

COOPERATIVE STUDIES
PROGRAM

GUIDELINES

FOR THE PLANNING AND CONDUCT OF
VA COOPERATIVE STUDIES

OFFICE OF RESEARCH AND DEVELOPMENT
DEPARTMENT OF VETERANS AFFAIRS

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I. INTRODUCTION

These *Guidelines* describe the key practices, procedures, and policies for the development, execution and management of VA Cooperative Studies Program (CSP) research. CSP, a division of the Veterans Health Administration (VHA) Office of Research and Development's Clinical Science Research & Development Service (CSR&D), was established to support and conduct multi-site clinical research studies (i.e., cooperative studies) that advance the health and care of Veterans and the nation. Overall, CSP efforts emphasize a commitment towards: 1) the highest levels of scientific quality and integrity; 2) research participant welfare; 3) good stewardship of resources; and 4) responsibilities to all individuals involved in a study and the larger community, as a whole. This booklet is a reference for VA researchers and supplements VHA Directive 1205 and VHA Handbook 1205.01. Together with CSP operational and policy documents used by CSP staff, these documents form the basis for a quality based approach for VA clinical research.

A. Cooperative Studies

Cooperative studies are ones in which investigators from two or more VA (or non-VA as appropriate) medical centers agree to collectively study a selected clinical problem in a uniform manner, using a common protocol with central coordination. While these studies are not typically conducted in the early development and refinement of new therapeutic techniques, they are particularly relevant in subsequent stages of evaluating the efficacy, effectiveness and/or safety of health intervention in humans. They also can be used to investigate etiology and prognosis, including topics related to genomic medicine. Consequently, these studies are advantageous in providing generalizable results that support inferences to a broad population. Clinical (including clinical trials and epidemiological), health services and rehabilitation research can benefit from a multi-site approach that facilitates the accumulation of participants that are:

- Sufficiently large in numbers to provide a definitive answer to the research questions. For medical conditions that are relatively rare, cooperative studies may be the only feasible approach, but even in more common conditions, knowledge can be accumulated more rapidly by pooling the observations made in several facilities.
- Sufficiently diverse to permit broad generalization of results.

As the largest integrated healthcare system in the nation, VA presents an ideal environment for conducting multi-site cooperative studies. In addition to the dedicated clinical research infrastructure provided by CSP, VA has a community of committed patients and investigators that are especially appropriate for conducting research that addresses medical problems and diseases prevalent in the Veteran population. Further, its service to Veterans in general provides a common mission for all research activities. The overall structure and network of medical centers and facilities enable multi-site studies that require uniformity of research methodology, strict maintenance to a protocol, adherence to ethical principles and regulatory policies, common technological platforms, and budgetary management. When appropriate, CSP works with other divisions of VA to conduct its research. These capabilities also make it a strong partner for conducting cooperative studies with other research organizations.

★ In a cooperative study, carrying out specific responsibilities in a structured manner is critical. These *Guidelines* help provide this structure. They also incorporate VA policy and provide more detailed information on CSP-specific activities. However, CSP recognizes that not all areas can be addressed and some flexibility is needed in the conduct of its studies. Exemptions to requirements stated in this document may be granted by the Director, CSR&D. Requests for exemptions should be made through the Director of the appropriate CSP Center. A successful cooperative study requires communication, cooperation, and a willingness to pursue a common goal. To help ensure these efforts, CSP staff and investigators are expected to adhere to these *Guidelines*. If additional information is needed, CSP Central Office (CSPCO) should be contacted.

B. Organization

CSP has eleven centers (see Figure 1) located across the U.S.: five statistical and administrative/data coordinating centers, one pharmacy coordinating center, four epidemiologic research centers, and a genomics laboratory that all report to CSPCO in Washington, D.C.

The five Cooperative Studies Program Coordinating Centers (CSPCCs), located at the VA medical centers (VAMCs) in Boston, MA, Hines, IL, Palo Alto, CA, Perry Point, MD, and West Haven, CT, have expertise in biostatistics and clinical research methods, project, administrative and budgetary management, and quality assurance. These centers help direct and support all phases of the research project, including proposal development, study implementation, central coordination of study conduct, data collection and management, interim statistical analyses, study progress monitoring, compliance, and final analyses for study publications.

Unique to CSP is the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CRPCC), affiliated with the VA medical center in Albuquerque, NM. The CRPCC was established to provide additional resources for all CSP studies, specifically ones involving drugs or devices. In addition to planning studies, responsibilities include study monitoring, serving as liaison to the Food and Drug Administration (FDA) and the pharmaceutical or device industries, providing expertise regarding FDA regulations, reviewing and distributing reports of adverse events (AE) and serious adverse events (SAE) collected during the course of the study, and centrally controlling and distributing study drugs and devices. The Site Monitoring, Auditing and Resource Team (SMART) resides at the CRPCC and is responsible for the training and oversight of Good Clinical Practices in CSP studies.

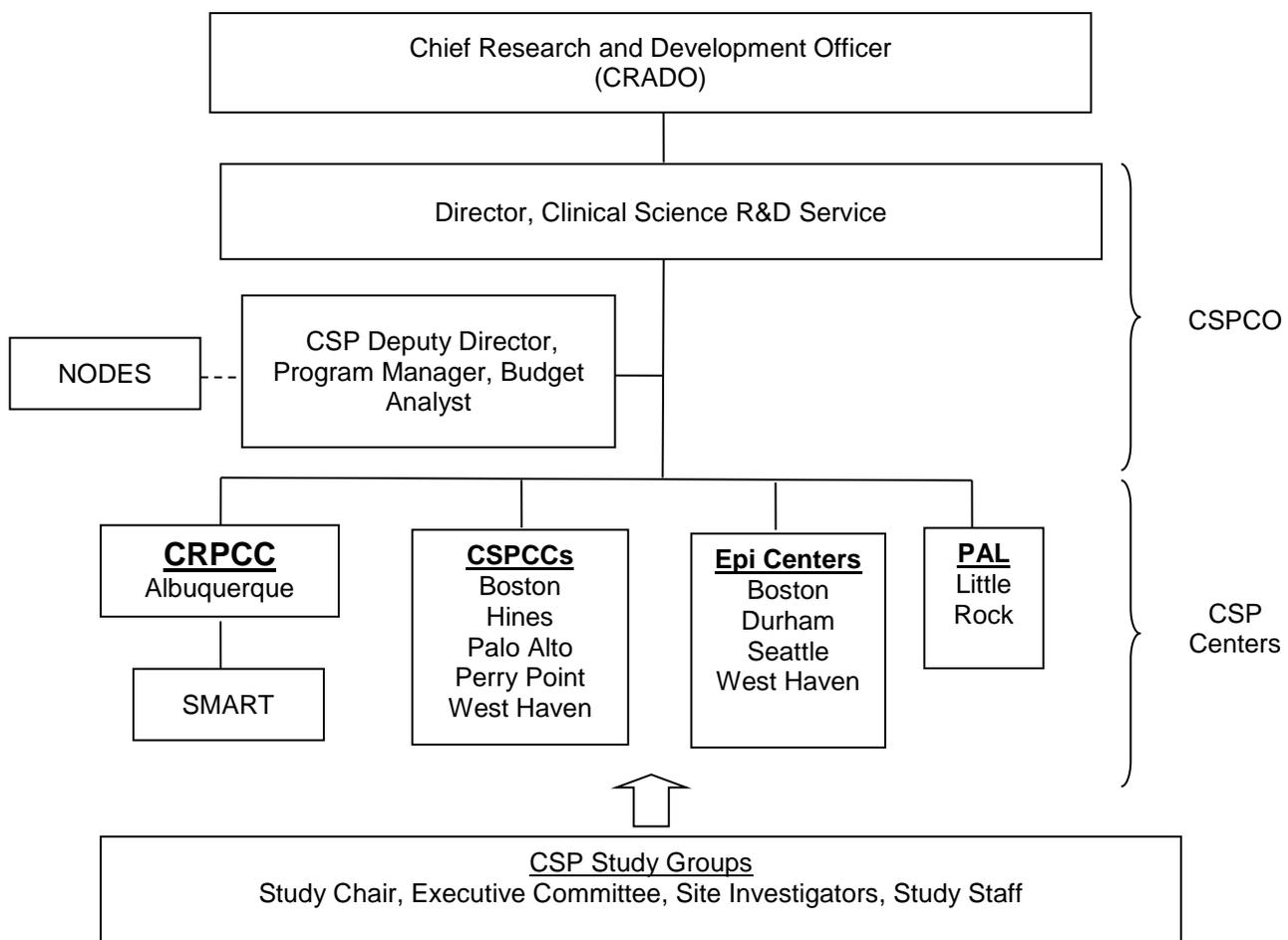
The four epidemiologic centers [three Epidemiologic Research and Information Centers (ERICs) and the Clinical Epidemiology Research Center (CERC)] conduct, coordinate, and support population and genetics research. They emphasize observational methods of large cohorts and approaches that do not require a randomized approach to addressing clinical questions. These centers are located at the VAMCs in Boston, MA, Durham, NC, Seattle, WA, and West Haven, CT.

The Pharmacogenomics Analysis Laboratory (PAL) at the Little Rock VA Medical Center is dedicated to helping CSP investigators with studies that have genetic and/or pharmacogenomic data. With technological and analytical resources for such activities, the PAL provides another dimension to how CSP addresses Veterans' healthcare needs.

CSP also partners with the Health Economics Resource Center (HERC) at the VA Palo Alto Health Care System. HERC economists provide design and analytical support in the conduct of CSP studies in instances where cost effectiveness, quality of life, or other economic questions are relevant.

While CSP studies are conducted at VAMCs with the appropriate capacity to conduct clinical research, it also supports a group of sites focused on carrying out multiple CSP research activities at once. These sites are part of the CSP Network of Dedicated Enrollment Sites (NODES) and are located at the VAMCs in Boston, MA, Dallas, TX, Hines, IL, Houston, TX, Long Beach, CA, Minneapolis, MN, Palo Alto, CA, Portland, OR, Salt Lake City, UT, and San Diego, CA.

FIGURE 1. CSP Organization



II. DEVELOPING A CSP STUDY

A CSP study begins with the submission of a Letter of Intent (LOI) (also referred to as a Planning Request) by an eligible VA Investigator to the Director, CSR&D in CSPCO. The investigator submitting the LOI is designated as the Principal Proponent. A Co-Principal Proponent is named when a clear and justifiable need exists, although this practice is discouraged. No more than two Co-Principal Proponents may be named.

A. Letter of Intent

An LOI should be no longer than 10 pages and contains the following information:

- Title & Principal Proponent Name(s).
- Objectives of the proposed research including concise mention of patients/participants, interventions, and outcomes.
- Relevance and potential impact of the study to VA and to Veterans and how the study will affect clinical practice.
- Feasibility and justification for conducting a multi-site study within VA.
- Summary of the preliminary research has been accomplished with data to support a large-scale evaluation.
- Proposed study design including the following items as appropriate:
 - population to be studied, with specific inclusion and exclusion criteria
 - interventions or /treatments and services to be compared
 - outcomes or endpoints to be evaluated
 - research design (e.g., randomized trial, observational cohort study) and rationale
 - sampling strategy
 - logical links between questions, data, and primary and secondary associations
 - number of participants and participating medical centers
 - duration of study
 - resources required (FTE (Full Time Equivalent) and estimated total costs)
 - methods of data collection
 - units of measurements, strategies for analyses
 - other details, as needed
 - Note: Investigators interested in a novel approach to conducting comparative effectiveness research using VA's electronic health record through the Point of Care Research (POC-R) initiative should contact CSR&D/CSPCO for information on any additional LOI requirements.
- Acknowledgment of VA policy to include women and minorities in clinical research.

Other documents that should accompany the LOI but are not included in the 10-page limit:

- Completed Form 10-1313-13 or equivalent. (See <http://www.va.gov/vaforms/> or <http://www.research.va.gov/funding/process/forms.cfm>)
- Statement of disclosure. A formal statement is required indicating that no financial or contractual relationship exists between the Principal Proponent(s) and any proposed organization involved in the trial that may constitute a real or apparent conflict of interest. If such a relationship or contract does exist, or appears to exist, the Principal Proponent(s) must provide full disclosure.
- Statement of eligibility. To be eligible for planning support, a Principal Proponent must either have at least a 5/8 VA appointment or have applied for and received a 5/8 appointment waiver from the Director, CSR&D within the previous year approving an LOI submission. In the latter case, a copy of the waiver approval establishing eligibility to receive funds should be attached to the request. A Principal Proponent may not be a VA Central Office employee.
- Cover letter from the Director and the Associate Chief of Staff for Research and Development (ACOS/R&D) from the VAMC of the Principal Proponent(s) acknowledging and approving the submission.
- Curriculum Vitae (CV) of the Principal Proponent(s) with address, email, telephone, and fax number(s) (not to exceed 10 pages).
- Potential Planning Committee Members. Names, addresses, telephone numbers and email addresses of five to seven experts that would be appropriate for the study Planning Committee should the LOI be approved. The list should include potential VA site investigators.
- List of On-going and Submitted Proposals. Indicate any on-going or submitted proposals that are directly related (e.g., pilot study, single-site, and smaller clinical trial) to the study proposed in the LOI and the funding source.
- Suggested Subject Matters Experts. A list of names and their affiliations may be included on a separate page who could serve as potential reviewers, Data Monitoring Committee members or other roles not directly related in study planning/conduct.

Seven copies of the LOI and CVs should be submitted in addition to an electronic version of these documents on a compact disc (CD). Incomplete submissions will not be processed. Other relevant background materials, including reprints and references, may be appended to this request. However, not all submitted material will necessarily be distributed to the reviewers. The LOI and all correspondence pertaining to it should be sent through the local VA research office to:

ATTN: CSP LOI (Planning Request)
Cooperative Studies Program (10P9CS)
VA Office of Research & Development
810 Vermont Avenue, N.W.
Washington, D.C. 20420

★ It is the Principal Proponent's responsibility to make appropriate grantsmanship decisions. Investigators who have questions about submission of an LOI are encouraged to contact CSPCO staff. An initial LOI has less detail than a full CSP study proposal. Accordingly, the clinical rationale and study design included in the LOI should be rigorous and well-described. The LOI should also clearly delineate the important gap-in-

knowledge that a future “full” CSP proposal would address. When it appears advantageous, the Director, CSR&D may suggest a consultation with staff at one of the CSP Centers.

B. Letter of Intent Review and Decision

Upon receipt, an LOI is first administratively reviewed for appropriateness for CSP. If accepted, the LOI is sent for external review which typically involves three or more subject matter experts who evaluate the scientific and clinical merit of the proposal. The decision on an LOI is made by the Director, CSR&D based on the reviewers' recommendations, program priorities, on-going and planned activities, and/or availability of funds. Disapproved LOIs receive a summary of reviewer comments. Decisions to approve study planning may also include a determination for the appropriate mechanism for planning (e.g., POCR). On occasion, preliminary planning (or pre-planning) activities may be approved when an LOI demonstrates potential for a becoming a CSP study but requires additional work. Responses to planning requests are made within approximately three months depending on whether additional information is needed to complete reviews and/or other situational factors.

When a study is funded for planning, the Principal Proponent is notified in writing by the Director, CSR&D. An approved LOI provides CSP resources and travel funding for a subsequent planning process, typically involving two planning meetings. These activities are geared towards completing a full proposal to be reviewed by the Cooperative Studies Scientific Evaluation Committee (CSSEC).

This letter indicates the CSP Center(s) to which the study has been assigned, the study number and full reviews (de-identified). The ACOS/R&D at the Principal Proponent's medical center is provided a copy of the notification as well. Subsequent to these notifications, the Director of the responsible CSP Center will identify the Study Biostatistician or Epidemiologist and Project Manager with whom the Principal Proponent will work. The CRPCC Director is also notified and, if the study involves drugs or devices, will assign a Clinical Research Pharmacist (CRP) to the study. If the study does not involve drugs or devices, s/he will assign a CRP AE Specialist to manage the adverse events aspects of the study. The HERC Director may be notified in order to provide further evaluation of the potential health economic aspects of the study and will assign a health economist to those studies that will include economic analysis.

Although most CSP studies are supported by the VA research appropriation, funding is occasionally provided from other VA sources or by outside sources such as the National Institutes of Health or the pharmaceutical industry. Acceptance of CSP planning support indicates agreement to abide by all applicable VA and CSP policies and procedures in the development of the protocol and the conduct of the study regardless of whether other funding sources are intended.

