center queue. If the enrollment coordinator was not successful in reaching the Veteran after leaving two voice messages, at least two weeks apart, and/or one follow-up mailing, followed by two voice messages at least two weeks apart, then no further attempts would be made. There would be no subsequent relocation efforts. No more than 20 phone calls total would be made to the Veteran prior to verbal consent, unless the Veteran requested additional callbacks.

B. Enrollment into the Cohort and Biorepository

Recruitment calls. A telephone script guided the enrollment coordinators through the enrollment process. At the time of this phone call, the Veteran should already have received a copy of the informed consent form. During the recruitment call, the coordinator would ensure that the Veteran

understood what the project was about, its importance, purpose, and nature, and what their participation would involve. Interested Veterans understood that they were consenting to:

- Completing a survey (estimated completion time: 1 hour)
- Providing approximately 2 teaspoons of blood
- Permitting review of medical records
- Providing access to data and blood from other VA and non-VA studies in which they participated
- Allowing for the possible use of their data and/or blood sample for future research
- Being contacted for updating of survey and/or contact information
- Being contacted about participation in future research projects

Enrollment process. After the review of the ICF, HIPAA, and Authorization form was completed and all questions had been answered, Veterans would be asked if they wished to participate in the project.

- If the response was negative, then the Veteran would be thanked for his/her time and interest in considering the project. They were encouraged to call the toll-free number if they changed their mind. After a Veteran declined participation, no further contact was initiated by the project team.
- If the response was positive, the Veteran signed the ICF and HIPAA authorization at that time and returned them, along with the Authorization for Use and/or Disclosure of Patient Health Information and the completed questionnaire, in the envelope provided. After all forms, had been verified as completed, the Veteran would be contacted for preferred times and location for the blood collection.

If the forms and survey had not been returned within two weeks of a Veteran's verbal consent to participate, an enrollment coordinator would follow-up with no more than two voice mail messages, left at least two weeks apart. If there was no response to these efforts, then no further contact would be attempted, and no subsequent relocation efforts.

Scanning process. Upon receipt at the coordinating center, the ICF, HIPAA Authorization, and Authorization for Use and/or Disclosure of Patient Health Information forms were reviewed thoroughly to ensure that all fields are completed correctly and that a signature and signature date are present. The coordinating center would also verify that the returned packet contained the completed survey. The enrollment coordinator obtaining informed consent would sign the ICF and scan all forms into an electronic forms repository. A hard copy of the signed ICF, HIPAA Authorization, and Authorization for Use and/or Disclosure forms were mailed to the Veteran along with a Return Copies cover letter. The original set of hard copy forms were temporarily stored at the coordinating center and then returned to CSPEC-Durham via delivery service with a chain of custody. Electronic copies of the database were returned to CSPEC-Durham by a VA-approved method such as a Secure File Transfer Program or CD-ROM or DVD (the latter with appropriate

encryption and password-protection and sent via person-to-person handoff or delivery service with a chain of custody).

If the Veteran returned their Opt-out Postcard, the coordinating center would scan the postcard into an electronic forms repository. The Veteran's reasons for not participating in the project were recorded. The Veteran was removed from all future contact and/or mailings, unless they selected the option to be re-contacted again at a later date. A report was generated, and this report, along with the returned Opt-out Postcards was returned to CSPEC-Durham via delivery service with a chain of custody.

Call Back and Remail Procedures. The coordinating center reviewed each received form for completeness. Any missing forms were recorded in the database, and the coordinating center made follow up telephone calls with the Veteran to resolve any discrepancies within 30 days after their identification. The ECC remailed materials using the Remail Letter. This document did not cover every possible remail scenario that may have occurred; rather, it provided examples of the reasons for remailing documents. As needed, the ECC could include additional instructions for the Veteran in the remail letter. Forms containing any portion of a Social Security Number or a date of birth were not remailed for correction. Instead, they were destroyed and new forms were mailed to the Veteran.

If it was ever necessary to send original documents containing PII back to the Veteran to resolve discrepancies, the ECC sent documents via a secure delivery service as detailed in VA Directive 6609.

Use of toll-free phone number. Throughout the recruitment and enrollment process, Veterans were encouraged to ask questions in each mail and telephone contact. At the end of each contact, participants were reminded that the toll-free telephone number was available for their use if they had additional questions. After recruitment for the cohort and biorepository had stopped, the toll-free phone number was transferred to cleared CSP 585 staff members at CSPEC-Durham. The voicemail for the project phone line was updated when the number was transferred to CSPEC-Durham.

Project completion. Once all forms were received and verified as completed, the coordinating center set up an appointment for blood specimen collection (See Section VII). Appointment confirmation letters were sent by the coordinating center. Within 10 days of completing the blood draw appointment and meeting all other requirements of the project, the participant was sent a thank you letter and a $50 gift card.

C. Cohort and Biorepository Recruitment & Enrollment Tracking System

CSPEC-Durham was responsible for developing a system to track recruitment and enrollment in collaboration with the Enrollment Coordinating Center in order to closely monitor adherence to the protocol and to resolve any problems that may arise. The system flagged issues such as the number, types, date, and time of contacts with Veterans that had been attempted and completed, by whom, and the outcome. Also, the system flagged reminders to call Veterans with their

requested information. The Enrollment Coordinating Center created a system for categorizing calls, i.e. with call disposition codes. For example, if the Veteran was temporarily unavailable, a callback could be requested at a later time. If the participant was unavailable for the project duration, the Veteran was coded as such, and no further contact was attempted.

If a problem was identified, an investigation began and the problem would be resolved in a timely manner, and the details noted in the system. This system also generated routine and special reports to CSPEC-Durham.

D. Blood Sample Collection

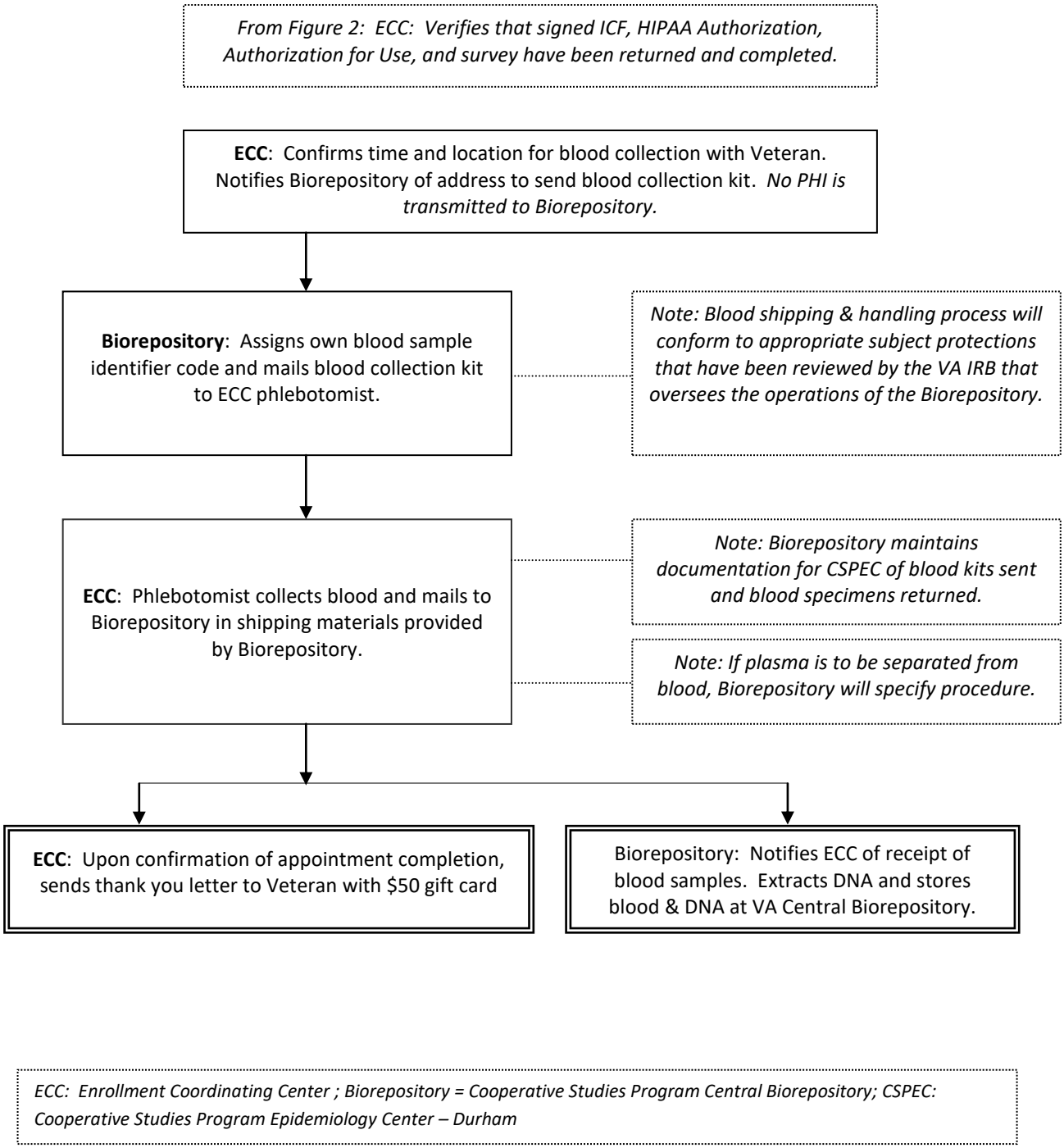
Blood samples were collected and the DNA extracted. The blood and DNA samples have been designated to be used for research purposes only. This includes genomic analyses (e.g. GWAS, methylation, etc.) coordinated by CSPEC-Durham and performed by PAL, all within CSP. Future, unspecified use of the specimens for research purposes could include additional genetic testing. The blood samples are being kept at the CSP Central Biorepository with appropriate subject protections that have been reviewed by the VA IRB that oversees the operations of the CSP Central Biorepository. The Albuquerque CSP Pharmacy has been designated as the backup Central Biorepository, and blood samples collected for CSP 585 may be stored there, or in another CSP approved biorepository, as well. The blood samples will be kept at a backup repository with appropriate subject protections that have been reviewed by the VA IRB that oversees the operations of the CSP Central Biorepository. Participants will be notified if it becomes necessary to transfer the samples to another backup biorepository in the future.

Samples were coded to maintain confidentiality. A unique identifier was used in the storage of blood specimens. At no time will the CSP Central Biorepository or PAL have access to patient identifiers, other than the specimen code. The key linking the specimens' unique identifiers to the participants is kept at the CSP Study Chair's site.

Donors will not be informed of the results of the specimen testing, and there are no implications for family members based on specimen testing results. Donors were not paid for the blood samples, and the samples will not be sold now or in the future.

The process for collecting the blood samples is outlined in Figure 3. The Enrollment Coordinating Center managed this process. No blood collection appointment was to be made without confirmation of a signed and returned ICF and other required forms. Once the forms were received and their completeness verified, a coordinator contacted subjects to confirm their preferences for place and time for blood collection and to answer questions about that process.

Figure 3. Blood Collection Process



ECC: Enrollment Coordinating Center ; Biorepository = Cooperative Studies Program Central Biorepository; CSPEC: Cooperative Studies Program Epidemiology Center – Durham

1. Specimen Collection

Project enrollment required the collection of blood from each subject. Blood was collected by a phlebotomist. The blood was drawn at the subject's home, workplace or other location requested by the subject. Each subject was asked to provide approximately 2 teaspoons of blood collected from a vein in the upper extremity.

If the blood specimens are used up, unusable because they are damaged, or are not of sufficient volume, then we may request additional specimens without requiring additional consent. However, if additional separate specimens are needed at a later date for other research, then the subjects will be asked to sign another consent form.

2. Specimen Shipping and Handling

Blood collection kits containing the necessary supplies were shipped as needed from the CSP Central Biorepository, currently in Boston, Massachusetts, to the phlebotomist. Once collected, the blood was shipped to the CSP Central Biorepository, the DNA was extracted, and the specimens were stored according to the procedures established by the VA Central Biorepository in accordance with SOPs reviewed by their IRB of record. All VA and Enrollment Coordinating Center personnel involved in the handling and shipping of blood specimens were certified for that responsibility. They were required to maintain their certification and training requirements for the duration of their involvement in the project.

The specimens will be transferred to PAL, located in Little Rock, AR, for the purposes of conducting a GWAS and other genomic analyses (e.g. methylation, etc.). The CSP Central Biorepository will transfer the specimens via a VA-authorized carrier with tracking. The specimens will be returned to the CSP Central Biorepository after analysis for long-term storage using these same secure methods of transfer. These analyses will be coordinated by CSPEC-Durham.

3. Specimen Tracking System

CSPEC-Durham was responsible for developing a blood collection tracking system in collaboration with the CSP Central Biorepository and the Enrollment Coordinating Center. The blood collection process was closely monitored, beginning with the scheduling of the appointment with the subject through the receipt of the specimens at the CSP Central Biorepository. The system flagged issues such as the blood kits not being received by the phlebotomist in a timely manner, specimens not being shipped to the CSP Central Biorepository the same day as collection, and kits or specimens being lost in the shipping process. Once a problem was identified, an investigation began and the problem was resolved in a timely manner. The system also generated routine and special reports for CSPEC-Durham.

4. Specimen Storage

Blood specimens were shipped to the CSP Central Biorepository and DNA was extracted. The blood and DNA specimens will be available for genomic analyses (e.g. GWAS, methylation, etc.) coordinated by CSPEC-Durham, as well as future research by approved investigators. The specimens will be stored indefinitely in the CSP Central Biorepository and may be stored in the backup repository at the Albuquerque CSP Pharmacy or at another CSP approved biorepository in the future.

E. Specimen Coding

Each subject was assigned a unique project identifier code at the time of recruitment. This identifier was used throughout the project in lieu of other personal identifiers for recruitment and enrollment tracking and for linking of survey data. An additional unique identifier was used in the storage of blood and DNA specimens. At no time did/will the CSP Central Biorepository or the backup repository have access to patient identifiers. The key linking the unique specimen identifier to the participant is kept at the CSP Study Chair's site. Only a limited number of authorized staff have access to the key, which is password-protected.

F. Specimen Analysis

Genomic analyses of DNA from the blood samples will be coordinated by CSPEC-Durham and performed by PAL. CSP 585 participants previously consented for their blood samples to be used for future studies, including genetic testing. The goal of these analyses is to identify genetic susceptibilities and epigenetic variants associated with Gulf War Veterans' Illnesses. The identification of risk genes for one or more of these conditions could inform novel research on the cause(s) of these illnesses.

G. Future Use of Specimens

Use of specimens will be for research purposes only and will be consistent with informed consent. Specimens collected through this project have become part of the CSPEC-Durham Data and Specimen Repository. In some cases, it may be necessary to recontact participants to provide information about additional studies involving direct contact (contact in person or by mail or phone). In these cases, participants will be provided with information about the new project so that they may volunteer for the project if interested. All research projects requesting the use of the specimens will be approved and monitored by appropriate VA oversight committee(s).

VIII. Withdrawal from Project

A participant may withdraw from the project at any time by completing a Withdrawal Request Form. A participant may request this form from project personnel by calling the project's toll-free telephone number and/or the project team at CSPEC-Durham. Historically, the Enrollment Coordinating Center would mail the participant a copy of this form, along with a cover letter. As of this amendment, project staff at CSPEC-Durham will mail participants a copy of this form, along with a cover letter, if requested. The participant will mail the signed and completed form to:

Cooperative Studies Program Epidemiology Center in Durham
508 Fulton St. (152)
Durham, NC 27705

If a participant withdraws from the project, researchers can continue to use information that has already been collected. No further health data will be collected after the signed withdrawal request has been received by the study chair, except for that which is available in public records.

If a participant withdraws from the project, his/her blood samples (and materials derived from it, including DNA) that are in the CSPEC-Durham Data and Specimen Repository, the VA Central Biorepository, or the backup repository will be destroyed. However, de-identified blood samples that have been sent to researchers at VA medical centers, other Federal health agencies, academic institutions, or drug/health companies cannot be retrieved.

IX. Data Collection

A. Types of Data

All data collected over the course of this protocol will be for research purposes only. Under this protocol, we established the Gulf War Era Research Database as a comprehensive and reliable source of health information on Veterans of this era. Our definition of health information is the definition found in VHA Handbook 1200.12, Section 3. Definitions:

> *The term "health information" means any information created or received by a health care provider or health plan that relates to the past, present, or future physical or mental health or condition of an individual or the provision of health care to an individual; or the payment for the provision of health care to the individual. "Health information" includes information pertaining to examination, medical history, diagnosis, findings or treatment, and includes such information as laboratory examinations, x-rays, microscopic slides, photographs, prescriptions, and other similar data. (page 2)*

The health information collected also includes substance abuse problems, mental health conditions, HIV, AIDS, and sickle cell anemia. Data was obtained directly from participants as

well as from existing sources that are internal and external to the VA, and that have been developed for both administrative and research purposes.

In order to develop the Gulf War Era Research Database, it is necessary to include HIPAA identifiers in the data acquisition process and in analyses to ensure that the data and individual are matched appropriately. Names, complete addresses, telephone numbers, birth dates, and real social security numbers will be maintained in a data file and merged with health information only as needed. Other HIPAA identifiers to be included in the research database are: dates pertaining to health information (e.g., diagnosis dates, procedure dates) and military service and deployments.

B. Major Sources of Data

There are several major sources of data for this project.

For the cohort and biorepository project, data was obtained directly from participants. Initially, we collected data through a survey questionnaire, and we will update this information approximately every 3-5 years. We will update contact information approximately every year.

For the qualitative project, data was obtained directly from Gulf War Era Veteran participants. These qualitative data collection activities included focus groups and interviews. Additionally, we obtained information from Gulf War Era subject matter experts through Key Informant phone interviews.

Data was also obtained from sources other than directly from research subjects. The two primary sources were:

- Other research projects, research data repositories, biorepositories or registries, from VA and non-VA sources, with the subject's approval (included in ICF and HIPAA Authorization) and approval from the source's IRB and/or R&D for re-use of the data.
- Non-research VA and non-VA sources such as the subject's administrative, medical, or other records (included in ICF and HIPAA Authorization). For data that are not available from a centralized source, we will conduct electronic and paper chart reviews to update subjects' vital status and obtain health information.

C. VA Data Resources

Many VA and VHA non-research data repositories exist to support operations. Some of the resources that we may access, with appropriate data transfer agreements and other patient confidentiality and data security measures in place, follow. Additional VA resources may become known over the course of the project.