C. Individuals / Groups Involved in CSP Study Planning

Planning a CSP study requires close cooperation and critical thought among several groups and individuals. It is an involved process in which the final study design can differ substantially from the LOI (for example, the specific interventions being compared, or even whether the study is randomized or observational, might change). Therefore, a diverse set of expertise is critical to these activities. The following describes key roles and responsibilities in this phase.

1. Principal Proponent

The Principal Proponent provides leadership in the planning process with collaboration from CSP Center personnel. Working closely with the Study Biostatistician or Epidemiologist, the Principal Proponent will:

- nominate the members of the Planning Committee for approval by the Director, CSR&D.
- coordinate available dates for the first planning meeting.
- develop an agenda and distribute relevant material prior to the first meeting.
- serve as Chair at meetings.
- coordinate the writing of the protocol.
- present and defend the protocol before the CSSEC scientific review.
- contact industry or other federal agencies for possible support.

2. Cooperative Studies Program Coordinating Center or Epidemiologic Center

During planning, several individuals from CSP Centers assist with various activities. However, among CSP Center personnel, typically the Study Biostatistician or Epidemiologist and/or Project Manager have primary roles. These individuals will:

- help select members of the Planning Committee;
- provide logistical support for the planning meetings, including identification of the meeting site, coordination of travel, and other related activities;
- design the biostatistical/methodological and operational aspects of the protocol, including statistical and experimental design, definition of endpoints and data to be collected, data flow and management, quality control methods, study monitoring plan, sample size determinations, planned interval and final statistical analyses, data summaries, forms design, and budget estimation;
- arrange for a protocol input from a CSP Human Rights Committee (HRC) if applicable;
- arrange administrative support (e.g., copying and distributing the proposal to members of the Planning Committee, and preparing and submitting the final document to CSPCO for review by CSSEC);
- assist CSPCO in developing agreements and contracts with non-VA collaborators for supporting the study.

3. Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CRPCC)

For studies involving drugs, biologics, or investigational devices, CRPCC personnel, typically the Study CRP AE Specialist, Pharmaceutical Project Manager or Program Manager, and SMART, will:

- assist in the development of the study design, particularly with regard to drugs, dosage regimens, manufacturing of solid dosage forms, procurement including outsourcing, packaging, randomization, and blinding strategies;
- assure compliance with drug or device accountability regulations and other legal requirements through the development of drug or device treatment and handling procedures;

- act as liaison between the pharmaceutical industry or manufacturers and the Principal Proponent in the possible procurement of study drugs or devices, and assist CSPCO in developing an agreement and contract with industry;
- provide comprehensive drug information to the study sites that include therapeutic category, pharmacology (mechanism of action and pharmacokinetics), approved uses, summary of clinical trials, dosage information, side effects or adverse reactions, drug interactions, and contraindications and precautions;
- prepare a Drug/Device Information Report (DIR) for each primary study drug or device and submit all DIRs to the CSPCC;
- act as Liaison with FDA in all regulatory aspects of the IND (Investigational New Drug Application) or IDE (Investigational Device Exemption) when CSP is the Sponsor;
- develop an adverse event reporting system for documenting and reporting routine and serious adverse events to assure compliance with FDA reporting regulations and CSP policy and procedures;
- evaluate monitoring needs and develop a monitoring plan;
- develop source documentation guidance and other tools to promote adherence to GCP;
- assist CSPCO in developing agreements and contracts with non-VA collaborators for supporting the study.

4. Health Economics Resource Center (HERC)

HERC coordinates most economics activity of CSP. For studies involving economic analysis, the Study Health Economist will:

- assist in the development of the study design, particularly with regard to the economic analysis;
- design the economic aspects of the protocol, including the economic methods to be used, how quality of life will be measured, how utilization of health care will be measured (including non-VA care), how costs will be determined, the statistical analysis for the economic part of the study, and the forms design for those data elements specific to the economic analysis.

5. Planning Committee

Assembling the Planning Committee is an important step involving submitting nominations with CVs for approval to the Director, CSR&D through the CSP Center Director. This process should be completed early as possible but no later than six weeks prior to the first planning meeting. Approvals are based on but not limited to subject matter expertise, interest and commitment to the planning process, diversity and no conflicts of interest. This group is ultimately responsible for preparing a final study proposal, which should reflect a collaborative in-depth effort with agreement on all major issues for scientific review

★ The Planning Committee includes the Principal Proponent, the Study Biostatistician or Epidemiologist, the Project Manager, the Study CRP AE Specialist, the Pharmaceutical Project Manager, and subject matter experts in clinical, logistical, and/or technological areas applicable to the study. Clinical expertise other than the specialty of the Principal Proponent should be considered for representation on the Planning Committee. A health economist, usually assigned by the HERC, may be included when this is an objective of the proposed study. If multiple disciplines are involved (e.g., medical and surgical), they should be reflected in the composition of the Committee. The total planning group

typically consists of eight to ten people. The Director, CSR&D, Deputy Director, CSP and CSP Center Director(s) are ex officio members. Other staff in CSPCO may be invited to participate. Participation does not require VA affiliation. If industry and/or other federal agency support is planned, a representative from that organization may be invited to participate in the planning process with CSPCO approval and in accordance to other requirements stated in these *Guidelines*.

6. Cooperative Studies Program Human Rights Committees

Any study involving human subjects requires protection of their rights and welfare in the study and should design participation activities that consider their perspective. CSP Human Rights Committees (HRCs) have been established at each CSPCC to assist in efforts.

During planning, the responsibility of the HRC is to advocate for the research participants' needs and review CSP proposals and documents associated with their participation (e.g., Informed Consent forms, informed consent process, study recruitment plan or materials, protocol), human rights issues, and ethical concerns. The HRC comments and concerns will be summarized into a written report containing general observations and/or specific questions, and will be submitted to the CSP Center Director through the Associate Center Director (ACD) for Quality Assurance (QA). The CSP Center Director will distribute the report to the Study Group and CSPCO.

The HRC provides an assessment of participation, safety and related requirements. This review is not a substitute for review by the local participating centers' R&D Committees and the Subcommittees on Human Studies, or IRBs (Institutional Review Boards, including local and VA Central IRB). An HRC is a consulting body and, as such, provides insight and suggestions to enhance required reviews conducted by other groups. HRCs cannot disapprove a CSP study but their input should be strongly considered in such decisions. CSP Centers may use the HRC as a more formal review body for non-CSP projects.

D. Planning a Cooperative Study: The Process

The planning process centers around in-person planning meetings and culminates in a final proposal for CSSEC review. Typically, there are two meetings that last two days each and involve much preparatory activity. Under special circumstances, additional planning meetings may be approved by CSPCO.

The Principal Proponent and CSP Center(s) initially discuss LOI reviews, key requirements for a proposal and needed expertise for planning discussions. Subsequently, the first planning meeting is held in the Washington, D.C., area to facilitate the attendance of the Director, CSR&D and other Central Office personnel. The final planning meeting is normally held in the vicinity of the assigned CSP Center to permit attendance of other relevant CSP Center staff. Meetings will not be supported unless all major participants are able to attend. Development of the protocol is a joint effort of the Planning Committee members. However, the primary responsibility lies with the Principal Proponent, the Study Biostatistician or Epidemiologist, and the Study CRP or AE Specialist.

If no activity toward planning the first meeting occurs within three months of authorized planning, further support will be discontinued. It is the responsibility of the assigned CSP Center Director to notify the Director,

CSR&D of any lack of progress and the need to discontinue planning support. If the circumstances in a given situation are unusual and justify an exception from this practice, then the CSP Center Director may request an extension from the Director, CSR&D.

The assigned CSP Center(s) is responsible for distributing materials to the Planning Committee prior to the first planning meeting. These materials include the original planning request, reviews, CSP documents, details on key scientific and methodological aspects of the study, and logistical documents. It is important that all Planning Committee members read all of these materials prior to the planning meeting.

At the first in-person meeting, the Planning Committee goes through a structured agenda addressing the study question, clinical impact, design, feasibility and key elements of a proposal. There should be preliminary discussion of potential participating medical centers and specific efforts for determining participant availability. This determination consists of prospective (preferred) or retrospective screening of actual participant intake by each of these medical centers using the inclusion/exclusion criteria agreed upon. The review should be over a sufficient period of time to provide a reasonable estimate of the availability of research participants. The CSP NODES should be included in these efforts. There are special considerations for enrolling non-Veterans into VA studies supported only by the VA research appropriation. Any plans for enrolling non-Veterans must be justified and obtain written approval by the Director, CSR&D prior to the second planning meeting. This approval does not preclude additional requirements needed at the VAMCs. All information on participant availability should be obtained before the second planning meeting.

Funding for the second planning meeting is contingent upon a successful first meeting as defined by having established a clear study question, appropriate design, feasibility and a plan for proposal completion. The second planning meeting should be held within 6 months of the first planning meeting. To obtain funding for continuing the planning process, the Principal Proponent is required to update his original planning request incorporating all agreed upon changes by the Planning Committee. This request will then be sent for approval to the Director, CSR&D through the CSP Center Director. The CSP Center Director, in a cover letter to this revised planning request, is required to reaffirm that the study is viable and that the planning activity should continue. If the Director, CSR&D requests additional information to make this decision or the Director, CSR&D disapproves continued planning; the information or any appeal to the disapproval must be submitted to the Director, CSR&D within 30 days of notification.

If appropriate, the Study CRP begins negotiating with the pharmaceutical or device company early in planning to try to secure commitments for pharmaceuticals, medical devices, or additional supplies for the study (typically a clinical trial). This negotiating may include VA Contracting and Acquisitions and the Office of General Counsel. In some cases a Cooperative Research and Development Agreement (CRADA) will be needed (see below). The Principal Proponent usually makes the initial contact with the company, and the Study CRP follows up with CSPCO personnel and completes the negotiations. The Director, CSR&D/CSPCO must be informed of all discussions. The Study CRP should attempt to secure a written commitment from each involved company during planning or at least prior to CSSEC review. It is important that these negotiations be completed prior to CSSEC review, if possible, so that the start of the study will not be delayed once funding is approved. If the Principal Proponent is in discussion with the pharmaceutical or device company to secure funds in support of the study, the CSP Center Director should be involved in these discussions and, if possible, a letter indicating this support should be obtained prior to CSSEC review. Also at

this time, consideration should be given to the potential need for additional intensive on-site monitoring based on the company's intent to use the data to support any regulatory filing. The pharmaceutical company would be expected to fund this monitoring activity. CSPCO will coordinate these efforts with the CSP Centers involved and provides guidance on appropriate mechanisms and procedures.

CSP laboratories including the CRPCC, PAL, or CSP Biorepository must be considered first as applicable. CSP Centers can provide the appropriate points of contact. These CSP staff members may also be members of the Planning Committee.

The Site Monitoring, Auditing and Resource Team (SMART) at the CRPCC will evaluate the need for site monitoring with the aid of the Planning Committee. The nature and extent of site monitoring will depend on the regulatory needs of the industry partner (if any), risks to participants, and other considerations specific to the study. Typically, a member from SMART does not attend planning meetings. The Study CRP AE Specialist serves as a link between SMART and the Planning Committee in determining monitoring and other GCP support needed for the study.

A plan for publications must be considered and incorporated into the planning process. Although it is early in the course of the study, it is recognized that publications are, in fact, the end product of a CSP study (see Section VI.C. of these *Guidelines*). Therefore, it is the responsibility of the Principal Proponent, the CSP Centers, and the Planning Committee to anticipate that product.

The final planning meeting is devoted to refining the protocol and data collection instruments, assessing preliminary participant availability estimates, formulating the final budget, and, if applicable, receiving input from the HRC. To ensure that the goals of the final planning meeting are accomplished, the Principal Proponent must circulate an essentially complete protocol including proposed data elements and instruments and informed consent documents to each member of the Planning Committee and, if applicable, the HRC several weeks prior to the meeting. A preliminary budget (including justification of equipment or unusual items, and brief but informative job descriptions) is also required by the CSP Center. If submission of this material is late or if it is substantially incomplete, as determined by the CSP Center Director, the final planning meeting will be rescheduled. After the final planning meeting, the CSP Center(s) will prepare the final proposal for submission to CSSEC, through CSPCO, by the required deadline.

E. Pilot Studies or Feasibility Trials

In some cases, it may be necessary to conduct a pilot study or feasibility trial before embarking on a full-scale study. In such cases, the CSR&D Cooperative Clinical Trial Award (CCTA) mechanism should be considered.

F. Collaborations

The following are general guidelines that should be followed in collaborations with non-VA groups, including industry:

- VA and the collaborator should recognize that they may have mutual but not identical interests in a research study and distinguish principles from practice.

- Collaborators, including industry representatives, may participate in planning meetings, Study Group meetings, Executive Committee meetings, and Publication Committee meetings subject to the ability to maintain confidentiality, uphold scientific integrity and avoid conflict, real or perceived.

The following items are primarily applicable in context of a formal agreement with a collaborator after a CSP study is approved for funding. However, these points should be discussed during the planning phase so that parties understand expectations early in the process before a collaboration is finalized.

- Agreements with non-federal entities involving intellectual property shall utilize a Cooperative Research and Development Agreement (CRADA).
- Agreements with other federal agencies use an Interagency Agreement mechanism.
- Industry representatives cannot participate in Data Monitoring Committee (DMC) meetings (unless requested by DMC), nor have access to DMC minutes.
- Industry representatives shall not have access to unblinded data prior to the end of participant follow-up.
- Industry funds must be contributed to a VA non-profit corporation (NPC) and funds must be under the control of the NPC, not industry or a VA investigator.
- Collaborators may receive courtesy pre-publication manuscript drafts for comments and receive acknowledgment for funding in study publications as agreed upon in an executed agreement.
- Industry shall not have any veto over publication.
- Industry representatives shall not release pre-publication data in any form.
- When appropriate, CSP can assist industry collaborators in preparing FDA regulatory filings and be reimbursed for extra effort. However, CSP staff cannot participate in any conversations with FDA on behalf of an industry collaborator related to such activities as it is a criminal conflict.
- If industry representatives are to provide site monitoring, their visits and reports should be coordinated and distributed through SMART.

G. The CSP Study Proposal

★ CSP study proposals must include elements that enable rigorous scientific peer review, communication of study methodology and intents to any parties requiring this information for oversight responsibilities. The Principal Proponent is responsible for finalizing the write-up of core scientific and clinical elements. To allow sufficient time for completing the proposal, a complete final draft must reach the CSP Center at the designated time, often several weeks before the CSPCO submission deadline. The CSP Center(s) is/are responsible for ensuring the entire proposal fulfills requirements and standards for submission to CSPCO. Deficiencies in any important aspect can result in the proposal being returned for appropriate action. The CSP Center Director has authority to disapprove submission if expectations are not met. While at the time of this printing, CSP was undergoing a transition to electronic/on-line submissions for CSP proposals, the following specifies the current proposal requirements:

1. Proposal

- a. Table of Contents

b. Letters of Submittal/Understanding

1) For an original submission:

If there are issues that should be called to the attention of CSSEC, the assigned CSP Center Director will include them in the cover letter. S/He will also comment on the appropriateness of the statistical analysis plan and highlight any budget issues that should be considered. Similarly, the CRPCC Director will call the attention to particular drug or device considerations that should be considered, and plans for conducting site monitoring visits based on regulatory needs, participant risks, or other safety and/or regulatory characteristics of the study.

2) For a resubmission of a proposal:

If the proposal is a resubmission, the following documents are also required:

- CSSEC Minutes: A copy of CSSEC review comments and recommendations made at the previous review.
- Letter from the Director, CSR&D to the Principal Proponent that summarizes the results of the previous CSSEC review.
- A statement by the Principal Proponent or the Study Biostatistician or Epidemiologist that summarizes the specific changes made in response to CSSEC recommendations, including a point-by-point response to each concern listed in the CSSEC report and notification letter.

c. Executive Summary/Abstract

The first page of the study protocol is an abstract that succinctly states the research question(s) and the salient elements of the proposed study design including such information as the relevance to VA, number of research participants and participating sites, duration of participant intake and treatment (follow-up), definition of participant samples, treatment arms (if appropriate), and endpoints.

d. Study Protocol

To the extent possible and appropriate, the study protocol should be a concise description of proposed procedures, reserving detailed discussion of specialized technical procedures for inclusion as supporting information in appendices in the second volume. Since different types of studies will require different formats, the following is provided as a guide rather than an all-inclusive list of what is contained in the main protocol.

- Primary and secondary objectives. A clear description of the short and/or long-term objectives of the study should be provided, and the hypotheses to be tested specified.

- Background information and references indicating previous and current related research. If appropriate, reference to meta-analysis studies should be included. If the study involves the use of drugs, pertinent pharmacological and toxicological data should be summarized with appropriate documentation. This introductory section should also include a justification for the proposed research and an explanation of its significance to VA.
- Experimental design of the study, including controls.
- Flowchart of the basic study design.
- Participant recruitment, participant selection criteria, and method of assignment of participants to comparative groups. Discussion and justification of any plans for enrolling non-Veterans should be included in this section.
- Intervention/methods of treatment including, if appropriate, provision for double-blinding (and procedures for breaking the blind).
- Methods of follow-up.
- Methods of assuring uniformity of intervention.
- Outcome measurements including specialized rating scales.
- Schedule of observations and laboratory tests and central readings and central laboratories, including plans for collection, use, and final storage of all bloods, tissues, and other specimens in a VA approved facility.
- Sample size issues including the assumptions used to determine number of research participants required, duration of participant intake period, and number of participating medical centers. Other studies that could compete for research participants should be noted.
- Statistical analysis section which describes how the major hypotheses or research questions will be tested, including the specification of major endpoints.
- Performance measures and the management plan for how study goals and milestones will be achieved.
- Plans for safety monitoring including the AEs and SAEs to be collected (all or a sub-subset), and a formal safety plan with safety stopping rules if appropriate.

- Quality assurance procedures including plans for centralized and on-site review or monitoring of clinical site practices. This section must clearly state that ready access to participants' medical records by CSP site visitors is a requirement for participation.
- Qualifications (training and experience) that will be required of the Site Investigator (SI) and funded support personnel at each participating site. These must be commensurate with the position descriptions that will be developed later for the study Operations Manual.
- Plans to assure security and confidentiality of study data.
- Data management and data security plans, Including plans for how data will be maintained at the sites and how it will be transferred to the CSP Center and other appropriate locations (e.g., the CRPCC and Chair's Office) to ensure compliance with VA data security policies and CSP policies.
- Plans for dissemination of study results, including manuscript preparation and writing.
- Economic Analysis. The inclusion of an economic analysis in the proposal may be appropriate. Economic analysis may be an important issue as alternative therapies are compared. When an economic analysis is included, the proposal should contain a separate section containing sufficient detail so that it can be evaluated by CSSEC. An appendix with the complete economic analysis plan should be included.
- Human Subjects Protection Considerations. In addition to the items below, VHA Handbook 1200.05, "Requirements for the Protection of Human Subjects in Research", should be consulted.

There should be a brief description of the procedures that will be used in the study to obtain an individual's voluntary consent to participate. This description specifies who can solicit consent, when consent can be solicited, and under what circumstances. The description may include details such as allowing the participant time to consider the issues or to consult others before giving consent, and providing the participant copies of the consent documents.

There should also be a comprehensive discussion of the ethical considerations that apply to the study. Related issues such as confidentiality of research data may also be included as part of the discussion, in addition to plans for sharing of confidential data. The proposal should identify all of the issues believed to be of importance from a human rights perspective. This would include rationale and justification for inclusion of an untreated control group, and protections for vulnerable participants if any are to be included. In discussing risks, there should be some indication of the degree of risk and a description of the safeguards to protect the participants. If surrogate or delayed consent is planned, this should be discussed and justified. HRC recommendations and/or related discussions are appropriate to include here.

One such issue that has both methodological and human rights implications is responsibilities for research participants at the conclusion of their participation. Plans for studies involving treatment evaluations, particularly those that are double-blind, should be described that include procedures for transitioning participants from the study to regular care at the end of the study or if the study is terminated early for other reasons. (See also Section VI, "Concluding a CSP Study".)

2. Appendices (Supporting Documents)

Appendices contain a variety of information that is of special interest to CSSEC. The following Appendices may be included:

a. Informed Consent Documents

1) Informed Consent Form

- Research participants indicate their willingness to participate in a CSP study by signing VA Form 10-1086, "Research Consent Form" (see VHA Handbook 1200.05). CSP follows all VA research policies for obtaining informed consent. The document should describe the study in language that will be easily understood by the participant or his/her representative so that an informed decision concerning participation can be made.

In addition, the consent form should inform the participant if CSP will use Social Security or VA claim numbers for identification for national database searches and review of medical records. Plans for future use of data should also be included. The consent form may also be used to seek permission to use collected biological samples in the future. Separate consent forms will usually be required for any substantial substudies such as genetic analyses.

2) Health Insurance Portability and Accountability Act (HIPAA) Authorization

CSP follows VHA Policy and guidance located in VHA Handbook 1200.05 when assessing the need for and developing the HIPAA Authorization form. The HIPAA Authorization must be a separate document.

b. Budget(s)

Every proposal contains a study budget including, costs for CSP Centers, study sites, the Chair's office, and/or a special laboratory budget. If the submission includes an economic analysis proposal, there should also be a budget for this component.

1) Study Budgets

The CSP Centers will prepare the budget in the required format and are responsible for following program guidance for determining costs and what is to be included. Items to be included are the salaries of supporting research personnel (including fringe benefits), capitation fees (if applicable and permitted), and consultation fees, equipment, supplies, investigational or study articles, other medications and chemicals, and costs of participant travel if required by the study. The budget should also note the FTE required for the study.

Funding for facility support services (lab, pharmacy) are not supported by CSP funds unless the study requires support beyond routine activities of personnel of these services (e.g., dispensing of supplied blinded study drug during normal working hours by the facility research pharmacist vs. 24-hour on-call to prepare injectable study drug).

CSP Center and, if applicable, HERC costs are also included in study budgets. Specifically, resources (e.g., personnel, equipment) from these centers are budgeted as part of the cost for a CSP study. In addition, the cost of Good Clinical Practice (GCP) monitoring, auditing and training, and other GCP support services provided by SMART must also be included.

If needed by the study, VA and non-VA consultants and special research laboratories will be funded to provide expert advice, central readings and assessments, quality control, and similar services. Funds to purchase equipment and supplies will be included only if the material will be used solely for the study. Funding for participant travel may be available based on study needs. When medical services are furnished as part of an approved CSP study to a participant purely for the research program and not as part of approved medical care to an eligible Veteran, it will be necessary to budget for these costs.

Although it is not VA policy to pay VA participants to participate in research when the research is an integral part of the participant's medical care, under some circumstances such payments are permissible to compensate for their time and inconvenience in having hospital visits and procedures that are solely for research purpose [see VHA Handbook 1200.05]. If such payments are deemed appropriate by the CSP Center Director, they should be included in the budget.

Funding for extra travel and attendance at non-routine meetings before and during the study should be budgeted as a separate item. Travel needs such as extra training meetings and site visits are examples of non-routine travel (see Section V. for a discussion of routine study meetings).

Use of CSP funds must adhere to research appropriation requirements. Salaries of Site Investigators (SI) are not supported by CSP funds. Information technology (IT) cannot be paid for by the VA research appropriation. It is imperative that the participating centers secure the necessary support for IT requirements to conduct the study. Funds and FTE provided for a CSP study are limited to the needs of the study and are not to be used to supplement other clinical or research activities.

Funds for a CSP study at a given VA medical center are considered line item allocations for personnel, equipment, supplies, and other operating costs, and are not to be changed from one category to another without prior CSP Center approval. Transfer of funds from one CSP study to another at the same medical center requires prior CSPCO approval. Unexpended CSP funds and FTE are not available locally for other research activities and shall be returned to CSPCO; unless prior approval for carry over is granted.

All final budgets are subject to negotiation with CSPCO following CSSEC review.

2) Special Laboratory Budget

Central laboratories require strong justification. In general, CSP studies are not the appropriate environment for exploratory work.

If a non-CSP laboratory is needed for the study, a detailed budget estimate must be included, indicating costs of personnel, laboratory supplies, shipping and packaging of specimens, and other necessary items. If appropriate, costs for storing bloods, tissues, or other specimens in a VA approved storage facility should be included. Prior cost comparisons involving non-CSP laboratories must be completed during the planning phase.

3) Economic Analysis Budget

If the study will contain an economic analysis, a detailed budget should follow the economic analysis protocol. The yearly totals appear as a line item in the study budget.

c. Curricula Vitae

The curricula vitae (CV) of the Principal Proponent and the Study Biostatistician or Epidemiologist are required. CVs of all other review meeting attendees should also be included. Each CV should follow protocol submission guidelines.

d. Statistical Analysis Plan (SAP)

This section contains plans for analyses that are as complete as can be envisioned for both interval (monitoring summaries) and final analyses. It includes a statement of the variables to be analyzed and the intervals at which summaries and analyses will be done. The SAP includes prototype tables, charts, data summaries, summaries of analyses, etc., and an outline of the format of the progress reports to be provided to the relevant committees. The anticipated final data summaries and biostatistical analyses are defined and described in detail. This section should include a discussion of the software and/or hardware to be used, and the validation plan for the statistical programs.

e. Data Management Plan (DMP)

This plan is intended to guide in the development of the data management system which includes specifics of case report form creation, data entry screens, data cleaning, data quality monitoring, data locking, and data security. The DMP should also include the software or hardware to be used, and the data management validation plan. This plan is intended to guide in the process of data management which includes specifics of data security, data collection, data entry, data merging, data cleaning, and data locking.

f. Case Report Forms (CRFs)

A prototype set of research Case Report Forms (CRFs) may be submitted as part of the CSSEC proposal. The forms should include most, if not all, data elements to be collected in the study, although not necessarily in final format. For “Just-In-Time” planning, where a study is being planned in a reduced time frame to meet submission deadlines, final forms development can wait until after the CSSEC review. However, the proposal should contain a representation of the important data elements to be collected.

Properly designed CRFs are required for the collection of complete and accurate data in a clinical study. CSSEC may evaluate patient burden and the necessity of proposed data collection for analysis; it is important to practice parsimony in developing CRFs. Forms should be designed to ensure that data collected will be unbiased and minimize possibility of error. CRFs should follow best practices and typically involve a joint effort by the subject matter experts and CSP Center personnel. CSP utilizes electronic data capture (eDC) in research trials. The implications of this should be considered in designing CRFs and outlining data management and statistical procedures for CSSEC submission. Prototype CFRs from the CSSEC proposal will be converted to electronic format during study initiation if applicable.

g. Drug and Device Information Section

When the proposed study involves the use of drugs or devices, the Study CRP develops a Drug/Device Information Report (DIR) on each primary study drug and/or device. This report provides comprehensive information on the pharmacology, toxicology, and previous experience in the proposed indication. It also provides information on known side effects, adverse events, contraindications, and precautions. The report supplements the information presented in the background and rationale section of the protocol, and may be expanded by the Principal Proponent or other members of the Planning Committee. When determined appropriate, investigator brochures or approved product labeling, prepared by pharmaceutical companies, may be included in the Drug Information Section in the Operations Manual and/or as an Appendix in the Protocol. As new information becomes available, it will be distributed to investigators after the study begins. Besides use by the CSSEC, this section is useful for Site Investigators and their R&D Committees and Subcommittees on Human Subjects, and their IRBs.

h. Drug and Device Treatment and Handling Procedures (DTHP)

A detailed procedure for handling drugs or devices is written by the Study CRP in accordance with VA and FDA regulations. The DTHP includes detailed instructions for the receipt, distribution, administration and use, proper disposition, and report requirements of the drugs or devices. The DTHP also outlines the responsibility of the local site pharmacy and local site investigator to meet all requirements detailed in the DTHP.

i. Medical Center Participation and Participant Availability

This section contains a list of medical centers that have expressed interest in participating in the study, and describes the methodology and results of the assessment of participant availability. Analyses of participant availability and possible recruitment strategies should be included.

j. Other Supporting Information

Additional sections can be included as appropriate. For example, if a central laboratory is needed, the protocol should include a detailed description of the procedures for obtaining specimens, tracking shipments, evaluating results, and transmitting data. Other material might include descriptions of training procedures, reliability studies, definitions of endpoints, or plans for on-site monitoring.

III. CSP SCIENTIFIC REVIEW

Scientific and clinical merit, ethical considerations, and study performance plans are evaluated by the Cooperative Studies Scientific Evaluation Committee (CSSEC). CSSEC is a scientific peer review body that is also a chartered Federal Advisory Committee managed by CSPCO. In addition to new CSP study proposals, CSSEC may review ongoing studies if there are major protocol changes, significant increases in the budget, if the study is not meeting initial projected recruitment goals, or at the request of CSPCO or the CSP Center. CSSEC reviews generate recommendations to the Director, CSR&D that are incorporated in decisions regarding funding and action.

A. CSSEC Written Reviews

Following study proposal submission by the CSP Center to CSPCO, clinical and biostatistical written critiques are prepared by CSSEC members and *ad hoc* reviewers, as needed. Reviewers are asked to comment on the clinical and overall importance of the project, its feasibility, the clarity and achievability of its objectives, the adequacy of the plan of investigation, the correctness of the technical details, the adequacy of safeguards for the welfare of the participants, and any other pertinent features of the proposal. The biostatistical reviewer also is asked to comment on the character and definition of response variables, measurement, data collection, and frequency of observations, sample size, plans for data processing and analysis, and any other relevant features. When written reviews are completed, they are distributed to the respective Study Group in a de-identified manner prior to the CSSEC meeting.

B. CSSEC Review Meeting Process

At the review meeting, CSSEC first holds a closed session to summarize and discuss the key critiques from the written reviews. After this briefing session, the Study Team (i.e., proponents) led by the Principal Proponent are brought before CSSEC. If the proposed study is a combination of medical disciplines or requires an area of expertise that the Principal Proponent is not well versed in, the Principal Proponent may request, prior to the meeting, to allow an additional consultant(s) to attend the CSSEC review to help defend those areas where s/he lacks appropriate expertise.

The Study Team is presented with the main critiques to be addressed as determined in the closed session. The Study Team should take relevant notes throughout the review. After critiques are presented, fifteen minutes are given to be used at the Study Team's discretion. Typically, addressing critiques immediately is recommended given time limits. Following this presentation, follow-up and/or new questions/discussion topics may arise and an interactive discussion with CSSEC occurs.

After the interactive discussion, the proponents are excused and CSSEC enters an Executive Session. The *ad hoc* reviewer remains and participates as a voting member in this closed session, during which the CSSEC considers the Study Team defense and formulates recommendations.

C. CSSEC Recommendations

One of four actions is taken initially as part of the formal recommendation:

- Unconditional approval. The study is approved without changes and is recommended for funding.
- Conditional approval. The CSSEC approves the study with the understanding that the Principal Proponent and the Study Biostatistician or Epidemiologist will make certain changes or additions to the protocol. When the changes are made and are approved by the Director, CSR&D and the Chairperson of CSSEC, the study will be recommended for funding.
- Reject or defer consideration of the study with recommendation for resubmission. The CSSEC may find the study worthwhile, but in need of major revisions. In this case, should the Principal Proponent choose to submit a revised protocol, the Director, CSR&D may waive the requirement for an initial planning request and review.
- Reject the study. The Principal Proponent will have an opportunity to review the CSSEC report. If the Principal Proponent wants to resubmit the proposal to the CSP, a new request for planning must be sent to the Director, CSR&D.

For new studies that are approved, CSSEC also assigns a numeric rating reflecting the scientific merit and priority of the proposal. This rating is from 10 to 50 with 10 as the best rating. The Principal Proponent, the CSP Center Director, and the Study Biostatistician or Epidemiologist are informed of the CSSEC recommendation and score immediately after the close of the Executive Session.

★ CSSEC actions constitute recommendations to the Director, CSR&D. Any level of CSSEC approval or score does not ensure funding. Written notification by the Director, CSR&D is the official action/decision on the proposed study. Studies approved but not funded are reviewed on a continuing basis and will be dropped from the funding waitlist if the Director, CSR&D determines that funding will not become available. If the Principal Proponent chooses to resubmit a proposal, a new request for planning must be sent to the Director, CSR&D.