- VISN data warehouses
- Corporate Data Warehouse

- VA registries, including the Gulf War Registry
- VA data centers
- Pharmacy Benefits Management and other pharmacy databases
- Emerging Pathogens Initiative
- Medicare-VA merge accessed through VIReC
- Beneficiary Identification Records Locater Subsystem (BIRLS) Death File
- VINCI databases (Salt Lake City)
- Electronic health record data, accessed through CAPRI, VistAWeb, and/or Joint Legacy Viewer as a primary source of health information on users of the VA healthcare system.

D. Non-VA Data Resources

Resources existing outside of the VA that we may access, with appropriate data transfer agreements and other patient confidentiality and data security measures in place, follow. Additional non-VA resources may become available to us over the course of the project.

- Centers for Medicare and Medicaid Services (CMS) data to obtain health information on non-users of the VA healthcare system as well as to obtain and confirm health information on users of VA health care system that may not be completely recorded in VA records. VA and VHA policies for use, transmission, distribution, storage, and disposition of CMS will be followed, as well as all CMS requirements and other applicable Federal regulations.
- Department of Defense databases
- Research studies conducted by non-VA researchers and/or with funding from sources other than the VA.
- Medical records from non-VA providers, with permission from the subject per signed Authorization for Use and Disclosure of Patient Health Information form.

As part of the process of enrollment into the cohort and biorepository project, we requested that participants who do not use VA health care providers or who do not use VA providers exclusively sign the Authorization for Use and Disclosure of Patient Health Information that authorizes non-VA providers to release medical care information to the VA. On a separate sheet, participants could fill in the names and contact information of their providers and then return the Authorization Form and the completed provider contact sheet in the envelope provided. We may forward a copy of the authorization form to each non-VA health care provider identified. In future re-contacts with participants to update survey and contact information, we may also request updates of providers.

E. Data on Non-Respondents and Non-Participants

Non-response and non-participation rates higher than typically seen and higher than optimal for this project were a problem. Without an ability to assess the nature of non-response and non-participation, we will have difficulty placing the information we collected into proper context, thereby limiting the value of all data that we collected.

We will use two approaches to assess the nature of non-response bias. First, we will compare demographic characteristics (provided by DMDC and PDHEP) between multiple types of non-responders, non-participants, and participants. This will allow us to determine whether the final participating sample carries a bias due to demographic factors. Second, we will acquire VA electronic medical records for all Veterans in the original DMDC and PDHEP samples who are also VA health system users. The data from these records will be used to assess the medical characteristics of the participant groups, both retrospectively and prospectively, and to further examine the presence of bias in the participating sample. For example, it is possible that Veterans with a high disease burden preferentially enrolled into the project. These combined data will allow us to better characterize non-responders and non-participants in terms of morbidity and mortality, which will be invaluable in placing our project into the proper context and maximizing the value of data collected on enrolled patients.

Data will be linked using the Veteran's social security number.

F. Historical Activity: Pilot Testing of the Survey (Cognitive Interviewing)

Prior to launching the full pilot project, the survey was tested in a small sample of Veterans. This in-person testing process (cognitive interviewing, also known as pilot testing or beta testing) is an important evaluation of how respondents understand survey items and construct or select answers to questions. During this process, we used retrospective verbal probing, in which the interviewer probes participants after they have completed the survey, to examine comprehension of the items and instructions, skip patterns, retrieval of relevant information from memory, decision processes, and response processes. The survey included some standardized, validated questionnaires for which the wording and response options cannot be modified. In such cases, emphasis was placed on understanding the instructions, skip patterns, and formatting, to ensure that participants could complete the paper-based survey unaided. Open-ended probes such as "tell me what you are thinking" or "say more about that" were used. Interview notes were sorted into categories such as 1) variability in interpretation of instructions, 2) unclear skip pattern, 3) overlap in content, and 4) inadequate response categories. The CSP research staff partnered with the Enrollment Coordinating Center to create and administer the cognitive interviews, as both parties could contribute extensive experience and expertise with previous self-report questionnaires. After each interview, the Enrollment Coordinating Center and CSP teams discussed issues raised and possible revision of items. After revising the survey, we interviewed more participants in a second round to review the modified survey. In total, we completed cognitive interviews with 17 participants.

Veterans were recruited by mail for the cognitive interview using an approved letter . The recruitment efforts were limited to the Durham, Raleigh, and Chapel Hill areas of North Carolina to facilitate Veteran access to the interviewing site. Veterans who participated in the cognitive interview provided written informed consent and HIPAA authorization at the beginning of the

interview session. They were not asked to provide a blood sample. All cognitive interview participants were provided with the same $50 gift card that regular project participants received. After the cognitive interview stage of the pilot was complete and the full pilot project began, cognitive interview participants were eligible for participation in the full pilot.

G. Analyses of Project Activities

Data will be analyzed to further characterize the study population, providing opportunities to compare this cohort to other Gulf War cohorts and to plan for additional research projects. For this purpose, the project team will use data from: DMDC; PDHEP; VA administrative data files; routine locator updates; enrolled participants; and other sources, as described above. Results will be shared in de-identified, aggregate/summary form with individuals within the project team, the Executive Committee, programmatic leadership, other project teams, Veteran groups, other stakeholders, and the general public if needed. Findings may also be shared through publications and/or presentations.

In addition to the analysis of nonresponse patterns and project activities described above, project staff will also conduct analyses on the survey data provided by biorepository enrollees, and on medical record data from biorepository enrollees who use the VA for their healthcare and those who do not use VA. In addition, we will perform analyses on the VHA medical record data available for any member of the original DMDC sample, as well as those Veterans who self-nominated (path C volunteers). This excludes those Veterans who have opted out of participation in the biorepository. These data will be used in support of a variety of epidemiologic and health services analyses regarding the health conditions, utilization, demographics, and clinical characteristics of this sample and the wider Gulf War Era population. The analyses of these system-level data may contribute immense value to the clinical operations and research communities with interests in the care of Veterans of this era.

H. Historical Activity: Qualitative Component

The purpose of the qualitative component of CSP 585 was to better understand Gulf War Era (GWE) Veterans' perspectives regarding participation in Gulf War Era research projects, specifically around barriers and facilitators to research participation, recruitment strategies and communication, and study processes and procedures. The qualitative component employed three different methods: focus group discussions, process evaluation interviews, and key informant interviews. These are summarized in Table 1, with additional details to follow.

Toll-free and/or local contact numbers were provided on recruitment materials for this qualitative component.

	Aim	Who	Sampling Method	Eligibility Criteria	Number of Participant & Sessions	Location & Mode
Focus Groups	To explore GWE Veterans' thoughts about Gulf War Era research projects, and to get feedback on recruitment strategies and preferences for such projects.	GWE Veterans	Community -based; CSP 585 sampling frame	Served during August 1990 to July 1991, is willing to be audio recorded during focus group discussion, and speaks English.	Up to 12 focus group discussions; up to 12 Veterans per focus group	National; in-person
Process Evaluation Interviews	To learn about GWE Veterans' experiences participating in and/or being recruited for the CSP 585 project, how they made their decision of whether or not to participate, and their perspectives on this and other potential Gulf War Era research projects.	GWE Veterans	CSP 585 sampling frame; volunteers	Served during August 1990 to July 1991 and speaks English; Enrolled in CSP 585, opted-out of participating in CSP 585, or did not respond to an invitation to participate in CSP 585.	Up to 30 Veterans; one-on-one sessions	National; phone
Key Informant Interviews	To learn about experts' perspectives on Gulf War Era research projects and gain insight into engaging Gulf War Era Veterans in research.	Individuals with knowledge or expertise related to the needs and experiences of GWE Veterans	Snowball	Has knowledge or expertise about experiences of GWE Veterans and speaks English	Up to 20 Key Informants; one-on-one sessions	National; phone

Focus Groups:

Aim: The aim of the focus group discussions was to explore GWE Veterans' perspectives about Gulf War Era research projects and to get feedback on recruitment strategies and preferences for such projects.

Target Audience: Gulf War Era Veterans were recruited for focus group discussions.

Sampling and Recruitment: Veterans were recruited through word of mouth from Veteran Service Organizations (VSOs) or other community organizations; word of mouth from Veterans, service providers, and/or others; tabling and/or presentations at community events; print media (e.g. posters, postcards, table tents, project newsletter) displayed/distributed at/by community organizations, VA medical centers, and/or other authorized locations; electronic media (e.g. website, web stories, social media, listserv email announcements) distributed by community organizations and/or the VA; and/or other methods recommended by partner organizations and/or advisors. Any print or electronic advertisements distributed through the VA were under the control of the respective facilities at which they are posted. Text from approved listserv announcement, social media announcement, newsletter blurb, and recruitment poster may have been used. From this text, Veterans were informed to contact CSP 585 staff to indicate their interest, and they were invited to attend a focus group depending on their availability and groups scheduled.

When outside the office and/or at events described above, we collected any contact information from interested Veterans via a sign-in sheet or a VA encrypted laptop for possible future recruitment. The sign in sheet or laptop was used to capture names, phone numbers and/or addresses. The laptop and/or sign in sheet was in possession of a VA-approved project team member at all times, or protected by lock (e.g., computer lock, locked bag, locked file cabinet, safe, private room with restricted access).The information on the laptop was transferred to secure servers at the Durham VA Medical Center and/or HSR&D Center of Innovation at the NC Mutual Building, and the sign in sheet was stored in a locked cabinet at CSPEC-Durham, as soon as possible (see "Data Storage" section below).