IV. INITIATING A CSP STUDY

Once a study is approved for funding, the Principal Proponent is designated as the Study Chair. The Study Chair and CSP Center staff must work together to complete several actions to enable the start-up and conduct of a CSP study. Given the amount of effort, there must be strong communication, understanding of responsibilities and tasks, and a general ability to operate as a cohesive team that will eventually take on important leadership roles.

A. Study Chair Responsibilities

The Study Chair is responsible to the Director, CSR&D through the assigned CSP Center Director, for the conduct of the study. S/he should not engage in other activities that affect his/her ability to be fully dedicated to the study or that may actually or potentially influence the integrity of the study. The appointment of a Co-Chair may be allowed (e.g., when a study involves two major disciplines). However, there must be a clear and justifiable need, and the request for a Co-Chair must be approved by the Director, CSR&D. This decision is made most appropriately at the time of the initial planning meeting, but may occur after CSSEC reviews the protocol. The Study Chair cannot be a VA Central Office official/employee, a current Chair of another CSP study, nor function as the Study Biostatistician or Epidemiologist. It is not advisable to be concurrently Study Chair and Site Investigator of another CSP study. The Study Chair may not serve as the Site Investigator at his/her own facility and should not be the director of a designated study central laboratory. Likewise, the National Study Coordinator in the Chair's office may not serve as Study Coordinator at his/her own facility.

There are a number of steps to be taken by the Study Chair and supporting CSP Centers before research participant intake can begin. These should be done in a timely fashion or there will be delay in funding and/or participant intake. Study Chair (or National Study Coordinator as designated by Study Chair) tasks include but are not limited to:

- revising the study protocol by incorporating changes suggested by CSSEC;
- nominating participating medical centers;
- coordinating and reviewing study CRFs content and structure, and submission for OMB approval (if needed);
- collaborating with the CSP Center(s) on development, printing, and distribution of a Study Operations Manual;
- collaborating with the CRPCC on pharmaceutical issues and/or safety plan and FDA issues;
- collaborating with SMART on GCP support services;
- nominating members to the Executive Committee;
- nominating members to the Data Monitoring Committee;
- hiring support staff at the Chair's Office;
- selecting the core lab(s), if required;
- supporting activities related for acquisition of equipment and/or supplies.
- developing and testing any special study procedures (e.g., randomization programs, study devices, specialized web sites, or voice response systems);
- planning the organizational/kick-off meeting;
- planning for a study newsletter;

- if applicable, working with CSPCO on any agreements and/or contracts with industry and/or other federal agencies. These need to be finalized prior to the organizational meeting;
- coordinating national conference calls/communication with participating site staff;
- submitting the initial VA Central IRB application, if applicable.

B. Selecting the Participating Sites

Site selection is based on indication of participant availability, site investigator commitment and other information. While CSP studies may involve collaboration with non-VA sites, the following primarily addresses sites to be funded by CSP. When the sites are identified, the Study Chair sends the list of nominations to the CSP Center Director. The CSP Center will ensure that all potential participating VAMCs have a Federal Wide Assurance (FWA) from the Office for Human Research Protections (OHRP) after review by the VA's Office of Research Oversight (ORO). Only sites/VAMCs having an active FWA will be allowed to participate (international sites may have others considerations). If the VA Central IRB is being utilized, participating sites must have a memorandum of understanding (MOU) to allow it to be the IRB of record.

VAMCs wishing to participate must have an individual who is willing to serve as the site investigator (SI) and eligible to receive VA research funding (i.e., at least 5/8 VA time or approved by CSPCO). There must be a Sub-investigator who can serve as leader of the Study Group in the absence of the SI. Usually, the SI will require active support from the SI's service and other services (e.g., Pharmacy, Clinical Laboratory). Investigators must have completed a Conflict of Interest disclosure form provided by the CSP Center. Participation of SIs and/or VAMCs is subject to Director, CSR&D approval.

C. Participating VAMCs

If selected, a VAMC SI is responsible for obtaining needed local approvals, documentation and administrative actions for participating in a CSP study. Included are Conflict of Interest disclosure forms. CSP Centers and/or CSPCO may provide guidance when needed. VA R&D Committee approval to participate implies that adequate staff, space, and other resources are available and that the VAMC has made a commitment to the study. Ideally, the R&D Committee review considers any circumstances that would seriously compromise the medical center's ability to achieve study goals (e.g., if there is a competing study involving identical or very similar participants).

After a VAMC is informed that it has been chosen to participate and obtains the necessary local approvals, the SI, with the assistance of the ACOS/R&D, prepares a formal request for funds to the CSP Center Director that is signed by the Medical Center Director. Acceptance of these funds implies agreement to comply with applicable VA research and CSP policies per VHA Directive 1205 in the conduct of the study. Any deviation from the approved budget requires the endorsement of the CSP Center Director and CSPCO approval.

CSP recommends that a single standard informed consent form be used at all participating centers; the ultimate responsibility for the welfare of the participant resides at the individual center. The informed consent form is developed by the Study Chair and may be reviewed by CSP groups during the planning phase. This version should be considered as a prototype. Similarly, local variations can be incorporated into the prototype

document with the approval of the IRB of record and the knowledge of the CSP Center. However, VAMCs shall not make revisions that result in a fundamentally different protocol being conducted relative to other sites.

Site investigators must retain copies of all approval documents from the medical center required for conducting VA research. Additionally, there are other forms required for regulated studies. Copies of these documents must be provided to CSP Centers upon request. These documents include committee minutes, approval memos, VA Form 10-9012 (Investigational Drug Information Record), FDA Form 1572 (Statement of Investigator) for studies conducted under an IND, or an Investigator's Signed Agreement for IDE studies.

If there has been a significant delay (e.g., more than 12 months) between approval by the local R&D Committee and the Subcommittee on Human Studies, IRB (local or VA Central IRB) and the initiation of the study for any reason (e.g., delay in release of funding, hiring freeze), it may be necessary for these committees to re-review the proposal or at least reaffirm their commitment to participate.

Enrolling participants from VA locations that are not a VAMC (e.g., satellite sites) may be approved by the Director, CSR&D under special circumstances. Any participation requires the CSP Center to ensure that the site has met all requirements for conducting human subjects' research and obtained needed approvals as specified by VA research policies. An investigator must be identified as the responsible party at the site and must complete all required training specified by VA and CSP policies. Relevant research documents must also contain accurate information relative to the site.

D. Forms Approval and Printing

Soon after notice of funding, the Study Chair shall work with the CSP Center(s) on CRF (case report form) development. CRFs should be finalized at a minimum three months prior to study kick-off or as directed by the CSP Center. If time permits, prospective SIs and Coordinators should be asked to review form content and structure early on in the study initiation phase, since it becomes increasingly more difficult to make changes later. Changes to final forms after the kick-off meeting can result in study delays. CSP Centers will follow CSP procedures for obtaining any needed approvals for CRF use.

E. Study Operations Manual and Training Materials

After funding is approved, the Study Chair, Study Biostatistician or Epidemiologist, Project Manager, Study CRP AE Specialist, study Health Economist, if applicable, and other study members prepare the Operations Manual. This manual is used by the Study Group at each participating site and is intended to ensure that the study procedures are followed in a uniform manner. It includes details of randomization procedures, administration of treatments, data collection, flow, recording, security and encoding, as well as procedures for reporting adverse medical events. A section on ethical conduct of the study is included as well as a section on complying with Good Clinical Practices. In addition, the SI's responsibilities to the Pharmacy Service concerning prescription writing or drug ordering, instructions for using investigational or study supplies, the Pharmacy Service's responsibility to the SI, and other items germane to the conduct of the study are clearly defined by the inclusion of the DTHP as a component of the Operations Manual. The manual is assembled and distributed by the CSP Center. Other training materials may need to be prepared for the Organizational Meeting (e.g., video or demonstrations).

F. Hiring and Training of Study Personnel

CSP study personnel are generally hired on term appointments. Under certain circumstances, use of an Intergovernmental Personnel Act (IPA) (through a non-profit organization or a service contract through the Acquisition & Materiel Management Service) may be used. The responsible CSP Center needs to be fully informed of all IPA agreements. Approval authority for IPA agreements is delegated at the local VAMC level.

All SIs, sub-investigators, study consultants, and funded support personnel will be required to submit Conflict of Interest disclosures. SIs will also be required to submit an Investigator's Agreement to Participate which clearly states what is expected from them as study investigators.

Training requirements for study personnel must be satisfied before participant entry begins. SIs and Site Study Coordinators must meet VA-mandated training requirements for research to participate in CSP studies per VHA Handbook 1200.05. Additionally, CSP requires SIs and primary Study Coordinators of interventional studies to receive in-person SMART GCP training, typically provided at the organizational meeting.

During the patient recruitment phase of the study, staffing will vary depending on estimated workload. Generally, participating VAMCs will employ full-time research/Study Coordinators, though less than full-time may be sufficient based on patient intake and follow-up workload. During follow-up, a part-time appointment may be sufficient.

G. Investigational New Drug (IND) Application and Investigational Device Exemption (IDE)

The CRPCC will determine if an IND or IDE is required and provide the necessary guidance regarding required FDA approvals and submissions. In almost all instances, CSP is designated as the sponsor of the IND or IDE. In regulated studies, the Study Chair and every SI who will be participating in the study must complete regulatory forms for the FDA through the Sponsor and meet other specific requirements, as needed. The CRPCC will coordinate the preparation and submission of the IND or IDE application in accordance with FDA requirements. The Study CRP AE Specialist will be the CSP Sponsor's Representative to the FDA and will work closely with the Study Chair to resolve FDA-related issues regarding the study. All correspondence with the FDA from study personnel is directed through the Study CRP AE Specialist.

The FDA will notify the Sponsor's Representative in writing of the date it receives an IND or IDE application. Drug and significant risk device studies may begin 30 days after the FDA receives the application, unless the FDA notifies the Sponsor to the contrary. Copies of FDA approved submissions must be filed in the Central Study File before study articles can be distributed to participating medical centers. CSP will obtain a signed FDA Form 1572 (Statement of Investigator) or Investigator's Signed Agreement (for device studies) from the Study Chair and each SI as soon as the participating medical centers are selected. Drugs or devices cannot be shipped until the signed documents have been received. Routine updating of FDA Form 1572 will be coordinated on behalf of the Sponsor at required intervals.

A medical device procured by CSP is the property of CSP, not the medical facility, as it is purchased by the research appropriation. The medical device may not be included in a medical facility's inventory.

Mechanisms through CSR&D are available at the end of a study for continuing use of the device or transfer to another facility.

In the rare case a non-CSP party is the study Sponsor, that party accepts the responsibility for filing the IND or IDE with the FDA. CSP requires a letter from the pharmaceutical company or manufacturer identifying its FDA assigned IND or IDE number. Written agreements will also be needed to address CSP requirements and for the other party to meet its obligations as Sponsor of the IND or IDE.

H. Organizational/Training Meeting

Prior to the recruitment of participants, CSP studies are funded for an organizational/training meeting. Meeting length depends on the level of training and information required to conduct the protocol safely and correctly, but is generally two to four days. Study personnel including SIs, Site Study Coordinators, the Study Chair and his/her staff, CSP Center study staff, CRPCC study staff, SMART staff, the study's Health Economist, if applicable, and Executive Committee members attend the meeting. However, the number and type of attendees may be subject to budgetary and other travel policy considerations. The primary purposes of the meeting are for attendees to: 1) know the protocol requirements; 2) know what is expected of them; 3) review the data collection forms to ensure and know how to complete them, 4) review VA and CSP policies on conducting research, and 5) discuss what SIs and Site Study Coordinators need to do to comply with GCP and regulatory requirements. If special medical techniques, data collection forms or electronic systems are to be used, training on these techniques/systems or use of the forms will be done at this meeting.

Most of the meeting is dedicated to reviewing the protocol and data collection forms and completing necessary training. CSP personnel review applicable policies and regulations and SMART reviews GCP. The CSP Center Director often speaks on behalf of CSP at this meeting. The Study Chair, his/her National Study Coordinator, the Study Biostatistician or Epidemiologist and CSP Study staff, and the Study CRP AE Specialist will generally provide info on the protocol requirements. When there is an economic analysis component, the health economics staff will conduct review and training concerning economic CRFs.

Given GCP training requirements, if the SI or primary Study Coordinator is unable to attend this meeting, s/he must request in writing an exception from the CSP Center Director. If exception is granted, the SI or Study Coordinator must attend the SMART in-person GCP training as soon as it can be arranged.

Additional details on meeting/travel arrangements are provided in Section V.C.

I. Recruitment

Achieving study recruitment targets is a primary CSP study goal. Strategies typically require IRB approval that is directed towards informing a public and/or clinical audience about the study. It is important that appropriate approvals for a communications plan be obtained by appropriate authorities at the local site. At VAMCs, all advertisements require R&D Committee and Human Subjects Subcommittee/IRB approval, and records of these approvals shall be maintained in the SI's files. Any communications plan must also be reviewed and approved by the Study Chair and the CSP Center Director. Study personnel may not contact Veterans directly by phone. If it is necessary to review medical records prior to obtaining a consent and HIPAA

Authorization, a partial HIPAA waiver for recruitment purposes must be obtained from the IRB of record. Advertising through local media has particular restrictions, and guidance from CSPCO must be sought first. Sites involved in CSP NODES may also have additional options available to them.

V. CONDUCTING A CSP STUDY

Each individual must know their responsibilities in conducting a CSP study. The assigned CSP Center(s) will work closely with all groups (Study Chair, participating sites, labs, CRPCC, HRC, Planning Committee, DMC, etc) to enable effective and efficient collaboration within CSP, ORD, and VHA and to help with compliance with applicable policies. However, SIs are ultimately responsible for knowing all requirements for conducting clinical research and including any local policies and regulations requiring further compliance. If an individual has questions about study responsibilities and/or requirements, s/he should ask the assigned CSP Center(s) responsible for the study.

A. CSP Study Management and Monitoring

The Director, CSR&D delegates responsibility for each CSP study to the assigned CSP Center Director(s), who will, in turn, keep him/her fully informed and will forward those actions or recommendations that require approval. The CSP Center Director will provide a detailed report of progress to CSPCO with special attention to participant accrual and/or problems that might affect the successful completion of the study. The Director, CSR&D may wish to discuss the contents of this report with the Study Chair and the CSP Center Director and recommend appropriate actions. Any study that does not reach at least 80% of the targeted accrual for the first year and have an acceptable number of sites meeting enrollment targets will be at risk for termination. The decision to continue a study is at the discretion of the Director, CSR&D.

Multiple groups have responsibilities for overseeing various aspects of the conduct and/or monitoring of a CSP Study: the Study Group, the Executive Committee, the Data Monitoring Committee (DMC), IRB(s), SMART, the HRC, and CSSEC. Before participant intake begins, the Executive Committee and Study Group meet to review the operational and monitoring aspects of the study. The DMC may also meet at this time or as close to study initiation as possible. After participant intake begins, appropriate progress reports are distributed to these committees by the CSP Center before regularly scheduled meetings, and interim updates are provided between meetings. Studies experiencing major problems or requesting major changes are reviewed by CSSEC as needed.

The standard schedule of meetings for the Study Group, Executive Committee, and DMC consists of an initial meeting for organizational, informational, and training purposes prior to participant intake, a meeting within a year after the initiation of participant intake, and annual meetings thereafter. In some cases, annual meetings may not be required, particularly during the follow-up phase. Ordinarily, meetings will not be held if the remaining period of participant follow-up is less than six months.

1. Study Group

The Study Group is chaired by the Study Chair and includes the Study Biostatistician or Epidemiologist, the Study CRP AE Specialist, the Pharmaceutical Project Manager, the Study Health Economist (if applicable), the CSP Project Manager, the National Study Coordinator, all Site Investigators, and any consultants to the study. CSP and CSR&D Central Office staff may also be included. Two to three weeks prior to Study Group meetings, the Study Biostatistician or Epidemiologist prepares and distributes a report to the Study Group. These reports will generally include aggregate information on study performance measures, such as accrual and withdrawal rates and data quality, background

characteristics, and adverse events. These data are usually not provided by treatment group. At their meetings, the Study Group reviews the progress of the study, discusses any problems the investigators have encountered, and provides suggestions for improving how the study is conducted. Results of blinded data related to study endpoints are not discussed with this group. The Site Study Coordinator(s) from each VA medical center and other CSP personnel may also attend these meetings. It is the Study Chair's responsibility to write a report of each Study Group meeting soon after the meeting, and send it to the CSP Center Director for distribution.