At the same time that we recruited through VSOs and community-based methods, we sampled individuals from the CSP 585 recruitment cohort that were previously identified (see "Cohort Identification"). In those cases, we mailed a letter to individuals inviting them to participate in a focus group. Individuals were selected based on having an address near locations where focus groups were held. Using an approved script, CSP 585 staff called some individuals who had not responded to the letter after two weeks of the letter being mailed. If individuals opted-out or could not be reached, additional names were obtained from our sampling frame to add to the recruitment process until we reached the desired number of participants. In total, up to 800 Veterans may have been mailed a letter inviting them to participate in a focus group.

Veterans scheduled for the focus group were mailed a confirmation letter and/or received a reminder call before the session. Additional phone calls were made if we needed to reschedule or cancel the focus groups (i.e., if recruitment numbers are too low or there are other logistical issues), to communicate logistical information, or if Veterans called with interest or questions. Voice messages were left if needed.

In the initial recruitment phone call (for both mail-based and community-based recruitment methods), we screened Veterans for eligibility criteria.

Sessions: Four focus group discussions took place with up to twelve Veterans per focus group. We conducted two of these with female Veterans only. Other focus groups were open to both men and women. Each focus group discussion lasted up to 2 hours and refreshments were served.

Focus group discussions took take place in private rooms, such as a vacant room in a VA medical center or conference room at a community site. Focus groups were conducted by trained researchers, and at least two researchers were present at each focus group discussion.

Researchers brought a registration list, which included names, study IDs, and contact information of registered participants, to the focus group discussion via paper copy and on a VA encrypted laptop. When participants arrived for the focus group session, they were asked to check in with a researcher to ensure that they previously registered. If a Veteran arrived who had not previously registered, and there was room in the focus group, researchers screened them for eligibility criteria, collected their contact information, and if they were eligible, invited them to join the focus group.

All participants were given an informed consent form and HIPAA authorization document, both of which a researcher reviewed with the group. Participants were invited to ask questions in the group setting, or ask a researcher individually. As part of the informed consent process, participants were instructed to keep the identities of other participants confidential. Participants were asked to sign the consent form and HIPAA authorization document if they were still interested in participating. Veterans had to give consent for the focus group to be audio-recorded in order to participate; this information was in the consent form they received. Copies of the consent form and HIPAA authorization document templates were available for participants to take with them. If a participant arrived after the focus group had begun, a decision was made about whether the individual may join the group; if they were able to join, a staff member met with them to complete the consent form and HIPAA form before they participated.

Next, participants were asked to complete a short information survey. Finally, the focus group discussion took place. Focus group discussions were semi-structured, with a focus on exploring the Veterans' perspectives on Gulf War Era research projects and obtaining feedback on

recruitment strategies and preferences for such projects. Researchers used an approved guide. As is typical in qualitative research, specific questions asked varied, though content of the questions remained consistent. One researcher led the discussion, while other researchers took notes. Researchers took notes on paper and/or an encrypted VA laptop and the discussions were audio-recorded.

Immediately following the focus group discussion, Veterans were offered a $50 gift card for their participation. Veterans were asked to sign their name to confirm receipt of the gift card, and a log of all gift cards issued will be maintained.

Registration lists, documents with participant information (including signed forms and completed information surveys) and any paper notes were in possession of a VA-approved project team member at all times, or protected by lock (e.g., locked bag, locked file cabinet, safe, private room with restricted access), to ensure that personally identifying information remained secure while the researchers travelled to and from focus group sites. Electronic registration lists were transported to and from focus group sites via a VA encrypted laptop and were transferred to secure servers at the Durham VA Medical Center and/or HSR&D Center of Innovation at the NC Mutual Building as soon as possible after the focus group. Audio recordings and digital notes were immediately stored on a VA encrypted laptop and were transferred to secure servers at the Durham VA Medical Center and/or HSR&D Center of Innovation at the NC Mutual Building as soon as possible. Paper notes, registration lists, and documents with participant information were stored in a locked cabinet as soon as researchers returned to CSPEC-Durham (see “Data Storage” section below).

Process Evaluation Interviews:

Aim: The aim of the process evaluation interviews was to learn about GWE Veterans’ experiences participating in and/or being recruited for the CSP 585 project, how they made their decision of whether or not to participate, and their perspectives on this and other potential Gulf War Era research projects.

Target Audience: One-on-one process evaluation interviews were conducted with GWE Veterans who have been enrolled in CSP 585, opted-out of participating in CSP 585, or did not respond to an invitation to participate in CSP 585.

Sampling and Recruitment: Individuals were sampled purposively using the CSP 585 recruitment cohort that has previously been identified (see “Cohort Identification” in the approved study protocol) in order to obtain a diverse sample of individuals who have been involved in different stages of the CSP 585 process. CSP 585 staff mailed a letter to the identified individuals inviting them to participate in an interview, along with an informed consent overview document. Letters were tailored to individuals who have already participated, opted out, or did not respond to invitations to participate in CSP 585. Using an approved script, CSP

585 staff called individuals who had not responded to the letter after two weeks of the letter being mailed. If individuals opted out of participating in the process evaluation interview or could not be reached, additional names were obtained from the sampling frame to add to the recruitment process until we reached the desired number of participants. In total, up to 800 Veterans may have been mailed a letter inviting them to participate in this interview. In the initial recruitment phone call, we screened Veterans for the eligibility criteria if necessary. If needed, we used our existing database to check for eligibility criteria related to previous participation status within CSP 585.

In some cases, staff called Veterans before the interview to remind them of the date and time. Additional phone calls may have been made for scheduling and logistical purposes or if Veterans called with interest or questions. Voice messages were left if needed. If requested, Veterans were mailed an additional copy of the informed consent overview document.

Sessions: We conducted one-on-one process evaluation interviews with up to 30 Veterans. Interviews lasted up to 1.5 hours. All interviews were conducted via phone. A researcher trained in qualitative research methods conducted these interviews.

At the time of the interview, participants participated in an informed consent process, led by the interviewer using an approved script. (We requested a Waiver of Documentation of Informed Consent and a HIPAA authorization waiver.) After receiving verbal consent, the interviewer verbally delivered an information survey to gather information about the participants over the phone and conducted the interview.

We conducted the interview using an approved interview guide. We asked questions related to the Veterans' experiences participating in and/or being recruited for the CSP 585 project, how they made their decision of whether or not to participate, and their perspectives on this project and other potential Gulf War Era research projects. As is typical in qualitative research, interviews were semi-structured and specific questions varied, though content of the questions remained consistent. During the informed consent process, Veterans were asked whether or not they consented to having the interviews audio recorded. If Veterans declined the audio-recording, the interviewer took notes during the interview, but did not audio record it. If Veterans consented to the audio recording, the interview was audio recorded and the researcher may have also taken notes. The Veteran's responses to the verbal information survey were also recorded. Unless the Veteran objected, a $50 gift card was mailed to the participant after the interview and tracked on a gift card log.

Audio recordings and digital notes are stored on a secure server at the Durham VA Medical Center and/or HSR&D Center of Innovation at the NC Mutual Building and paper notes are stored in a locked cabinet (see "Data Storage" section below).

Key Informant Interviews:

Aim: The aim of the Key Informant Interviews was to learn about experts' perspectives on Gulf War Era research projects and gain insight into engaging Gulf War Era Veterans in research.

Target Audience: Individuals who have knowledge and/or expertise related to the needs and experiences of Gulf War Era Veterans were invited to participate in Key Informant Interviews. Key informants may have included VA employees, leaders of VSOs, members of the Research Advisory Committee on Gulf War Era Veterans' Illnesses, researchers, or others with knowledge and expertise of Gulf War Era Veterans.

***Sample and Recruitment*:** We created a list of potential key informants to contact based on our own knowledge of the field, recommendations from key informants and others, interactions at outreach events, Internet searches, and literature searches. Potential key informants were sent an email from a researcher's VA email account to invite them to participate in an interview; an informed consent overview document was attached. Email is a standard mode of communication among professionals, and as such, it is an appropriate contact method for recruiting key informants. Furthermore, we did not ask key informants for personal health information. We called and/or emailed individuals who had not responded after one week of the email being sent. After scheduling the interview, participants may have been emailed an appointment confirmation, unless another communication preference was specified. Up to 100 individuals may have been contacted inviting them to participate in a key informant interview.

CSP 585 staff may have called or emailed key informants, based on their communication preference, before the interview to remind them of the date and time. Additional phone calls or emails were made for scheduling and logistical purposes or if the individual had additional questions. Voice messages were left if needed.

Sessions: We conducted one-on-one interviews with up to 20 key informants. Interviews lasted up to 1.5 hours. All interviews were conducted via phone. A researcher trained in qualitative research methods conducted these interviews.

At the time of the interview, participants participated in an informed consent process, led by the interviewer using an approved script. (We requested a Waiver of Documentation of Informed Consent and a HIPAA authorization waiver.)