2. Executive Committee

The Executive Committee, chaired by the Study Chair, consists of six to ten members and includes the Study Chair, the Study Biostatistician or Epidemiologist, the CSP Project Manager, the Study Health Economist (if any), the Study CRP AE Specialist, the Pharmaceutical Project Manager, the head(s) of any special central support unit(s) related to the study, the National Study Coordinator from the Chair's Office, two or three Site Investigators, and selected consultants when necessary. The Director, CSR&D, CSP Deputy Director, assigned CSP Center Director, and the CRPCC Center Director are ex officio members. If there are no more than five investigators for the entire study, they may all be members of the Committee. This Committee acts as the management group and decision-making body for the operational aspects of the study, and is responsible to CSPCO. It decides on all proposed changes in the study, any subprotocols or substudies or use of the study data, and on publications of study results, and recommends actions on medical centers whose performance is unsatisfactory. All major alterations in protocol design or operation of the study recommended by the Executive Committee must have the appropriate approvals as discussed in Section V. D. Protocol Changes. As with the Study Group, the interim results of blinded portions of the study will not be presented to this group.

3. Data Monitoring Committee

The Data Monitoring Committee (DMC) usually has five to eight members and includes experts in the subject matter of the study, one or two independent biostatisticians, and other appropriate technical or scientific specialists. Any study that involves a study intervention will have a DMC. Epidemiological studies are highly encouraged to have a DMC and must consult CSPCO on whether to have one or not. The Study Chair, the Study Biostatistician or Epidemiologist, and the Study CRP AE Specialist are nonvoting study representatives and the Director, CSR&D (and designees) and CSP Center Director are nonvoting CSP (Sponsor) representatives. DMC meetings are closed, and additional attendees, such as industry collaborator representatives, may not attend these sessions unless specifically invited by the DMC for the purpose of clarifying specific issues under consideration. The Study Chair and Chair's office staff will not attend closed sessions of DMC meetings when unblinded treatment comparisons are discussed except under unusual circumstances when requested by the DMC and approved by the CSP Center Director and/or Director, CSR&D.

It is the responsibility of the Study Chair to nominate members for the DMC to the CSP Center Director. The Study Biostatistician or Epidemiologist and/or the CSP Center Director usually will assist the Study Chair in selecting biostatistician nominations. Alternate nominations for any of the members

may be suggested by the Director, CSR&D. Whenever possible, diversity in expertise and affiliation is recommended. Past experience is highly encouraged.

The DMC provides a continuing critical and unbiased evaluation of the study's progress, and formulates operational policy consistent with the best current biomedical research practice. It usually meets prior to study initiation and at least annually in person thereafter. The DMC will also review aggregate safety data reports. It does not initially evaluate the scientific merit or methodology of the study nor does it subsequently participate in the study's conduct; these functions are performed by other committees. The DMC maintains the confidentiality of interim results that are presented at scheduled meetings.

As part of the study proposal, the Study Biostatistician or Epidemiologist prepares an outline of reporting procedures including prototype tables and graphs that will be used to present study data, including aggregate safety data (Appendix SAP of the study protocol). The DMC is encouraged to provide a critical review of these proposed biostatistical monitoring procedures at its first meeting and to make recommendations or suggestions for improvement. At subsequent meetings, it may request new or different data displays. The Study Biostatistician or Epidemiologist prepares and distributes a report prior to meetings and at least one interim report between meetings. The Study CRPAE Specialist may assist the Biostatistician or Epidemiologist with safety data, as needed for the report. If data provided to the DMC are unblinded, tables containing these data will not be provided to the Study Chair, who must remain blinded. At the discretion of the DMC, the Study Chair may be provided with unblinded baseline data. The Study Chair reviews the progress of the study and informs the DMC of all proposed changes in the protocol and data collection forms or plans for analyses. After a full discussion of all study issues, the DMC meets in Executive (closed) Session (with the Study Biostatistician or Epidemiologist and unblinded Study Representatives) to review unblinded data and formulate recommendations. The DMC may choose to meet in an Executive Session without study or CSP representatives to formulate recommendations.

In addition to the report of the DMC meeting, the DMC Chairperson will prepare a short report to be distributed to the Human Subject Subcommittees, IRB(s) informing them of any safety issues or lack of safety issues in the study. Since these groups will not have access to unblinded data results, the report will provide them assurance that the DMC is monitoring the safety of research participants, and will make them aware of any safety issues. The report needs to be worded such that unblinded study results are not revealed unless absolutely necessary. Consultation with CSP in such cases may be necessary.

During the course of the study, the Study Chair and other members of the Study Group, including the Study Biostatistician or Epidemiologist, shall not consult with DMC members without the approval of the CSP Center Director.

4. Human Rights Committee

Members of a CSP HRC conduct site visits to participating VAMCs, accompanied by a member of the CSP Center. The purpose of these visits is to evaluate the consent process and/or study processes at that study site from a human rights perspective. If possible, HRC members will observe at least one

informed consent being given and will talk with research participants about their efforts in the study. Upon returning from the site visit, the HRC will write a report of the visit and send it to the CSP Center Director. The report shall not identify the participant(s) by name. Typically, at least one HRC site visit is made in connection with each study at some time during its ongoing phase.

B. Responsibilities in a CSP Study

The successful planning, organization, conduct, and conclusion of a CSP study require the active cooperation of many individuals. Since participation in a CSP study is voluntary, all involved should have a clear understanding of their responsibilities and commitments. Agreement to participate implies a willingness to adhere to the research protocol and VA/CSP policies in all respects. The approval for participation by the R&D Committee implies that it is feasible to conduct the study at that site, and that the VAMC is prepared to provide the necessary and appropriate support. Involvement in a CSP study is demanding. A Study Chair and the SIs must be willing and able to devote time and energy to its success.

Study personnel should recognize, from the outset of a CSP study, that funding of an approved study will not be continued in the absence of objectively demonstrated satisfactory performance (e.g., number of participants enrolled, quality of data acquisition, and adherence to GCP). The Study Chair and Study Biostatistician or Epidemiologist must monitor various aspects of performance closely throughout the study and routinely provide this information to the appropriate persons or groups. Personnel at participating sites must be notified if their performance is less than satisfactory. The Executive Committee must know that remedial action may be necessary and take such action promptly. The DMC must be prepared to make difficult decisions and recommendations, especially if poor performance appears to be placing the success of the study in jeopardy. In addition, the Director, CSR&D may decide to terminate the study if it is determined that the study is not achieving its objectives.

C. Meeting/Travel Arrangements

Study-related meetings require significant planning and effort on the part of the Study Chair and/or the CSP Center. Funding for any CSP study-related travel will be provided from CSPCO centrally managed travel funds in accordance with the study budget. If attendance is cancelled from any reason, the traveler must inform the CSP Center organizing the meeting. Once at the meeting, all attendees understand that information is privileged and confidential and must handle it accordingly. Federal employees are further subject to the Trade Secrets Act regarding meeting materials and information.

D. Protocol Changes, Exceptions, and Deviations

Subsequent to CSSEC and IRB approval, no person or group including the Study Chair, Study Biostatistician or Epidemiologist, the Study Group, the Study Health Economist, if applicable, the Executive Committee, the DMC, and the Study CRP or AE Specialist may unilaterally or collectively allow exceptions and/or make changes to the study protocol without the appropriate approvals via the protocol amendment process. The Study Chair may provide protocol interpretations and clarification. An intentional deviation from the protocol is not permitted except to deal with immediate safety hazard for a participant. If such a deviation occurs, the SI must promptly report it to the Study Chair, CSP Centers, and the IRB of record so that an assessment of study-wide implication and possible need for a protocol amendment and any communications

can be made. Other unplanned or inadvertent deviations from the protocol may also require prompt reporting to the Study Chair, CSP Center(s), and IRB(s) of record.

The Study Chair, Study Biostatistician or Epidemiologist, and Study CRP or AE Specialist should discuss proposed study protocol changes before presenting such changes for approval. The Study Biostatistician or Epidemiologist and Study CRP or AE Specialist, must prepare an “Executive Summary of Proposed Study Protocol Change” form for their respective Centers that delineate the change, the need for the change, who the study’s executive discussants were, and the impact of the proposed change. Proposed changes must be reviewed and approved by the Executive Committee and the DMC. The Study Chair, Study Biostatistician or Epidemiologist, and Study CRP or AE Specialist should prepare an Impact Statement describing the impact of the protocol changes on participants, CSP Centers, and participating VAMCs. In all cases, the involved CSP Center Directors and the Director, CSR&D must approve proposed study protocol changes. The Director, CSR&D will make the decision whether the proposed study protocol changes require the approval of CSSEC.

After the Director, CSR&D and/or CSSEC (when required) approves the proposed change, the ACOS/R&D at each participating VAMC must be informed, since the protocol changes may require resubmission to the local R&D and Human Subjects Subcommittee, IRB(s). If the study is being conducted under an IND or IDE, protocol changes must be submitted to FDA prior to implementation.

E. Change in Funding Support

Changes in the study budget must be approved by CSPCO. Major changes may require further CSSEC review. Requests for additional funding at participating VAMCs must be initiated by the SI through the office of the ACOS/R&D at the VAMC, with the appropriate justification and delineation of needs including personnel (FTE, GS grade, and costs), equipment, and operating costs. This request should be forwarded to the Study Chair for approval and then to the assigned CSP Center Director. If the CSP Center Director recommends approval and the Director, CSR&D concurs, the office of the ACOS/R&D and the SI of the site will be informed for subsequent action.

As noted previously, funds and FTE provided for a CSP study are limited to the needs of the study and are not to be used to supplement other clinical or research activities. Inappropriate use of CSP funds may jeopardize all research funding at the VAMC. Unused funds will be withdrawn from the VAMC.

Study extensions that require a minimal increase in the approved study budget may be reviewed administratively by the Director, CSR&D for approval. Requests for extensions that do not meet these criteria will require review by CSSEC and final approval by the Director, CSR&D.

F. Ethical and Regulatory Considerations

1. Informed Consent

All individuals wishing to participate in a CSP study must provide informed consent form (signed and dated). Each interested participant must be permitted to read (or have read to him/her) the informed consent form in order to have an understanding of the study, risks and benefits, and use of data before discussing it with the investigator or his/her designee. The informed consent form must be discussed with

the potential participant by the SI or his/her designee. This discussion is done face-to-face unless other provisions are specified in the protocol. While the SI need not be present while the informed consent form is discussed and signed, s/he or another appropriate physician/clinician familiar with the study must be available sometime during the informed consent process to answer any medical questions that the potential participants might have. In discussing the study with the potential participant, the SI may provide additional details beyond those contained in the informed consent form, but no substantive addition, deletion, or modification to these statements are allowed. This document is the tangible evidence of what the SI tells a prospective research participant. A copy is given to the participant when s/he signs the forms. If anesthesia, surgery, or other procedures are to be used, informed consent must also be obtained on an SF-52.

Several elements must be included in the consent document according to VA and other regulations. They are included in the consent form checklist provided by the CSP Center. Although the local IRB or VA Central IRB may add additional requirements, the checklist elements must remain in the informed consent form. HIPAA authorization will be obtained per guidance in VHA 1200.05. For policy regarding who may consent to the participation of individuals with impaired decision-making capacity, refer to VHA Handbook 1200.05. For participants that are able to sign only with an "X", refer to VHA Handbook 1004.01. A dated progress note must be placed in the participant's electronic medical record indicating that the participant has given informed consent and has entered the study (See VHA Handbook 1200.05 for further details).

A copy of each participant's signed informed consent document and HIPAA Authorization must be sent to the CSP Center to verify that every participant has given consent. In addition, the signed informed consent documents must be copied, distributed, and filed as follows:

- The original is retained in the SI's Study File
- A copy is provided to the participant
- A copy (or scanned image) is placed into the participant's electronic medical record
- A copy is sent to the local VAMC's pharmacy if the study involves a pharmaceutical unless the signed consents can be viewed in the electronic medical record and the pharmacist provides written assurance that the signed consent was verified prior to dispensing
- A copy is provided to the assigned CSP Center

When non-VAMCs are participating in a CSP study and the site's IRB has a policy of not allowing informed consent forms to be sent off station, a letter signed by the SI verifying the date the participant signed the informed consent, and the consent form version used will be acceptable in place of the actual signed informed consent form, if approved by CSPCO. Approval needs to be obtained for each site individually.

Failure to obtain informed consent and/or HIPAA authorization will result in disciplinary sanctions by the Director, CSR&D, and could result in the dismissal of the SI. Data from participants without a properly signed and dated informed consent form and HIPAA authorization will be excluded from all study reports. CSP Centers can provide specific policy requirements and/or guidance as needed.

2. Participant Confidentiality

It is CSP policy to protect the confidentiality of participant study data to the fullest extent permitted by law. In order to protect participant confidentiality, participant identifiers, such as names or social security numbers, will not routinely be placed on study CRFs. A unique study generated participant identifier number will be assigned to each participant. This unique number will be placed on each study form to allow forms for a participant to be identified. In addition, an alphanumeric code may be entered on each form to provide a means of checking that the participant's study number on the form is correct. That is, a CRF will be accepted as being from a specific participant only if the unique participants study number and alpha code (if used) match.

Individual identifiable information (III) will be maintained at the participating VAMCs. However, in many studies, it may be necessary for the CSP Centers to have participant III such as addresses or social security numbers for scientific and/or safety reasons. Examples include the need to obtain data from VA central databases, long-term follow-up of participants by the CSP Center, or letters/surveys that are mailed to participants from the CSP Center. When such information is required by CSP, it must be provided on a separate form or recorded on VA Form 10-1086 (Informed Consent), which is submitted to the CSP Center. This information must be provided to the CSP Center according to the protocol's data security plan, the CSP Data Security Policy, and the local medical center's data security policy, if the VA medical center has additional requirements. At the CSP Center, participant III, contained either on paper and/or and electronically, will be maintained separately from the study's case report form data to avoid non-authorized personnel to link participant identifiers to study data. On occasion, Certificates of Confidentiality may be obtained for a CSP study.

When CSP representatives visit participating VAMCs for study-specific purposes, access to participants' electronic medical records must be provided for quality assurance purposes.

3. Annual Reviews

VA policy governs reviews of human subjects research which are done at least annually by the medical center's R&D Committee and the Human Subjects Subcommittee, and IRB. Reviews may be conducted more frequently at their discretion. It is the Site Investigator's responsibility to comply with requirements related to these reviews.

The assigned CSP Center will notify SIs in advance, with a copy to the ACOS/R&D, of an impending review to facilitate scheduling with the appropriate committee. The CSP Center will also provide the SIs with any material requested for this yearly review, except for unblinded outcome data. The ACOS/R&D must notify the SI in writing of the approval after continuing review by the IRB and any other appropriate committees. The CSP Center will also collect and maintain copies of the appropriate committee minutes of the yearly reviews. If it is not the policy of a committee to release the minutes of its meetings, a letter from the committee Chairperson (e.g., IRB Chairperson) on the letterhead of the Chairperson's institution, with his/her signature block stating that the yearly review has taken place, and giving the date and outcome of the review, will be acceptable. If the written notification (minutes or Chair letter) of the review

is not received at the CSP Center by the anniversary date, the participating center will be placed on administrative hold. This hold will mean that the VAMC's participation, particularly in randomizing study participants, cannot proceed until the appropriate documentation of the yearly review has been received at the CSP Center. Sites will need to care for participants already randomized to ensure participant safety until any holds are lifted.

G. Study Data

Data are to be reported only on VA (and if necessary, OMB) approved CRFs supplied, placed on-line, or provided in an electronic data capture system. However, investigators must understand what source documents are, and their responsibilities for maintaining them. The SI is responsible for assuring the accuracy and completeness of all data submitted. In general, data reported on the forms should be reviewed by the SI at each participating medical center before being submitted. Submission to the CSP Center implies verification by the SI. Data to be reviewed by individuals or groups other than those mentioned above (e.g., central readings of EEGs, EKGs, coronary arteriograms) are detailed in the study protocol. The protocol may also call for study data to be sent to the Study Chair for medical review. Some studies may utilize electronic forms and distributed data entry. Review processes for such data will vary depending on individual study requirements. In these cases, data are entered at the participating medical center and submitted to the CSP Center electronically using appropriate data security measures. Collection, maintenance, and transmission of data must adhere to VA requirements for the management and protection of data.