Next, we conducted the interview using an approved interview guide. We asked questions related to key informants' perspectives about Gulf War Era research projects, including CSP 585, and their ideas about how to engage GWE Veterans in research, as well as background information questions about their work experience. As is typical in qualitative research, interviews were semi-structured and specific questions varied, though content of the questions remained consistent. At the end of the interview, researchers may have asked the interviewee if

they had suggestions of any other key informants that we should contact, and if so, we requested their name, phone number, and email address. This is the snowball method mentioned in the table on page 30. During the informed consent process, key informants were asked whether or not they consented to have the interview audio recorded. If key informants declined the audio-recording, the interviewer took notes during the interview, but did not audio record it. If key informants consented to the audio recording, the interview was audio-recorded and the researcher may have also taken notes. With the exception of VA employees, a $50 gift card was mailed to key informants after the interview, unless they objected or did not provide a mailing address. These gift cards were tracked using a gift card log.

Audio recordings and digital notes are stored on secure servers at the Durham VA Medical Center and/or HSR&D Center of Innovation at the NC Mutual Building, and paper notes are stored in a locked cabinet (see “Data Storage” section below).

Additional Recruitment Notes:

If we reached the maximum number of participants for one type of qualitative session (Focus Groups, Process Evaluation Interviews, or Key Informant Interviews), we informed any interested participants who contacted us that we are no longer recruiting for the session. Interested Veterans were offered the opportunity to participate in another qualitative session, if they met the eligibility criteria. If interested Veterans were not available or eligible for one type of qualitative session, they may have been offered the opportunity to participate in another, if they were available and eligible to participate. However, each individual could only participate in one qualitative session. If an individual was both a Gulf War Era Veteran and an expert in the field, and they contacted us about participating in a focus group or process evaluation interview, we asked them to consider participating in a Key Informant interview instead. Finally, if Veterans or key informants contacted us with an interest in participating in the qualitative component or the CSP 585 project in general, even if they did not hear about the project from recruitment methods listed above (advertisements and/or letters), they may have been screened and offered the opportunity to participate in a qualitative session if they were eligible. If there were not any sessions available or offered in their area, we recorded interested individuals’ names and contact information so that we may contact them if additional applicable sessions were offered in the future.

For all types of qualitative sessions, interested participants were asked to provide and/or confirm contact information including their name, phone number, and/or address at initial contact. Key informants were the only group who were asked to provide their email address (instead of or in addition to their mailing address) based on the reasons discussed above.

Future Contact:

Gulf War Era Veterans who participated in the qualitative component may be contacted about this project or other Gulf War Era research projects in the future. Location services such as LexisNexis may be utilized to identify accurate contact information for CSP 585 participants.

Data Storage:

All participants in the qualitative component were assigned a Study ID to maintain confidentiality. These Study IDs were different from the unique IDs assigned in the CSP 585 cohort and biorepository project. Study IDs were assigned to individuals selected for recruitment from the sampling frame, as well as to individuals who independently volunteered to participate.

Data is stored according to procedures outlined under "Storage of Research Data" in the CSP 585 protocol. Interviews (when applicable) and focus groups were recorded using the Sparky device, which stored the audio recordings on a VA computer or VA encrypted laptop. These recordings were transferred to secure servers at the Durham VA Medical Center and/or HSR&D Center of Innovation at the NC Mutual Building as soon as possible.

Data Analysis:

The CSP 585 team conducted data analysis on all qualitative data under the guidance of CSP 585 co-investigator Dr. Corrine Voils, who is located at the Middleton VA in Madison, WI. First, all audio recordings were transcribed by CSP 585 project staff and/or transcriptionists at the VA Salt Lake City Health Care System. When appropriate, transcriptionists from the VA Salt Lake City Health Care System were given direct access to the project transcription subfolder. These transcription files/data remained behind the VA firewall at all times. When the audio recordings were transcribed, any mention of participants' name was redacted, and transcripts are saved according to procedures outlined under "Storage of Research Data." CSP 585 staff analyzed the data according to qualitative data analysis techniques, which may have included coding, memoing, and creating matrices and other analytical products. We may write about and/or give presentations about the combined information we collect. Any talks or papers about this project will not identify individual participants.

X. Protecting Privacy Interests of Participants

Privacy interests were protected primarily by allowing participants to choose the extent, timing, and circumstances of their interactions with the project. For example, after receiving an invitation letter to participate in an interview or focus group, the individual had the option of calling CSP 585 staff to opt out at any point. If the decision was to participate, then the individual could initiate a telephone call with the project staff to ask questions about the project

and any documents mailed to them. If a call was initiated by the project staff, the individual was asked if the time was convenient to discuss the project. Phone interviews were scheduled at a time convenient for the participant. If at any time, the individual declined to participate in an interview or focus group, then the project staff honored that request.

XI. Protecting Participants against Undue Influence or Coercion

Veterans were protected against undue influence or coercion via several mechanisms including: the payment amount ($50), method of payment (gift cards) and timing (after completing a phone interview (except for key informants who are VA employees) or immediately after a focus group) were reasonable and commensurate with other studies with similar requirements; and the informed consent process was conducted by trained staff. Veterans were encouraged to ask questions about the project before and during the recruitment process and, if enrolled, throughout their participation in the project. If a Veteran indicated his/her refusal to participate, then that wish was politely accepted and no further contact with the Veteran was permitted unless initiated by the Veteran. Participants were told that their participation or non-participation will not affect their treatment or eligibility for VA benefits in any way.

XII. Readability Evaluation of ICF

We used the Flesch readability and the Flesch-Kincaid grade level scores to evaluate the ICF for this project. The results for the cohort and biorepository project were: Reading ease score: 62.0; Grade level score: 8.7. The 8th grade level reading scores will allow for increased generalizability to the Veteran population.

XIII. Payment to Participants

Reimbursement to participants for their time and effort has been proven to increase participation rates. A wide range of payments exists within CSP, ranging from $0 to over $100 for comparable or near comparable studies. We believe $50 for completing a focus group and/or interview is commensurate with these contributions, but it is not so high as to influence a subject's decision to participate.

The Enrollment Coordinating Center purchased gift cards. Social security numbers are not needed to process the gift cards. One gift card in the amount of $50 was mailed by the Enrollment Coordinating Center to Veterans participating in the cohort and biorepository project within 10 business days of completing the blood draw appointment and confirmation that all other requirements for project enrollment had been met. If it was necessary to collect another blood sample because the first blood sample is unusable, the Enrollment Coordinating Center mailed another $50 gift card to the participant.

XIV. Re-contact of Participants

A requirement for participation in the cohort and biorepository project was agreement to be re-contacted. Reasons for re-contact are the following:

1. Update survey, provider, and contact information. Project staff will update survey and provider information approximately every 3-5 years and will update contact information approximately yearly. A stamped pre-addressed envelope will be included for participants who choose to complete and return the survey and/or contact information update form. The VA Central IRB will approve surveys before they are sent to participants.
2. Provide feedback about the experience of participating in different aspects of the project.
3. Ascertain interest in other (future) research projects. Future research projects may involve surveys, interviews, donation of additional specimens, or other research methods. Such studies must be approved by appropriate VA review committees. If participants are interested in joining other studies, they will be asked to sign another consent form. The same Veteran will not receive a mailing about future research projects more than four times per year.
4. Provide project newsletters on a periodic basis.

If the participant is interested in participating in a future project that will include additional data or specimen collection, s/he will be asked to sign another consent form.

All other reasons for contact will require an amendment to the current protocol. The amendment(s) will be submitted by the study chair to the VA Central IRB.

XV. Potential Risks and Benefits

A. Potential Benefits

There is no direct benefit to participants in this project. However, the participants' blood samples, clinical information, and responses to the survey may help researchers understand diseases, illnesses, and conditions. These research studies may result in improvements in ways that diseases and illnesses can be prevented, diagnosed, and treated in the VA and society at large. Participants' feedback during the qualitative research activities may help researchers improve future Gulf War Era research projects.

B. Potential Risks or Harms

All procedures carry risks. Although this is a minimum risk observational project, potential risks or harms from this project included the following:

- Potential risks during the historical blood collection procedures of having blood drawn from a vein were slight pain, bleeding, bruising, and, rarely, infection at the site where

the needle is inserted. There was a possibility of fainting or light-headedness, but these occurrences are rare.

- The potential risk of completing the survey is emotional distress of responding to questions about their physical health and their military service at the time of the Gulf War.
- There is a slight risk of a breach of security. If information about the participant is leaked, VA will not be able to guarantee that it will be protected.
- Information shared with individuals outside the VA is not protected by the VA.

C. Procedures/Activities to Minimize Risks or Harms

The following procedures and other activities will be and/or have been used to minimize the potential risks or harms listed above:

1. Blood draw (historical): A blood draw of approximately 2 teaspoons of blood is a procedure that typically occurs in the course of clinic visits and will be familiar to the participants. To minimize risks, the blood was drawn by a professional who had been specially trained to draw blood. Also, to minimize any anxiety or inconvenience, the blood was drawn at a place and time convenient to the participant, including the participant's home, workplace, or other convenient location.

2. Survey: Outside of a research context, Veterans are asked questions about their military service history, medical history, treatments, and quality of life by clinicians and patient advocates in the routine course of managing their care. Also, it is not uncommon for the same or very similar questions to be posed in routine encounters with family, friends, acquaintances, and even strangers, including those who are not health care professionals, both inside and outside their homes. During future recontact activities, the survey will be mailed to the participant's home to be completed at their convenience. If they are interrupted, distressed, or fatigued they may choose to complete the survey over the course of several sessions. They have the option to refuse to respond to any and all of the questions, and without explanation.