To protect study integrity, prevent bias in decision making due to knowledge of what has happened with participants already in the study, and ensure that study results are not prematurely released, the CSP Center with the advice and/or consent of the DMC and Director, CSR&D strictly control the release of study information and data outside of CSP. The CSP Center will typically provide Study Chairs, Executive Committees, and SIs with study progress reports that include aggregate information on background characteristics, adverse events, study performance measures such as accrual and withdrawal rates, and data quality. However, these data will not be provided broken down by treatment groups until after the study is over and the database has been locked. Exceptions to this policy can be made as circumstances warrant, with the approval of the DMC. Information on outcome measures will not be provided except when the DMC recommends that the Study Chair be unblinded. The DMC can request the Study Chair be provided with study outcomes so they can have a more meaningful discussion with the Chairperson when they are about to make a major decision (such as terminating the study or a treatment arm). Approval by the Director, CSR&D will be sought in these situations.

Clinical trial data sets will not be released to requesting individuals until the database is locked. This policy is to ensure that all reports of study results are consistent, and investigators will all be using the same database. Exceptions to this policy require a DMC recommendation and final approval by the Director, CSR&D, or the request needs to be included in the original CSSEC approved study protocol. Examples of exceptions include: the need to send data outside the CSP Center in order to have tests centrally scored, such as a neuropsychological test battery; release of data from an approved subprotocol that is completed prior to the end of the main study and where results cannot reasonably be expected to influence the main study; and, in studies with long follow-up periods, the use of background variables (after this section of the database has been locked) to prepare manuscripts that are not related to study outcomes. Provision of epidemiological

study data prior to study completion shall be addressed on a case-by-case basis and subject to Director, CSR&D approval. In addition to the above CSP guidance, release of VA data will follow VHA Handbook 1200.12 and use CSP Data Use Agreements for instances not already indicated in the protocol.

H. Reporting of Adverse Events, Serious Adverse Events, and Unanticipated Adverse Device Events

Procedures for collecting and reporting of all AEs and ADEs are determined by the study planning committee and outlined in the study protocol. Exact procedures for reporting AEs and ADEs are to be specified in the study Operations Manual. Studies using the CSP Electronic Data Capture (eDC) system for Adverse Event reporting must use the minimum set of approved, standardized form content and data elements developed by the Program. For studies with an IND or IDE, annual reports of AEs, SAEs, ADEs, and UADEs are provided to the FDA.

★ The SI must report all SAEs and UADEs to the appropriate groups and office(s) (e.g., CRPCC, CSP Center, Study Chair's Office, ACOS/R&D, and/or IRB of record) using the format of communication (e.g., FDA Form 3500A or study specific SAE or UADE form) specified in the study protocol or Operations Manual. The timeframe for reporting these events will be defined in the study protocol or Operations Manual, but will not exceed 72 hours after the SI becomes aware of the SAE or UADE. Exceptions to this policy will be those SAEs and UADEs identified in the protocol or other documents (Operations Manual, Investigator's Brochure) as not needing immediate reporting such as an established, expected SAE associated with the treatment. These exceptions will be reported in the same manner as other study adverse events. The SI also has the responsibility to follow IRB and R&D Committee requirements for reporting unanticipated problems involving risk to participants or others, and any other reportable events as may be specified by the IRB or R&D Committee. The SI is responsible for notifying all appropriate individuals at the local facility, and for documenting such communications in the Investigator Study File. If an SI is unsure of reporting requirements, s/he should contact the CSP Center and Study Chair immediately.

The assigned CSP Center is responsible for summary reporting of SAEs and UADEs to the DMC as part of the study progress reports. The CRPCC Director will work with the CSP Center Director to inform CSPCO of SAEs and UADEs reported to FDA, or other sensitive adverse events that the Director, CSR&D needs to be made to be aware of. The CRPCC Director or CSP Center Director, as appropriate, should also verify with the SI that the local administration (ACOS/R&D, Chief of Staff, Hospital Administration) has been notified. Events reported to the Director, CSR&D will usually be done after consultation with the Study Chair. Notification to the Director, CSR&D should occur within 72 hours of the CSP Center and CRPCC Directors being notified.

When required, the SI shall cooperate with individuals at their respective VAMC to determine responsibilities for reporting to the Office of Research Oversight (cf. VHA Handbook 1058.1) and/or their Research Compliance Officer (RCO).

I. Breaking Study Blind

Many CSP studies involving drugs are blinded so that a participant and/or the SI/Study Chair do not know which treatment a participant is receiving. Maintaining this blind is critical to the study's integrity. However, emergency drug code envelopes that have study treatment assignment information are prepared by the

CRPCC and shipped with the study drug or device to the participating medical center prior to the study starting. Each envelope is numbered with a unique participant randomization number, and contains the treatment assignment for that participant. These envelopes are placed in the custody of the participating medical center pharmacy service (for VAMCs) for the duration of the study. The blind (or treatment assignment) should only be broken if knowledge of the specific drug is essential to the immediate medical management of the participant. In such an emergency, the Pharmacy Service may open the envelope and reveal the treatment assignment for a given participant to the SI or treating clinician. However, before doing so, the SI and the Pharmacy Service must comply with protocol procedures. Such procedures often include contacting the Study Chair or Study CRP before breaking the code. The Study CRP is available 24/7 for unblinding purposes.

The VAMC's Pharmacy Service must notify the Study CRP at the CRPCC as soon as possible by telephone whenever a drug code envelope is opened. The emergency drug code envelope and its contents must be returned to the CRPCC within 72 hours of the code break. Upon receipt of the code envelope, the CRPCC will immediately inform the Study Biostatistician or Epidemiologist via telephone, and send a copy of the envelope, which is filed with the study documents at the assigned CSP Center. When the study has been completed (or terminated early) the unopened envelopes must be returned to the CRPCC. The CRPCC will verify and record which envelopes were or were not intact and notify the Study Biostatistician or Epidemiologist of their condition. Drug code envelopes should not be confused with the randomization code envelopes (if used).

J. Dual Enrollment

It is CSP policy that a participant be enrolled in only one drug or device intervention, randomized clinical study at any one time. It is permissible for participants to be in other non-interventional studies while participating in a CSP study (e.g., surveys, long-term follow-up cohort studies). Exemptions to this CSP policy will be allowed for individual participants on a case-by-case. Exemptions on the basis of an entire study are rare. Exemption requests will require the agreement in writing of all of the following individuals or groups: (1) the Site Investigators of both studies; (2) the Study Chair of the involved studies; and (3) the appropriate CSP Center Director(s). Exemptions sought on a per study basis are obtained using a similar process with the exception that letters from individual SIs would not be required. The Director, CSR&D makes the final decision. Only after the Director, CSR&D has given final approval, will the participant be allowed to participate in both studies. Approvals for exemption are primarily based on what is best for the participant and to protect the integrity of the involved studies. SIs/Study Chairs should be vigilant of these requirements as non-compliance may result in a protocol deviation.

Screening forms in every CSP study should solicit information about other studies in which a participant might be participating. These issues should also be addressed at the Organizational Meeting of every CSP study. Study Operations Manuals may describe various types of studies or known studies where exemptions to the participant participating in only one interventional clinical study could be granted.

K. Subprotocols / Substudies

Subprotocols (or substudies) to CSP studies are generally discouraged since they add burden and costs to study personnel, study participants, and CSP. Subprotocols should be proposed at the time of planning and

included in the original proposal and added to the budget to be reviewed by CSSEC. In exceptional circumstances, subprotocols requiring the collection of additional data, tests, procedures, or biologic samples that are proposed after CSSEC review will only be entertained by CSP when the entire study is on target with respect to expected accrual and budget. Investigators not obtaining CSP approval prior to the submission of a substudy for outside funding [e.g., National Institute of Health (NIH) and industry] will not be supported by CSP, and will be subject to VA informing the funding agency for appropriate action.

If a Study Chair or SI insists on proposing a subprotocol, the following steps should be followed:

1) Complete a formal protocol that includes background and justification, objectives, participant selection, informed consent documents, methods, data to be collected, sample size determination, and budget.

2) Review and approval by a majority vote of the study's Executive Committee and Data Monitoring Committee. This decision must include discussion on the research participant requirements and impact on the main CSP study. All oversight committee approvals are conveyed to the Director, CSR&D as recommendations for action. Recommendations are subject to further inquiry and/or action by request of the Director, CSR&D.

3) If funding is required, non-CSP sources such as the National Institutes of Health (NIH), the Agency for Healthcare Research and Quality (AHRQ), VA's Merit Review Program, private foundations, or pharmaceutical companies should first be contacted. The Biomedical Laboratory Research & Development Service and the Clinical Science Research & Development Service may review subprotocols of investigators in CSP studies who want to perform Merit Review studies related to the CSP study. Such reviews will require a letter of support from the Director, CSR&D. Any application for non-CSP funding shall recognize all obligations of the applicant and subprotocol to CSP.

4) If non-CSP funding sources are not available, the subprotocol may be submitted to CSP to request funding. Submissions to CSP shall be sent out for scientific review. Timing for such review is subject to CSPCO discretion.

5) If the main protocol is conducted under an IND or IDE, any subprotocol must be submitted to FDA prior to implementation.

6) If CSP funding is approved by the Director, CSR&D, the subprotocol must be reviewed and approved by the R&D and appropriate IRBs.

All policies that govern CSP projects also apply to subprotocols, including those related to manuscript review and approval.

L. Communications

At the discretion of the Study Group, if study newsletters are prepared and issued regularly, it is done by the National Study Coordinator or designee. The newsletter is a primary means of keeping site personnel informed between meetings. The newsletter should contain items of general interest to the site personnel,

progress and performance reports, treatment-related issues, and discussion of any problems that arise. The newsletter should never include unblinded data or study results. The CSP Center and/or Study Chair may distribute the newsletter via email and/or post it on the study website (e.g., SharePoint).

M. Site Visits

Site visits by the Study Chair, the Study Biostatistician or Epidemiologist, the Study CRP or AE Specialist, or other technical experts are not a routine part of CSP studies. However, they may be required in certain cases. When site visits are considered essential, they should be included as a special line item in the study budget. If an unforeseen problem arises that can be resolved only by visiting the site, a site visit may be funded if endorsed by the CSP Center Director, approved by CSPCO, and travel funds are available.

A site visit report should be sent shortly afterwards to the Study Chair and CSP Center Director for appropriate action. If applicable, a summary of the specific actions recommended by the Executive Committee to correct deficiencies that have been discovered can be added as an attachment.

On occasion, the FDA, as a part of their Biomedical Compliance Monitoring Program for Sponsor, Monitors, and Clinical Investigators, will visit a CSP Center, CRPCC, or participating VAMC. When the FDA announces its impending visit, SMART is responsible for working closely with the Study Chair, the Study CRP or AE Specialist, and the individuals being visited to prepare them for the FDA visit. Occasionally, collaborating pharmaceutical companies, whether sponsoring the IND or IDE or not, may wish to conduct site visits to assure compliance with FDA regulations. Such visits must be approved and coordinated by the CSP Center(s) and respective VAMC Directors.

N. Good Clinical Practice (GCP) Monitoring Visits/Audits

CSP studies are conducted in accordance with Good Clinical Practice (GCP). GCP helps to safeguard research participants' welfare and assure the validity of data resulting from the clinical research. CSP will assist SIs in complying with GCP requirements through its Site Monitoring, Auditing and Resource Team (SMART). SMART serves as the oversight quality assurance arm of CSP for GCP compliance. SMART conducts two types of site visits for CSP studies, monitoring visits and audits. The monitoring visits are conducted by the SMART Monitoring Group as an arm of study management to ensure compliance with GCP requirements at participating VAMCs. The scope and frequency of these visits are dependent on study characteristics. CSP trials intended to produce data for submission to FDA receive frequent and intense monitoring visits funded by the organization that anticipates submitting the data (e.g., NIH or an industry partner). Other studies receive fewer visits but, at a minimum, every site in a CSP study receives a monitoring visit at study start-up. The second type of visit is an audit. Routine audits are also conducted at one or more sites per year independent of monitoring and study management. In addition to the monitoring and auditing visits planned for the trial, study leadership may request a for-cause audit when problems at a VAMC are known or suspected. The request may be made through the CRPCC Director by the CSP Center Director. CSPCO may also request a for-cause audit at any time.

O. Replacing a Site Investigator or Study Chair

CSP studies frequently take several years to complete. During that time, a SI or a Study Chair may find s/he cannot continue with the study. In such cases, suitable replacements should be found as quickly as possible in order to maintain the continuity of the study.

If an SI cannot conduct the study through its completion, s/he should give as much advance notice as possible to the Study Chair and, if possible, suggest an appropriate replacement. The Study Chair should then inform the assigned CSP Center Director of the proposed change. If the study involves drugs or devices, the CSP Center Director will inform the CRPCC. The local ACOS/R&D should obtain endorsement of the center's R&D Committee for this change and inform the CSP Center Director, forwarding the R&D Committee minutes when they are available. IRB approval is also needed. In cases of "emergency," with little or no advance notice, and where the designated alternate SI (i.e. sub-investigator) is unavailable or unwilling to assume the responsibility, temporary assignment of an investigator by the VAMC is permissible until the formal replacement process is completed. If no suitable or available replacement for the departing SI exists, the VAMC's participation in the study will be terminated. The CSP Center will notify the CRPCC of all SI changes.

If the Study Chair cannot continue to lead the study, s/he should inform the CSP Center Director as early as possible so that nominations can be made to the Director, CSR&D. The nominee does not necessarily have to be from the same VA medical center as the original Chair. If the individual accepts the nomination, his/her VA medical center will be contacted to obtain the approval and support of the VA medical center and its R&D Committee. The local ACOS/R&D should initiate a letter endorsing the nominee as described previously. In cases of an "emergency," where there is little or no advance notice, the Director, CSR&D may temporarily appoint someone as Study Chair until the formal process is accomplished. However, if no suitable or available replacement Chair exists, the Director, CSR&D shall determine the action to be taken, including study termination.

If an IND has been filed for the study, new SIs and/or new participating VAMCs will be required to sign FDA Form 1572 (Statement of Investigator) for submission to the FDA. If an IDE has been filed for the study, new SIs and/or new participating VAMCs will be required to sign an Investigator's Signed Agreement. In the case of either an IND or IDE, addition of new participants may not be instituted until approved by the Sponsor.

P. Putting a Site on Probation

If a participating site is not performing at the expected level, discussions should occur between the Study Chair and the SI. If this action fails to correct the problem, the Executive Committee, with an endorsement from the DMC when possible, may propose to place the site on probation. The proposal should be sent to the CSP Center Director for a decision. If the CSP Center Director concurs, the Study Chair should issue a probationary letter which states the reason(s) why the VAMC/site was placed on probation, and clearly specifies the criteria the SI must meet to be taken off probation in a specific time period. This letter should be sent to the SI through the CSP Center, which will forward the letter with a copy to the local ACOS/R&D and to the CRPCC.

After the probationary period has elapsed, the Study Chair should issue a follow-up letter to the SI evaluating the performance during the period. The letter should clearly state that the VAMC is either taken off probation for good performance, will remain on probation because the terms of probation have only been partially met, or the SI has failed to meet the probationary requirements. In case of failure, steps may be taken to decrease support or drop the VAMC from the study. In either case, a letter should be written to the CSP Center Director and CRPCC Director stating the rationale and the proposed action. The CSP Center Director will then notify the Director, CSR&D of the action taken.

In the event that the SI clearly acknowledges the lack of performance and even desires to be dropped from the study, the SI cannot act as an independent agent in the local decision. Instead, the SI shall contact the local ACOS/R&D, or write to the Study Chair with a copy to the local ACOS/R&D acknowledging the lack of performance and the desire to be dropped. The SI will still be responsible for any research participants enrolled in the study until appropriate transition from the study is completed.

Q. Early Termination of a Site

During the course of a study, it is sometimes necessary to drop one or more sites from the study. Such action should be approved by the CSP Center Director, who will then notify CSPCO. Early termination is usually based on recommendations from the Executive Committee and the DMC and, most often, reflects inadequate enrollment, a judgment that performance targets cannot be achieved for various reasons and/or serious noncompliance with GCP and/or other policies. This action will always be taken in response to what is considered the best interests of the study. A decision may not necessarily reflect on an individual or VAMC and incorporates several factors.