3. We will make every effort to protect the participant's confidentiality and to assure that his/her identity does not become known. All electronic data will be maintained on VA secure servers. All paper information will be stored in a locked file cabinet

4. Participants' blood and DNA specimens and/or data have been placed in the CSPEC-Durham Data and Specimen Repository, which will oversee sharing the data with approved researchers.

5. Participants were informed that their individual research results will not be shared with their personal physicians or placed in his/her medical records.

6. All participants were given the project's toll-free number during the enrollment process and were instructed to call if they were injured from the blood draw or became upset while completing the survey. At all times, there was an option and a clear process to refuse participation or to refuse continued participation.

7. For qualitative research activities, participants were given the phone number for project staff and encouraged to contact them with any questions or concerns.

D. Managing Information from VA and Non-VA Participating Sites

This project requires the participation of VA and non-VA sites, which poses some risks of data breaches that may result in loss of participants' confidentiality and privacy. These sites are necessary to determine their appropriate roles and processes as well as effectiveness for a full-scale project. Appropriate Data Use/Transfer Agreements and IRB approvals will be in place before any data are transferred. The section below on Privacy and Confidentiality details protection methods for obtaining, transmitting, and securing PHI.

The participating sites and individuals who will have access to project data are described below.

- The CSP research staff who will have access to the data are: key Central Office staff, a study chair, co-investigators, a research management and operations director, a project manager and project coordinators, research assistants, and statisticians who require access to accomplish study objectives. The exact staffing will vary by stage of project.

- Through September 2, 2016, the Enrollment Coordinating Center had access to names, information about address, phone numbers, social security numbers, dates of birth, gender, rank, branch and project ID codes. The enrollment coordinators, blood collection professionals, and their supervisors required contact information for mailings and telephone calls. Their number varied over the course of the project. The Enrollment Coordinating Center also received the survey, informed consent form, HIPAA Authorization, and Authorization for Use Form to electronically scan for direct entry into the project database. Personnel with access to the PHI on these forms were the project manager, project coordinators, biostatisticians, statistical programmers, call center staff, and mail center staff.

- Information may be shared with the VA's Post-deployment Health Epidemiology Program (PDHEP) to update research records. Personnel with access to the PHI are the PDHEP director, epidemiologists, and statisticians.

- The list of Gulf War Era Veterans obtained from DMDC and PDHEP will be shared with the VA's Million Veteran Program (MVP) to identify a cohort within MVP that served in the first Gulf War. PHI data to be shared include, but are not limited to: names, addresses, phone numbers, birth dates, social security numbers, deployment status and

demographic information. Personnel with access to the PHI are the MVP investigators, epidemiologists, programmers, and statisticians.

Policies and procedures. Information regarding participant protection that must be reported to VA Central IRB generally fall into two categories: (1) protocol violations and deviations (including those that were initiated to prevent or eliminate immediate hazards to participants) affecting the rights, safety or welfare of the research participant, the participant's willingness to continue participation, or the integrity of the research data including risks to confidentiality or privacy due to breaches in data security; and (2) serious unanticipated adverse events and serious unanticipated problems involving risks to participants or others.

The study chair, local site investigators, and VA and other Federal employees must report protocol deviations or violations and any serious adverse events and unanticipated problems to the VA Central IRB within 5 working days after being made aware of the occurrence. Non-routine events and information requiring a report to VA Central IRB will be submitted on the applicable forms and within the timeframe designated by VA Central IRB Handout on Reporting and in VA Handbook 1058.01. When in doubt about the need to report a situation, we will discuss with the VA Central IRB Coordinator.

Transmission of reports to VA Central IRB. VA Central IRB Form 129 is required for reporting protocol deviations or violations, and Form 119 is required for reporting serious adverse events and unanticipated problems. These forms are transmitted to VA Central IRB via a secure SharePoint site.

Education of Sites. VA Central IRB SOPs 114, 125, 126, and 128 detail the policies and procedures to be followed and include the appropriate reporting forms. Non-serious unanticipated problems involving risks to participants or others are reported to the VA Central IRB in the continuing review application submission. CSPEC-Durham staff and the Enrollment Coordinating Center were trained by SMART on the nature of serious and other adverse events and reporting requirements in case they should occur. The SOPs and copies of VA Handbook 1058.01 and the VA Central IRB's Table of Reporting Requirements will be included in the Project Operations Manual as a reminder of these reporting requirements. These documents were updated and additional education was provided as needed.

E. Data Safety Monitoring Plan

This is a minimal risk observational project and thus no data safety monitoring plan or committee was convened. However, an Executive Committee, consisting of the study chair and investigators and CSP Central Office representation, convenes at regular intervals to monitor project progress and protocol compliance. If required by CSP Central Office or VA Central IRB,

we will develop a data safety monitoring plan and/or convene a data safety monitoring committee.

XVI. Confidentiality of Data

At various stages of the project, the Study Chair may transmit and receive de-identified data and identified and coded data sets as appropriate to the circumstances. If needed, de-identification will be accomplished according to the two methods described in VHA Handbook 16051, Appendix A, Paragraphs 2a (statistical de-identification will be documented) and 2b (removal of all 18 individually identifiable information will be documented). Likely circumstances for which de-identification may be necessary include the transmittal of data to co-investigators.

The link and codes to the data containing PHI is kept at CSPEC-Durham. The Study Chair and the lead statistician will share primary responsibility for assuring security of the link or code.

A. PHI from Participants and Existing Databases

PHI will be obtained directly from project subjects in the survey. Also, subjects may provide corrected or updated health information that may include, but not be limited to, dates, contact information, or name change as the project progresses.

By signing the cohort and biorepository ICF, HIPAA Authorization, and Authorization for Use and/or Disclosure of Patient Health Information, subjects participating in the cohort and biorepository project provided access to health, contact, and demographic information, including PHI, from their previous participation in VA and non-VA research studies, as well as access to VA and non-VA medical records, VA, DoD, and other federal administrative databases and registries as needed to add to the VA Gulf War Era Research Database. These sources are required to maintain the currency and relevance of the cohort by continuing to follow participants' health status and other health information over time.

Health and military service information will also be obtained from existing VA and DoD databases. Data will include PHI (name, phone number, address, date of birth, SSN, and dates of diagnoses, clinic visits, hospitalizations, immunizations, treatments, laboratory test results, radiological findings, medications, service, deployment, discharge). The sources of this information may include: DMDC/VADIR and other existing VA and DoD national database resources, such as the Gulf War Registry, VISN data warehouses, the Corporate Data Warehouse, VA registries, VA data centers, Pharmacy Benefits Management, Emerging Pathogens Initiative, Centers for Medicare and Medicaid Services, VA-Medicare merge, Vital Status File, VINCI databases, BIRLS, and others that may be identified over the course of the project.

B. Social Security Numbers

In order to develop the Gulf War Era Research Database, it is necessary to include HIPAA identifiers in the data acquisition process and in analyses to ensure that the data and individual are matched appropriately. Real social security numbers will be maintained on a secure VA server in a restricted database schema and merged with health information only as needed. Only the study chair and statisticians will have access to the file containing the SSN. Other security measures include:

- When SSNs are transmitted for data acquisition purposes, they will be transmitted in electronic form and encrypted.
- SSNs will be stored in electronic form on secure VA servers.
- Use of SSNs will be limited to circumstances for which there is no practical alternative.
- Gift cards will be used instead of checks for payments to participants to avoid use/transfer of SSNs.

C. Contact using Existing PII

A list of Gulf War Era Veterans to be used for the pilot project was obtained from DMDC and PDHEP. Names, addresses, phone numbers, birth dates, real social security numbers, and demographic information will be requested. The PII was used to find current contact information and to mail the invitation packets.

D. Access to Project Data

The participating sites and individuals who will have access to project data are repeated from *Section XV. Potential Risks and Benefits, Part D. Managing Information from VA and Non-VA Participating Sites* above:

- CSP research staff: key Central Office staff, a study chair, co-investigators, a research management and operations director, a project manager and project coordinators, research assistants, and statisticians who require access to accomplish study objectives. The exact staffing will vary by stage of project.

- Through September 2, 2016, access to contact information (names, information about addresses, phone numbers), SSNs, dates of birth, gender, rank and project ID codes had been given to the Enrollment Coordinating Center. The Enrollment Coordinators and their supervisors required contact information. The number of coordinators and supervisors varied over the course of the project. Other personnel employed by the Enrollment Coordinating Center responsible for the collection of blood samples included appointment schedulers, phlebotomists, and supervisors. Their number varied over the course of the project.

- Information provided may be shared with the VA's Post-deployment Health Epidemiology Program (PDHEP) to update research records. Personnel with access to the PHI are the PDHEP director, epidemiologists, and statisticians.

- The list of Gulf War Era Veterans obtained from DMDC and PDHEP will be shared with the VA's Million Veteran Program (MVP) to identify a cohort within MVP that served in the first Gulf War. PHI data to be shared include, but are not limited to: names, addresses, phone numbers, birth dates, social security numbers, deployment status and demographic information. Personnel with access to the PHI are the MVP investigators, epidemiologists, programmers, and statisticians.

E. Protection of Data during Transmission

Between VA Sites. To securely transfer sensitive information between VA sites, a shared network folder or encrypted (PKI) email will be the preferred methods. Shared network folders provide temporary access to a specified recipient at the other VA facility to an isolated folder on a Durham VA file server. This access is restricted to a designated folder for a specified period of time. For smaller data files, encrypted email with PKI encryption software is an efficient and fast option. All files containing PHI will be encrypted and password protected. Passwords will be communicated by phone, email, or in person.

To Non-VA Sites. To transfer sensitive information to non-VA sites, such as the Enrollment Coordinating Center, transmissions using a Secure File Transfer Program and portable media such as a CD-ROMs and DVDs will be used. The data files placed on the portable media and/or the entire media itself will be encrypted and password protected. The actual transfer of physical media will be achieved through person-to-person hand-off or via delivery service with a chain of custody. Before a data transfer is made, appropriate data use or data transfer agreements and IRB approvals will be in place.

XVII. Information Security

A. Software and Web Applications

The project has used available VA-approved software to meet our project management needs and the general requirements for constructing and using the Gulf War Era Research Database. If additional requirements become apparent, we will consult with OI&T staff about software that may be specially obtained for this project. All such requests will be reviewed by the ISO and OI&T staff to ensure that security and other requirements are met. Requests will be processed through the VA Acquisition Approval System. Also, a protocol amendment to the VA Central IRB will be submitted.

B. Storage of Research Data

Electronic project research data at CSPEC-Durham will reside on secure servers at the Durham VA Medical Center. Research data are backed up nightly to OI&T servers or to backup tapes that are stored in a locked secure location. Daily server backup tapes are handled by IT personnel only. The file servers to be used for this project include vhadurhsrdfile1 and the database server VHADURSQLH5.V06.MED.VA.GOV\HSRDSQLPROD03. T. The servicer is Durham VA Medical Center OI&T staff. Paper copies of research data will be stored in filing cabinets that are kept locked at all times. Offices are locked when not in use. In addition, CSPEC-Durham office suite requires the swiping of a VA-issued card. The office building itself is secured by security guards on duty 24/7/365, there are security cameras at all entrances, and building swipe cards are restricted to employees.

Project research data that reside on servers at non-VA sites, such as the Enrollment Coordinating Center, will fulfill all applicable security requirements as detailed in VA Handbook 6500.6, *Contract Security*, in particular, Appendices A (Checklist for Information Security in the Initiation Phase of Acquisition), B (VA Acquisition Regulation Solicitation Provision and Contract Clause), and C (VA Information and Information System Security/Privacy Language for Inclusion into Contracts, as Appropriate). The project research data will not reside on any servers at non-VA sites after September 30, 2016.

C. Retention and Destruction of Research Data

Study Chair Site. Data in the Gulf War Era Research Database will be added to the CSPEC-Durham Data and Specimen Repository and stored indefinitely. There is no time limit on its usefulness for research purposes.

At this time, electronic and paper research data and research records will be stored indefinitely until disposition instructions are approved by the National Archives and Records Administration and are published in VHA's Records Control Schedule (RCS 10-1).

If specific instructions for destruction are not published in RCS 10-1, then we will follow Durham VA Medical Center institutional policies for the destruction of paper and electronic records.

Guidelines for electronic file erasures are detailed in National Institutes of Standards and Technology (NIST) Special Publication 800-88. When possible, the VA recommends overwriting the data (by IT personnel only). If this is not possible, the information is degaussed and destroyed by IT personnel.

Paper copies containing PHI are placed in VA approved shredder units located within CSPEC-Durham office suite.

Other VA Sites. Participating VA sites will follow VA policy for retention and destruction of research data, including local facility instructions.

Non-VA sites. No VA data will be retained by the Enrollment Coordinating Center after the contract/subcontract is completed. Per VHA Handbook 6500.6, *Contract Security*:

- The Enrollment Coordinating Center will be held to the retention/ destruction requirements outlined in Appendix B which states that the Enrollment Coordinating Center/subcontractor must not destroy information received from VA, or gathered/created by the Enrollment Coordinating Center in the course of performing this contract without prior written approval by the VA.
- Any data destruction done on behalf of VA by the Enrollment Coordinating Center/subcontractor must be done in accordance with National Archives and Records Administration (NARA) requirements as outlined in VA Directive 6300, *Records and Information Management* and its Handbook 6300.1 *Records Management Procedures*, applicable VA Records Control Schedules, and VA Handbook 6500.1, *Electronic Media Sanitization*.
- Self-certification by the Enrollment Coordinating Center that the data destruction requirements above have been met will be sent to the VA Contracting Officer within 30 days of termination of the contract.

D. Protection of Data from Improper Use or Disclosure

Durham VA Medical Center's procedure for reporting loss or theft of computer devices, unauthorized use, loss, or disclosures of PHI, or violations of information security requirements is to report the incident immediately (within 1 hour of discovery) to the VA Police, Supervisor, ISO and Privacy Officer. Loss or theft of computer devices or PHI will also be reported to the VA Central IRB as an adverse event.

All CSP research personnel and the Enrollment Coordinating Center/subcontractor personnel who have access to VHA records will be instructed, in accordance with VA policy, on the requirements of Federal privacy and information laws and regulations, VA regulations and policies, and VHA policy. The Enrollment Coordinating Center also signed VA Rules of Behavior developed specifically for the Enrollment Coordinating Center/subcontractors and completed training per VA policy.

The project manager will document that all project staff are current with the VA Office of Cyber and Information Security Awareness Training Course. The data security and privacy procedures summarized in that course will be included in the project operations manual. These guidelines include logging off or locking the computer when walking away from it; no sharing of access codes, verify codes or passwords; not allowing anyone else to use the computer under your password; and disposing of sensitive information in the appropriate shredding bins.

Data access will be terminated when project personnel are no longer part of the research team.

No data will be stored on the hard drive of a PC, except when temporarily required during outreach or qualitative research activities (as described earlier).

The results of the research may be published in scientific papers as aggregate results rather than as individual results, and so the subject's name, photo, or identity will not be used.

XVIII. FDA-Regulated and Other Products

This project does not require use of FDA-regulated drugs, biologics, or devices.

XIX. Expiration of Project

The information stored in the Gulf War Era Research Database and added to the CSPEC-Durham Data and Specimen Repository, as well as the blood and DNA samples stored at the VA Central Biorepository, will be kept indefinitely. There is no expiration date for the project.

Appendix A. ICF Signature Page with Post-it Note

Department of Veterans Affairs

RESEARCH CONSENT FORM

Version Date: December 19, 2012, 2012

Participant Name: _____ Date:_____

Title of Study: ___Gulf War Era Cohort and Biorepository _____

Principal Investigator: _Dawn Provenzale, MD, MS _____VA Facility: __Durham VA_____

Principal Investigator for Multisite Study: __Dawn Provenzale, MD, MS _____

AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

Dr./Mr./Ms_____has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

You voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it.

I agree to participate in this res		**s document.**
_____ Participant's Name	**DO NOT SIGN THIS FORM** until you have spoken with an Enrollment Coordinator on the phone.	_____ Date
_____ Name of person obtaining conse		_____ Date

SUBJECT'S IDENTIFICATION

VA CENTRAL IRB APPROVAL STAMP

VA Form **10-10-86**
MAR 2006

VA Central IRB Template August 8, 2011

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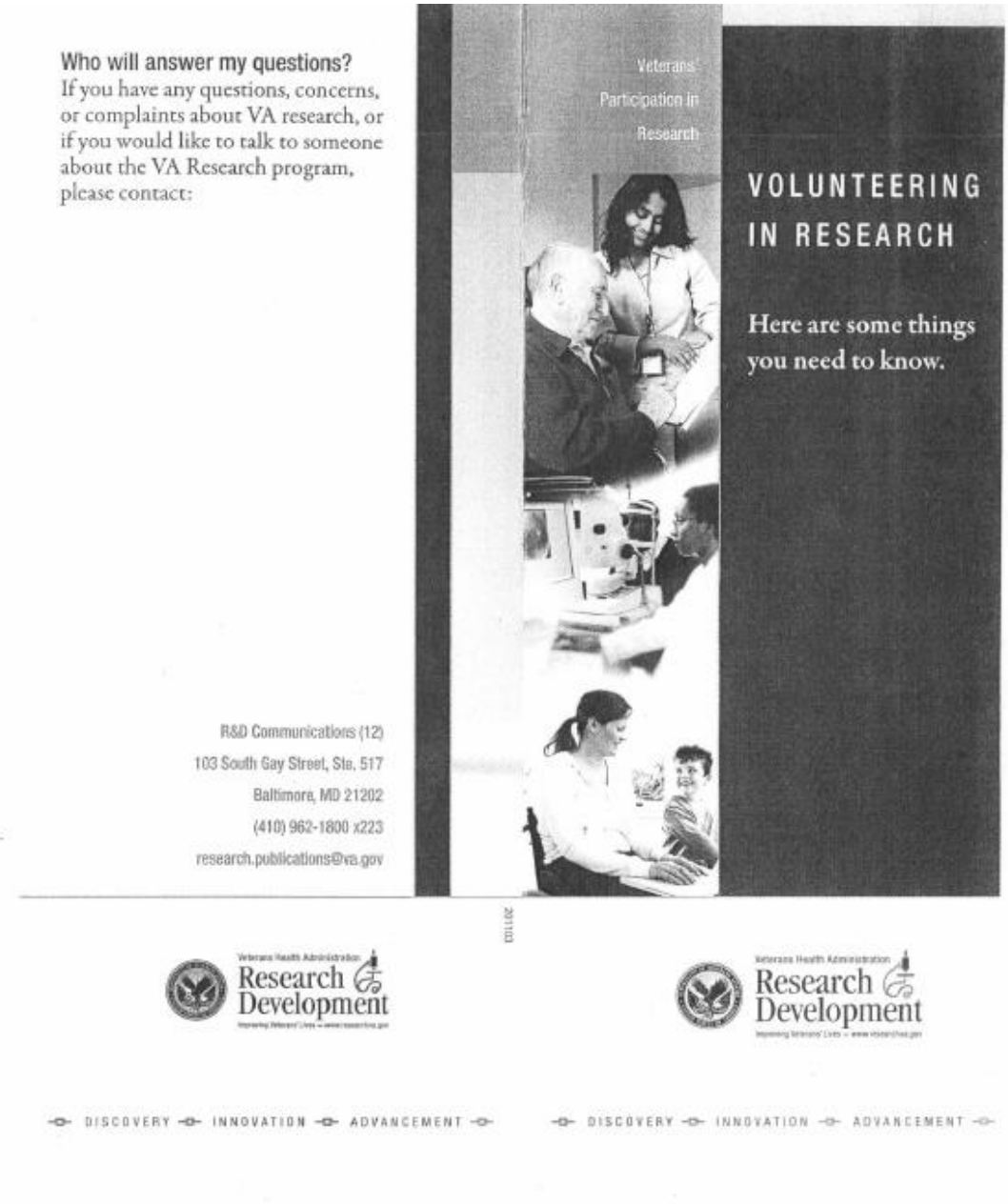
Appendix B. Volunteering In Research Brochure