For instances of serious or continuing GCP and/or regulatory non-compliance, CSP will make every effort to promptly bring the SI into compliance, and if unable, will terminate the SI's involvement. Termination for non-compliance will be reported to the local R&D Committee, local RCO, CSPCO, and FDA (if applicable).

VAMCs that lose their FWA during the course of a study may not continue in human subjects' research. For research participants at these sites, the CSP Center must immediately either submit a request to CSPCO to continue the participants in the study at a participating VAMC that has a valid FWA, IRB approval, and a SI who has agreed to assume all study related activities for these participants, or develop a plan to safely transition the participants out of the study. The transition plan may be to have no further contact with the research participants after informing them that their participation is stopped, or amending the protocol to allow the participants to transition out of the study while giving permission only for medical record review at the end of the study.

If study equipment purchased by CSP is needed at another VAMC, the CSP Center Director will notify the ACOS/R&D at the terminated VAMC that the CSP equipment is to be transferred. If funds are not available for shipment, a request should be made to the CSP Center Director for such purpose. In the event that a new VAMC is not yet identified, the Study Chair, and Study Biostatistician or Epidemiologist may wish to have the equipment transferred to a location to be determined. In the event that the equipment is not needed by CSP, it can be made available for other use following CSPCO approval.

Some VAMCs are supported on rare occasions by a capitation plan instead of a set site budget. The Executive Committee may set the criteria for terminating a capitated VAMC. Actions related to terminating such sites who fail to meet these standards are typically carried out and/or directed by the CSP Center.

R. CSP Study Files

Sponsor files for CSP studies are maintained by and at the assigned CSP Center, the CRPCC, and the SMART office (not necessarily all at any one site), and include copies of consent forms, CRFs, protocols, committee reports, drug accountability data, regulatory documents, and other documentation related to the review and conduct of the studies. The Study Chair, SI, and laboratories should also maintain copies of all data forms and study related correspondence, in accordance with VA Record Retention Policy. This applies in the case of hard copy or electronic study files.

S. Periodic Reports

1. Local

Every VAMC that conducts research is required to provide certain information on its activities on an annual basis (VHA Handbook 1200.5). For such reports, the local R&D office at each VAMC will be responsible for providing instructions to their investigator and compiling the information. Each Study Chair and SI is responsible to their respective VAMC for providing any requested information in accordance to local processes.

2. CSP

CSP also produces various reports over the course of a study. The Study CRP or AE Specialist will coordinate activities related to required Annual Progress Report submissions to the FDA when CSP is the sponsor. CSP Centers will work with different groups to prepare DMC and varied other progress reports. Reports shall be submitted to CSPCO or other offices and/or individuals as directed by CSPCO. Requests for information and/or reports that are not already required by VA or federal policy and/or are not considered part of standard practice for the conduct of clinical research must go through the Director, CSR&D.

VI. CONCLUDING A CSP STUDY

Once study participants have completed protocols and all data are collected, there are still several critical steps that must be taken to ensure proper close out of a CSP study. Particular care must be given to properly addressing matters related to research participants, study data, reports and publications, and any subsequent study-related responsibilities.

A. Closing Down

In some instances, research participants will still require treatment after completing their participation in a CSP study. The individual's treating physician/SI should plan the transition from any study treatments to whatever should appropriately follow afterwards. Final results of the study will ordinarily not be immediately available for the physician's guidance. If a participant has done well on a drug that is still investigational based on the physician's clinical judgment and the physician would like to continue its use before final results are available, the source of the medication (e.g., pharmaceutical manufacturer) must be contacted by the treating physician for any compassionate care use. When the final results do become available upon publication of the primary results manuscript, letters reporting these study results are typically sent to all research participants through the SI with IRB approval.

Specific plans for handling the closeout phase, unblinding, and notifying SI and participants of study results are typically included in the study protocol. To aid the SI in notifying the IRB of study closure, the CSP Center provides a letter outlining a planned schedule of closure events relevant to IRBs when terminating their review of research projects including:

- Date of last participant visit
- Mechanism used to assure care of participant officially returned to Primary Care Physician (PCP) and documenting this with a note in CPRS
- Anticipated date of database closure at the CSP Center
- Anticipated end date of primary analysis activities.

When follow-up on all participants enrolled in the study has ended, the CSP Center has the responsibility for final data summaries and analyses of the study, which are completed within a reasonable time after receipt of the last study data at the CSP Center. The Executive Committee is responsible for approving the publication and presentation of all data and results of the study. Specific CSP policies and policies related to CSP publications are further specified elsewhere and available upon request from CSPCO. Material(s) for publication should ordinarily be submitted within one year of receipt of all data at the CSP Center. The Executive Committee may be funded for one meeting during this year to prepare the manuscript(s) for final publication. The CSP Center is responsible for reporting all status of all of these activities to CSPCO.

At the close of the study, the assigned CSP Center should have possession of all study data. The CSP Center will maintain readily accessible files on the study after its completion and data will be evaluated for archiving based on the VA system of records. If it is not appropriate to archive at that time, the data files will be reevaluated annually. Participating medical centers must retain study files and records after the study is completed in accordance with National Archives and Records Administration requirements as indicated in the VHA Records Control Schedule (at the time of this printing, such records must be held indefinitely until further

notice). The CSP Center is responsible for managing all study related files, including electronic files that it maintains.

The CRPCC, in cooperation with the Study Chair, the Study Biostatistician or Epidemiologist, and the participating VAMCs, will direct the return of all surplus drugs or investigational devices that were centrally distributed. The CRPCC will provide a final accounting of drugs or devices utilized by participants. The surplus drugs or devices will be disposed of in a manner determined by the CRPCC.

The Sponsor of an IND or IDE is required to submit a Final Report to the FDA shortly after completion of the study. The Study CRP or AE Specialist will coordinate this activity on behalf of CSP if it is the Sponsor. Each investigator is required to notify their respective R&D Committee and Human Studies Subcommittee or IRB that the study has ended at their site.

At the completion of the study, the CSP Center (e.g., Associate Center Director for Operations or Project Manager) will contact the other CSP Centers to determine if equipment purchased specifically for the study can be usefully deployed to other studies. If so, the CSP Center will arrange for its transfer through the appropriate mechanism. Otherwise, such equipment will be disposed of accordingly. This action does not apply to medical devices. CSP Centers will work with VAMCs to use the Research Equipment Quick Use Initiative Program (REQUIP) if applicable in the collection, re-assignment, and extended use of any CSP purchased equipment.

B. Final Study Meeting

The Study Group and the DMC, if possible, will have a combined final meeting as soon as the major analyses and results of the study are available for distribution and discussion. This meeting usually occurs after the manuscript writing meeting of the Executive Committee or its designated writing subcommittee(s). At this meeting, the Study Chair and the Executive Committee present the major study results and their interpretation to the SIs. The Study Group's discussion of the results may provide the manuscript writers with other useful interpretations, and provide a forum for discussion among the SIs.

C. Publications

As stated earlier in these *Guidelines* (Section II.D.), the importance of publications cannot be overstated given the commitment of time and resources by several individuals and groups. CSP considers scientific publications and proper dissemination of study findings to be of utmost importance.

CSP study publications are to be made in a timely fashion. While processes, requirements and policies for these publications are described in the CSP Publications policy, the Study Chair, the Study Biostatistician or Epidemiologist and the CSP Center Director play key roles in ensuring timeliness and quality. If progress on the major results manuscript is not sufficient, the CSP Center Director and Director, CSR&D may designate other individuals to write the manuscript. The CSP authorship policy is provided in Appendix B. Generally, authorship on papers shall be in accordance to accepted criteria by the general scientific community. CSP Center Directors are delegated responsibility for ensuring a manuscript meets CSP publication requirements

prior to submission. The CSP Center will notify CSPCO and ORD Communications when a manuscript is accepted for publication.

The presentation or publication of any or all data collected by SIs is under the direct control of the study's Executive Committee with all actions subject to Director CSR&D approval. This control applies to whether the publication or presentation provides the results of the principal undertaking or the results of an ancillary analysis.

When a major manuscript has been submitted, a copy of the manuscript should be sent to CSPCO. Upon acceptance for publication, the Study Chair and the Study Biostatistician or Epidemiologist are asked to provide lay summaries and relevant information to assist in public affairs and other communication activities. CSPCO will work with the appropriate offices to coordinate such efforts for major publications.

D. Administrative Repercussions

The CSP policies for data analysis and dissemination of results apply to all members of the Study Group (Study Chair, SIs, Study Biostatistician or Epidemiologist, etc.). If a Study Chair or SI has been discovered to be misusing study data, has submitted unauthorized manuscripts for publication, or released results prior to the lifting of any embargoes or agreed upon times, the following administrative actions may be taken (at the discretion of the Director, CSR&D):

- removal as investigator;
- forfeiture of research funding; and/or
- prohibition from receiving VA research funding for a period to be determined by the Director, CSR&D (and possibly other ORD Service Directors) and commensurate with the seriousness of the infraction.

Individuals may also be subject to civil or criminal penalties or fines based on the Trade Secrets Act. Requests for research misconduct investigations may also be initiated by the Director, CSR&D.

E. Custodianship of Data

The policy regarding custodianship of data should be communicated to investigators in the planning and organizational stages by the Study Chair and CSP Center. CSP is the custodian of all data collected from a study it supported. All SIs must release their data to the participating CSP Center at the appropriate time. While most data should be submitted to the CSP Center shortly after it is collected, there may be special circumstances when an SI or a central laboratory investigator may keep the data for longer periods of time. In these circumstances, the CSP Center Director will determine when the appropriate time is to submit the data to the CSP Center.

All analyses related to the objectives of the study and publication plan as specified in the study protocol will be performed by CSP. Economic analyses, if applicable, will be carried out by the health economics staff. All raw study data will reside at the CSP Center and will not be released until objectives, as stated in the protocol and manuscripts in the protocol publication plan, have been completed. The CSP Center will act as the repository of all data from its studies. The Director, CSR&D is the individual responsible for the use, management and retention of all CSP study data.

F. Release of Study Data Sets

While CSP is the custodian of study data, the program does not seek to limit the use of the data, but rather to ensure that these data sets are being used in scientifically and ethically sound ways while protecting the rights and welfare of research participants. After or near the completion of planned study manuscripts, SIs are encouraged to submit proposals to the Executive Committee for using data that will meet appropriate scientific and ethical standards. SIs should be aware, however, that the CSP Center's main responsibility is to prepare the needed analyses for the primary results manuscript(s) and secondary manuscripts as spelled out in the protocol or planned by the Executive Committee. Secondary analyses by the CSP Center may be delayed until the primary analyses and manuscripts are completed. As such CSP resource uses follow these priorities. Alternatively, the CSP Center may provide the SIs with appropriate data sets if they have the resources to use these data sets. Submission to journals of secondary manuscripts should usually wait until the primary manuscript has been accepted, but the Executive Committee can request exemptions to the Director, CSR&D.

The Study Executive Committee may consider further uses of the data, provided that these uses do not conflict with the study protocol, informed consent, CSP policies, VA policy, or other regulations. Potential uses include analyses of the data, publication of the results of analyses, or distribution of copies of all or part of the study dataset. Raw data may be provided to other investigators after all planned objectives and manuscripts are completed. Both VA and non-VA investigators who are not part of the Study Group, must request data through the Executive Committee (if still functioning), the CSP Center Director, and the Director, CSR&D. If the Executive Committee no longer exists, the CSP Center Director has purview for any CSP study data requests. If, in the judgment of the CSP Center Director, the Study Chair and/or Executive Committee cease to exercise their responsibilities in an appropriate manner, CSP will take over the management of access to the study data. Any requests for CSP data by VA or other investigators will be reviewed by the CSP Center and require final approval by the Director, CSR&D.

All recipients of CSP data beyond what is stated in the original protocol must sign a Data Use Agreement with specific terms related to, but not limited to, the authority for releasing data, data use, data management and security, adherence to informed consent, privacy and HIPAA requirements, any reporting requirements, human subjects protection, and responsibilities to CSP. The CSP Center will provide the investigator requesting the data with a de-identified database to prevent identification of research participants. HIPAA guidelines for de-identified data sets will be used, when possible. Investigators are typically provided with only limited data sets sufficient to complete the proposed research.

At the time of this printing, discussions related policies for public access to federally funded research data were in progress. CSP policies may be modified to meet any final decisions related to such access.

G. Continuing Analytic Activities

In general, the ORD Merit Review mechanism (e.g., through CSR&D or HSR&D) should be used to request funding for continuing analytic activities after the completion of the primary manuscript, or for ones not included in the original CSSEC submission and budget. Supplemental funds from CSP may be requested for

analytic activities at the discretion of the Director, CSR&D. Typically, such requests undergo scientific peer review, including CSSEC review, before a final decision is made.

VII. CONCLUSION

The planning, review, initiation, and completion of a CSP study are complex processes requiring close communication and cooperation among all participants. CSP values efficiency, effectiveness, safety, and innovation in its activities and takes its commitment to the scientific, Veteran and general populations seriously. Principles towards these ends shall be promoted and efforts to continually improve pursued.

Suggestions for ways to enhance scientific, operational, and ethical aspects of conducting CSP studies that should be included in subsequent editions of this document are welcome. CSP may be contacted at CSP@va.gov.

APPENDIX A - GLOSSARY OF ABBREVIATIONS AND ACRONYMS

ACOS	Associate Chief of Staff
ADE	Adverse Device Effect
AE	Adverse Event
AHRQ	Agency for Health Care Research and Quality
BLR&D	Biomedical Laboratory Research & Development Service
BPLS	Biopharmaceutics Pharmacokinetics Laboratory Section (research laboratory)
CERC	Clinical Epidemiology Research Center
CPRS	Computerized Patient Record System
CRADA	Cooperative Research and Development Agreement
CRADO	Chief Research & Development Officer
CRF	Case Report Form
CRP	Clinical Research Pharmacist
CSP	Cooperative Studies Program
CSPCC	Cooperative Studies Program Coordinating Center
CSPCO	Cooperative Studies Program Central Office
CRPCC	CSP Clinical Research Pharmacy Coordinating Center
CSR&D	Clinical Science Research & Development Service
CSSEC	Cooperative Studies Scientific Evaluation Committee
CTMS	Clinical Trials Management System
CV	Curriculum Vitae
DIR	Drug Information Report
DMC	Data Monitoring Committee
DMP	Data Management Plan
DTHP	Drug/Device Treatment and Handling Procedures
eDC	Electronic Data Capture
ERIC	Epidemiological Research and Information Center
FDA	Food & Drug Administration
FTE	Full Time Equivalent
FTEE	Full Time Equivalent Employee
FTS	Federal Telecommunications System
FWA	Federal Wide Assurance
GAO	Government Accountability Office
GCP	Good Clinical Practice
GS	General Schedule
HERC	Health Economics Resource Center
HIPAA	Health Insurance Portability and Accountability Act
HRC	Human Rights Committee
HSR&D	Health Services Research & Development Service
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IPA	Intergovernmental Personnel Act
IRB	Institutional Review Board

LOA	Letter of Agreement
LOI	Letter of Intent
LSI	Local Site Investigator
NIH	National Institutes of Health
NODES	Network of Dedicated Enrollment Sites
OGC	Office of General Counsel
OHRP	Office for Human Research Protections
OMB	Office of Management and Budget
ORD	Office of Research & Development
ORO	Office of Research Oversight
PAL	Pharmacogenomics Analysis Laboratory
PCP	Primary Care Physician
PHI	Protected Health Information
PM	Project Manager
POC-R	Point of Care Research
PPM	Pharmaceutical Project Manager
R&D	Research and Development
RR&D	Rehabilitation Research and Development Service
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
ShEEP	Shared Equipment Evaluation Program
SI	Site Investigator
SMART	Site Monitoring, Auditing and Resource Team
UADE	Unanticipated Adverse Device Effect
VA	Department of Veterans Affairs
VA CIRB	VA Central Institutional Review Board
VACO	VA Central Office
VAMC	Veterans Affairs Medical Center
VHA	Veterans Health Administration

APPENDIX B - CLINICAL SCIENCE RESEARCH & DEVELOPMENT / COOPERATIVE STUDIES PROGRAM AUTHORSHIP POLICY

Sections:

- I. Purpose
- II. Abbreviations, Acronyms And Definitions
- III. Scope
- IV. Authorship Criteria
- V. Roles And Responsibilities
- VI. Ethical Considerations
- VII. Copyright
- VIII. References

I. Purpose

This section outlines the purpose of this policy.