Who will answer my questions?
If you have any questions, concerns, or complaints about VA research, or if you would like to talk to someone about the VA Research program, please contact:

R&D Communications (12)
103 South Gay Street, Ste. 517
Baltimore, MD 21202
(410) 962-1800 x223
research.publications@va.gov

Veterans' Participation in Research

VOLUNTEERING IN RESEARCH

Here are some things you need to know.

2011D

Veterans Health Administration
Research & Development

DISCOVERY INNOVATION ADVANCEMENT

Veterans Health Administration
Research & Development

DISCOVERY INNOVATION ADVANCEMENT

What questions should I ask before volunteering?

If you are asked to participate in a research study, you might want to ask the questions on this tear out to help you decide whether or not you want to take part in the study.

Tear this page out and take it with you to remind yourself of some of the questions to ask.

Veterans Health Administration
Research & Development

DISCOVERY — INNOVATION — ADVANCEMENT

What if I do not want to take part in a research study?

- If you decide to take part in a study, you do so as a VOLUNTEER. This means YOU decide.
- If anyone asks you to take part in a research study, you have the right to say "no."
- Your decision will not affect your VA health care or benefits.
- You need to weigh both the potential risks and potential benefits of the study.
- You can change your mind and leave a research study at any time without losing any of your VA health care benefits.

The VA Office of Research & Development's Center On Advice and Compliance Help (COACH) offers free educational materials to help assure that Veterans receive adequate information when they consider participating in VA research. You can order additional copies of this brochure and other brochures, a video on VHS tape or DVD-ROM, and posters at:
www.research.va.gov/programs/pride/resources/order.cfm

VA COACH
Center On Advice & Compliance Help

Veterans' Participation in Research

Volunteering in VA Research

Here are some things you need to know

The Department of Veterans Affairs (VA) ranks as one of the nation's leaders in health research. Thousands of studies are conducted at VA medical centers, outpatient clinics, and nursing homes each year. This research has significantly contributed to advancements in health care for Veterans and other Americans from every walk of life.

For example, VA researchers have:

- Used microelectronics and microchips (very small electronic components), as well as robotics, to create artificial limbs (prostheses) that look, feel, and work more like natural arms and legs.
- Developed the nicotine patch to help people stop smoking.
- Invented the cardiac pacemaker.
- Performed the first successful liver transplant.
- Played a major role in the development of the CAT (or CT) scan.
- Helped to develop new drugs and treatments for diseases such as HIV/AIDS, diabetes, Alzheimer's, and osteoporosis.

These important health care advances are only possible because Veterans volunteered to take part in research projects.

What is a research study?

A research study is an organized way of learning more about a problem or answering a question.
A research study may be done to:

- Understand health needs, concerns, or feelings people have about an illness or their general health.
- Test if a product, such as a drug or piece of equipment, is safe and effective.
- Determine the best way to treat or prevent an illness.
- Find out what health care practices work best.

Like your medical record, the information in your research record will be kept confidential.

Are there benefits to being in a research study?

There may or may not be a direct benefit to your health or health condition if you take part in a research study. No one can predict the exact outcome of a research study or how it might affect you. The study may not help you personally, but your participation may provide information that will improve the lives of others in the future.

What is informed consent?

Informed consent is the process of learning important facts about the research study before you decide whether or not to volunteer. If you agree to volunteer, it should be based on a clear understanding of what will take place in the study and how it might affect you.

Informed consent begins when the research staff explains the study to you. These facts include details about the study, tests or procedures you may receive, the benefits and risks that could result, and your rights as a research volunteer.

Once your questions have been answered and you fully understand the facts about the research study, you will be asked to sign an "informed consent form." You should take your time when you read the informed consent form. If you have any questions, ask the research staff to explain. It may be helpful to talk with family members, friends, or your health care providers before you make a decision.

What questions should I ask before volunteering?

If you are asked to participate in a research project, you might want to ask the following questions to help you decide whether or not you want to take part in the study.
Tear this page out and take it with you.

- Who is doing this study and what questions might it answer?
- Who reviewed or approved this study?
- What could happen to my health, good or bad, if I take part in this study?
- Is it possible that I will receive a placebo (inactive substance)?
- What tests or procedures will I have during the study?
- How long will this study last?
- If I decide to participate, how will it affect my daily life?
- Will I have to make extra trips to the VA?
- Could my condition get worse during the study? What happens if it does?
- Will I be charged anything or paid anything to be in this study?
- Who will be in charge of my care? Can I continue seeing my own doctor?
- Who will be told I am taking part in this study? What information will they receive?
- What happens to any specimens that I give?
- What happens after the study ends?
- Will I be told the results of the study?
- How do I end my participation in the study if I change my mind?
- What other options do I have if I decide not to take part in this study?
- Whom do I contact for questions and information about the study?

Appendix C. VA Contact Information

VA Contact Information

For information or questions about the
Gulf War Era Cohort and Biorepository, call: 1-855-GWE-VETS.

If you are experiencing emotional distress and would like to talk to a trained VA professional, call:

1-800-273-TALK (8255) and PRESS 1

Or send a text message to 838255

Or visit the online chat at http://veteranscrisisline.net

Other contact information for U.S. Department of Veterans Affairs:

"New to VA" website:	http://www.va.gov/opa/newtova.asp
Helpline: Agent Orange and Gulf War	1-800-749-8387
VA Benefits	1-800-827-1000
VA Health Care Benefits	1-877-222-8387
VA Health Care Benefits website	www.va.gov/healthbenefits
Education and Training	1-888-442-4551
Telecommunication Device for the Deaf	1-800-829-4833

Appendix D. Recruitment Letter for Cognitive Interview

Department of Veterans Affairs

DEPARTMENT OF VETERANS AFFAIRS
Medical Center
508 Fulton Street (152)
Durham, NC 27705

May 8, 2013

«V_FULL_NAME»
«V_MAIL_ADDR»
«V_C_S_Z»

Dear «V_SALUT» «V_LNAME»,

It has been more than 20 years since the first Gulf War began in 1990. As a Veteran of the Gulf War Era (1990-91), we are inviting your participation in a new project sponsored by the Department of Veterans Affairs. The project is called, "Gulf War Era Cohort and Biorepository," and its aim is to develop a resource for future research studies that will be focused on expanding our knowledge of the conditions that are affecting Gulf War Era Veterans like you. The project is open to all Gulf War Era Veterans, whether or not you were deployed to the Persian Gulf area, or whether or not you receive health care services from the VA.

The project mainly involves collecting information from a survey, national VA resources, and prior studies of Gulf War era Veterans, as well as collecting blood specimens. However, before we begin our full recruitment into the study, we would like to pilot test the survey with veterans. We want to be sure that the questions make sense and see how long it takes people to complete the survey. The pilot test should take about an hour and a half and you will receive a $50 gift card for your time and effort.

The pilot test will take place at the offices of SRA International in Durham, near the intersection of Highway 55 and Interstate 40. I have included a map and directions to the office for your convenience.

If you have any questions or are interested in participating in the pilot test, please call Kathy Hampton at 919-313-7579.

If we do not hear from you soon, we will call to see if you are interested in participating in the pilot test.

Thank you very much for considering our invitation to help us with this important project. We hope you accept our invitation, and we look forward to talking with you.

Sincerely,

Dawn Provenzale

Study Chair and Director
Epidemiologic Research & Information Center

PID «PID»
Doc CTL 201303-2.0 (03/22/2012)

Appendix E. Veterans Crisis Wallet Card