- A. This policy provides standards and procedures to Cooperative Studies Program (CSP) staff members and investigators for their inclusion as authors on CSP publications. Outlined are authorship criteria, procedures for designating groups as authors, determining author order, and assigning appropriate credit in acknowledgments. The policy also outlines roles and responsibilities, summarizes ethical considerations of authorship and the copyright rule for federal employees.
- B. Several work products are generated from CSP studies. This policy is not intended to address all possible considerations in determining authorship, but should be given strong consideration in relevant discussions. While the main emphasis of this policy is on CSP publications, principles may be applied to other contexts not specifically addressed here based on community standards and/or reasonable judgment.

II. Abbreviations, Acronyms and Definitions

- A. The following abbreviations, terms and acronyms apply to this policy. Further details may be obtained from the CSP Universal Glossary.
 - 1. CSP – Cooperative Studies Program
 - 2. CSP Centers – CSP research groups identified in VHA Directive 1205 that report to CSP Central Office including: CSP Coordinating Centers, CSP Clinical Research Pharmacy Coordinating Center, Epidemiologic Research & Information Center, Clinical Epidemiology Research Center, and the Pharmacogenomics Analysis Laboratory
 - 3. CSP Staff Member – VA employee with primary job duties at a CSP Center or CSP Central Office
 - 4. CSR&D – Clinical Science Research and Development Service
 - 5. EPGP – Epidemiology & Population Genomics Program
 - 6. Executive Committee – CSP study group as defined in the CSP Guidelines involved with making major CSP study decisions related to the protocol, operations, and/or policies and responsible to the Director, CSR&D
 - 7. ICMJE – International Committee of Medical Journal Editors
 - 8. IRB – Institutional Review Board
 - 9. ORD – VA Office of Research & Development
 - 10. Study Chair (or Co-Chair) – individual as described in the CSP Guidelines who is the scientific/clinical lead of a CSP study responsible to the Director, CSR&D
 - 11. VACO – VA Central Office
- B. For the purpose of this policy, the following definitions apply.
 - 1. Author – An individual who makes substantial contributions to the conception, design, and/ or

acquisition of data or analysis and interpretation of data for a publication; has responsibility for drafting the publication or revising it critically for important intellectual content; also, an approver of the final version to be published.

2. Co-author – An author who is not the first author and who contributes to the development of an information product and who substantively participates in decisions and/or contributes to processes resulting in the publication; typically, this individual is involved early in the process.
3. First Author – An author who receives primary credit for the publication and has overall responsibility for the integrity of the product; this individual often serves as the primary contact for all matters related to the publication.
4. Plagiarism –The appropriation of another person’s ideas, processes, results, or words without giving appropriate credit (cf. VHA Handbook 1058.2).
5. Publication – A scientific/scholarly work product resulting from CSP supported activities that are intended to disseminate information on findings, study activities, and/or thoughts and opinions to scientific communities and the public; it may refer to journal articles, editorials, commentaries, and letters published in scientific journals, book chapters and books, scientific conference abstracts, presentations, and technical reports.
6. Study Group – All persons with key responsibilities in the conduct and completion of a CSP study, including the Study Chair, CSP Staff Members, Executive Committee members, investigators and study coordinators at participating sites, and VACO/CSR&D personnel that contribute in an ongoing and substantial way to the development, execution and completion of the study. Since activities can span a lengthy period of time, individuals who are involved may change. Therefore, Study Group members are not necessarily only presently involved individuals.
7. Writing Group – Authors who are Study Group members specifically responsible for writing a publication

III. Scope

- A. This policy covers instances when authorship is being considered for CSP Staff Members, CSP Study Group members, and/or VACO/CSR&D personnel for any CSP publication for which VA has primary responsibility. It covers publications that intend to (1) list VA/CSP employees individually or by group name as authors and that (2) are prepared as a part of CSP Staff Members’ and investigators’ federal employment (including WOC and IPA employees). These publications include those written solely by VA employees or by VA employees in collaboration with partners, those published or disseminated by VA, and those written by VA employees but published or disseminated by other organizations. Since the main context considered is for CSP supported activities, particular consideration is given to CSP study processes and roles when applicable.

IV. Authorship Criteria

- A. CSP generally encourages providing opportunities for authorship among a wide range of Study Group, CSP Staff Members, and external collaborators. Executive Committees on behalf of Study Groups should establish mechanisms for recognizing and rewarding not only authorship but the other numerous essential contributions to medical science/public health science and to the process of developing and disseminating publications. The Study Chair and Executive Committees are also recognized to be in the best position to know relative contributions of individuals (including Study Group, CSP Center Staff Members, and VACO personnel) whether for authorship purposes or otherwise. While not required, Writing Groups should also consider inviting individuals to be co-authors who may have particular expertise and/or insight to contribute to the public value of the publication. However, CSP also acknowledges that authorship is an earned honor and not automatically conveyed simply by a role or position.
- B. CSP subscribes to the criteria for determining who qualifies for authorship based on the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals,” developed by ICMJE and last updated October 2004 (<http://www.icmje.org/>) (Reference A). As the ICMJE updates the “Uniform Requirements,” these criteria will be evaluated and updated as appropriate for CSP’s needs.

1. Determining Who Qualifies for Authorship

- a. Authorship credit should be based on three conditions, *all of which* must be met:
 - i. Substantial contributions to conception and design, acquisition of data, and/or analysis and interpretation of data;
 - ii. Drafting the information product or revising it critically for important intellectual content; and
 - iii. Approval of the final version to be disseminated (e.g., published or presented).
 - b. Acquisition of funding, general supervision of researchers/authors, or review and approval of product publication, by themselves, do not justify authorship.
 - c. All persons designated as authors should qualify for authorship and all those who qualify based on the above criteria should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.
 - d. At least one author, usually the first, should take responsibility for the integrity of the work as a whole, from inception to publication/distribution, subject to applicable CSP policies.
 - e. The CSP Center Director responsible for coordination of the study also has responsibility for the integrity of the work given his/her role as supervisor of CSP Center staff involved in the publication and duties per VHA Directive 1205.
 - f. CSP Executive Committees shall discuss these authorship criteria and document in the study protocol any other considerations prior to the start of the study and determine First Authorship on publications. Additional responsibilities are stated in the CSP Guidelines. Modifications may be made over the course of the study as conditions warrant. They should be aware that some journals may limit the number of authors on a manuscript and take this factor into consideration in their decision making.
2. Determining Author Order
- a. The order of authorship on the byline should be a joint decision of the coauthors. Author order should be discussed early and revised as needed. Authors should be prepared to explain the rationale for the order in which authors are listed.
3. Designating Groups as Authors
- a. Authorship is increasingly attributed to a group. All members of the group who are named as authors should fully meet the criteria for authorship. Group members who do not meet these criteria should be listed, with their permission, elsewhere, such as in the acknowledgement section (see below). When the author list appears on the publication list with a term such as “for the study group,” or with the members of the study group listed as a “single author” together with members of the writing committee, and where the study group membership is shown as a footnote or appendix, it is not necessary for every member of the group to approve the manuscript.
 - b. In general, the primary paper resulting from a CSP study should include the names of all significant group members from study sites, coordinating centers and, where applicable, from Central Office. In general, these will be included under the “Study Group” designation, and included as a footnote or appendix.
 - c. For publications that will appear in journals or other publications, consult the publication for samples of how group authorship is attributed.
 - d. The CSP Guidelines address group authorship formats. Options for designating a group as author include the following:
 - i. Identifying some individuals in the byline as authors who have written “on behalf of” or “for” the named group. The other members of the team may be listed elsewhere. [Sample byline: X, Y, and Z on behalf of the CSP Study # Investigators]
 - ii. Identifying the writing group in the byline, with authors in the writing group listed in a footnote. The other members of the team may also be listed elsewhere. [Sample byline: Writing Group* for the CSP Study # Investigators]
 - iii. Identifying the author group name only in the byline. Elsewhere in the publication, authors should be clearly identified. Other team members who do not qualify for authorship should be listed separately (Reference B).[Sample byline: The CSP Study # Investigators]

4. Assigning Appropriate Credit in the Acknowledgments Section
 - a. CSP recognizes that publications often result from years of effort and contributions by many individuals and that individuals change their level of involvement over time. An acknowledgment section would be an appropriate method for providing credit to individuals who previously had a key role for making a publication possible but do not meet authorship criteria.
 - b. In making acknowledgements, a more specific heading may be used, such as “members of the response team” or “participating investigators,” and the functions or contributions described—for example, “collected data” or “provided and cared for study participants.” All persons acknowledged must give written permission to the lead author, because a reader may infer their endorsement of the data and conclusions. Financial and material support should be acknowledged.

5. Considerations for Authorship in Key CSP Publications
 - a. CSP studies typically produce several types of publications. The following provides examples of common CSP publications and the individuals and/or groups who typically play a key role in the publication that may meet authorship the specific criteria above. These examples are strictly illustrative in nature and should not be viewed as proscribing who should or should not be an author nor seen as an exhaustive list.
 - i. Primary results paper – Typically, the most important product of a CSP study that present results on the primary objective(s). Potential authors may include: Study Chair, Study Biostatistician, Study Pharmacist, Health Economist, Executive Committee members, national study coordinator, site investigators, key collaborators, CSP Center Director/Staff Members, and CSR&D/CSP Central Office staff.
 - ii. Methods paper – Often the publication that describes key considerations, challenges, and/or innovations in the design of a CSP study. Potential authors may include: Study Chair, Study Biostatistician, Study Pharmacist, Planning Committee members, CSR&D/CSP Central Office staff.
 - iii. Secondary analysis paper(s) – Given the amount of data collected in a CSP study, secondary analyses often result in important results to be disseminated. Potential authors may include: Secondary analysis proponent, Study Biostatistician, Study Chair, Executive Committee members, statistical programmers, and site investigators. Other individuals may also be invited to collaborate on these publications.

V. Roles and Responsibilities

This section outlines author roles and responsibilities; specifically, roles and responsibilities pertaining to planning, research, writing/review/revision, and clearance phases of a publication.

A. Author Roles and Responsibilities

1. Authors employed by VA must list their VA in their affiliation first. If an author was employed by VA but is no longer at the time of publication, then a statement to this effect should be included along with their current affiliation.
2. **First Author.** In addition to meeting the criteria for authorship, first authors have these additional responsibilities:
 - a. Provide leadership for the writing team in determining author order, establish writing assignments and deadlines for written contributions and coauthor reviews, and ensure an open forum for coauthors to share their concerns and suggestions.
 - b. Compile drafts, distribute them for review, and provide specific direction for reviews and revisions.
 - c. Ensure that all ethical considerations (e.g., IRB review, disclosure of conflicts of interest) have been addressed.
 - d. Communicating and adhering to the requirements of this policy.
 - e. Ensure approval by the CSP Center Director.
 - f. Ensure that CSP CO and/or ORD Communications is notified.
3. **Coauthors.** Contributors to the development of publication should participate in initial decisions about authorship and other contributions as soon as possible — i.e., when the study begins, when a plan for data analysis is developed, and/or when an invitation to

submit an article is received. Coauthors should participate in setting assignments and deadlines for written contributions and coauthor reviews. Each coauthor should provide assigned written sections and reviews in a timely manner. Coauthors are also involved in the selection of the journal for manuscript submissions. The writing team should revise author order as necessary to reflect evolving contributions of team members.

B. CSP Center Roles and Responsibilities

1. Implementation, Training, and Mentoring. Each CSP Center's Director should ensure that this policy is implemented and that appropriate staff receive sufficient training and mentoring in CSP's authorship policy and center-specific procedures.
2. Ensure compliance with applicable VHA and ORD publication policies including VHA Handbook 1200.19.
3. Ensure that all CSP staff (including Central Office) have been thoroughly considered in discussions of authorship.
4. Dispute Resolution. The CSP Center Director should resolve disputes about author designation, author order, or serious delays in the writing/review/revision process if they cannot be resolved at Executive Committee or Writing Group levels. Disputes that cannot be resolved by the center should be taken to the Director, CSR&D for final arbitration and ruling.

VI. Ethical Considerations

To ensure public trust and the credibility of CSP and its staff, authors should avoid the following breaches of ethical principles.

A. Withholding Information

1. CSP authors are ethically obliged to release information immediately when required to protect public health. Concerns about future publication in journals should not preclude timely release of information. Such release must be approved by the Director, CSR&D.
2. CSP authors shall not withhold relevant information from a publication for the purpose of generating multiple publications from a research project or data set.

B. Redundant Publication

1. In general, reports of scientific findings shall not be submitted to more than one journal at a time for review. Once findings are published, authors of subsequent related publications should make the prospective publisher aware of all directly related reports already published, in press, or submitted for publication. If information is republished, the readers should be made aware of the original report through a footnote or reference. Further guidance on redundant publication has been issued by the ICMJE in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

C. Plagiarism

1. Careful attention to proper attribution is increasingly important in today's electronic document environment, where information or entire passages may be easily inserted—and left in without proper attribution.
2. Plagiarism is included in the federal definition of reportable scientific misconduct. The Director, CSR&D has oversight responsibility for all CSP activities. Additionally, the Chief Officer, Office of Research Oversight, is the primary official responsible for all matters related to scientific misconduct for VA research. References may be obtained upon request.
3. Self-plagiarism – the reuse without attribution of portions of previously published manuscripts, is to be avoided.

D. Disclosing Conflicts of Interest

1. Objectivity is an important value in science and is the basis for public trust. To ensure the scientific integrity and objectivity of information products authored in whole or in part by CSP Staff and study team members, it is important to avoid situations in which financial or other interests might compromise or give the appearance of compromising the work.
2. A conflict of interest exists when an author has financial or personal ties to activities that could

inappropriately influence the design, conduct, or reporting of scientific work or could influence conclusions drawn from such work (Reference A, Reference C). Financial ties include compensation for services (e.g., consulting fees or honoraria), equity interests (e.g., stocks, stock options, bonds, or other ownership interests), and intellectual property rights (e.g., filed or pending patents, copyrights, and royalties from such rights). Financial relationships to industry can also be more indirect—for example, through spouses or dependent children or from previous employment with a commercial entity. The CSP Guidelines address scientific integrity and expectations for the ethical conduct of all CSP activities, including publications. Further guidance on financial conflict of interest may be obtained from CSP Central Office, the Office of General Counsel and/or ethics officials based at VA regional counsel offices.

3. Although financial ties are among the most serious threats to scientific objectivity, other threats include pressures related to scientific advancement, professional competition, recognition from peers, and media attention.
4. Disclosure of financial or other conflicts does not eliminate the potential for bias but rather provides additional information in which the objectivity of the science or information can be evaluated. These disclosures are typically obtained at CSP planning and/or the start of a CSP study.
5. For CSP publications, authors must comply with VA guidelines for disclosing conflicts of interest.
6. A statement indicating that views expressed are solely those of the author(s) do not represent those of the Department of Veterans Affairs must be included.

VII. Copyright

- A. Works created by federal employees as part of their official duties cannot be copyrighted in the United States. Upon acceptance of information for publication and receipt of a copyright transfer form from a publisher, federal authors should sign the form where it specifies that they were a federal employee when the work was prepared and thus that there is no copyright to transfer.

If the publisher does not provide such a form or there is no allowance on the form to sign as a federal employee, then the federal employee should submit the following notice in a signed letter:

I was an employee of the US Federal Government when this work was conducted and prepared for publication; therefore, it is not protected by the Copyright Act, and copyright ownership cannot be transferred.

- B. If there are multiple authors, some of whom are nonfederal, the federal employee should follow the procedures specified above.
- C. Although the content of a publication authored by federal employees may not be copyrighted, some publications (e.g., journals) may copyright the format in which the information is published. This copyright on format may inhibit VA's ability to freely copy the published information. If the publication is of such a nature that wide distribution is desirable (e.g., guidelines), the authors should seek a license from the publication to freely copy and distribute the information as it was published. This license should be negotiated prior to publication. VA's Office of the General Counsel is available to assist in this process.

VIII. References

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