COOPERATIVE STUDIES PROGRAM

GUIDELINES

FOR THE PLANNING AND CONDUCT OF

COOPERATIVE STUDIES

OFFICE OF RESEARCH AND DEVELOPMENT

DEPARTMENT OF VETERANS AFFAIRS

MAY 2007

CSP

COOPERATIVE
STUDIES PROGRAM

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I. INTRODUCTION

The purpose of this document is to describe the practices, procedures and policies for the organization and operation of Cooperative Studies Program (CSP) studies in the Veterans Health Administration (VHA). Cooperative studies are those in which investigators from two or more VA (or non-VA, as appropriate) medical centers agree to collectively study a selected problem in a uniform manner, using a common protocol with central coordination.

Although cooperative studies are generally not appropriate for the early development and refinement of new therapeutic techniques, they are particularly advantageous in the later stages of evaluation of safety, efficacy and cost effectiveness of health care interventions that have already had the necessary preliminary trials in humans. Clinical trials and health services research studies of this type as well as some epidemiologic studies can benefit from a multi-site approach that facilitates the accumulation of patient samples that are:

- Sufficiently large 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, the VA presents an ideal environment for conducting multi-site cooperative studies. The VA has a patient base that is especially appropriate for research that addresses medical problems and diseases prevalent in the veteran population. Its network of medical centers and facilities and the VA administrative structure facilitate the conduct of multi-site studies that require uniformity of research methodology, strict maintenance to a common protocol, adherence to ethical principles and regulatory policies and fiscal control. In this setting, it is also more likely that the essential patient follow-up will be completed.

The Cooperative Studies Program, a division of the Department of Veterans Affairs' Office of Research and Development's Clinical Science Research & Development Service (CSR&D), was established to provide coordination and collaboration for multi-site clinical research studies that fall within the purview of the VA. When appropriate, CSP works with other divisions of the VA to promote cooperative studies.

CSP has eleven centers (see Figure 1) located across the U.S.: five statistical/administrative coordinating centers, one pharmacy coordinating center, four epidemiological research centers, and a health economics center. The five Cooperative Studies Program Coordinating Centers (CSPCCs), located at the VA Medical Centers in Boston, MA, Hines, IL, Palo Alto, CA, Perry Point, MD, and West Haven, CT, provide administrative and budgetary management, clinical research methods support and also ensure their compliance with Cooperative Studies Program policies and standards. This support encompasses all phases of the research project, including proposal development, study implementation, central coordination of study conduct, data management, interim statistical analyses and study progress monitoring and final analyses for study publications. There are Human Rights Committees established at the Coordinating Centers that review the ethical aspects of proposed studies.

Unique to CSP, is the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC), affiliated with the VA Medical Center in Albuquerque, NM. The CSPCRPCC was established to provide additional resources for all CSP studies that involve drugs or devices. Personnel from this center help in the planning and development of the study, participate in monitoring the study, serve as liaison between the CSP, the pharmaceutical industry and the Food and Drug Administration (FDA), provide guidance and information on FDA regulations, review and distribute reports of serious adverse events collected during the course of the study, and centrally control and distribute study drugs and devices. Also located at this center is the Site Monitoring, Audit and Review Team (SMART), the unit of CSP responsible for Good Clinical Practices (GCP) Quality Assurance.

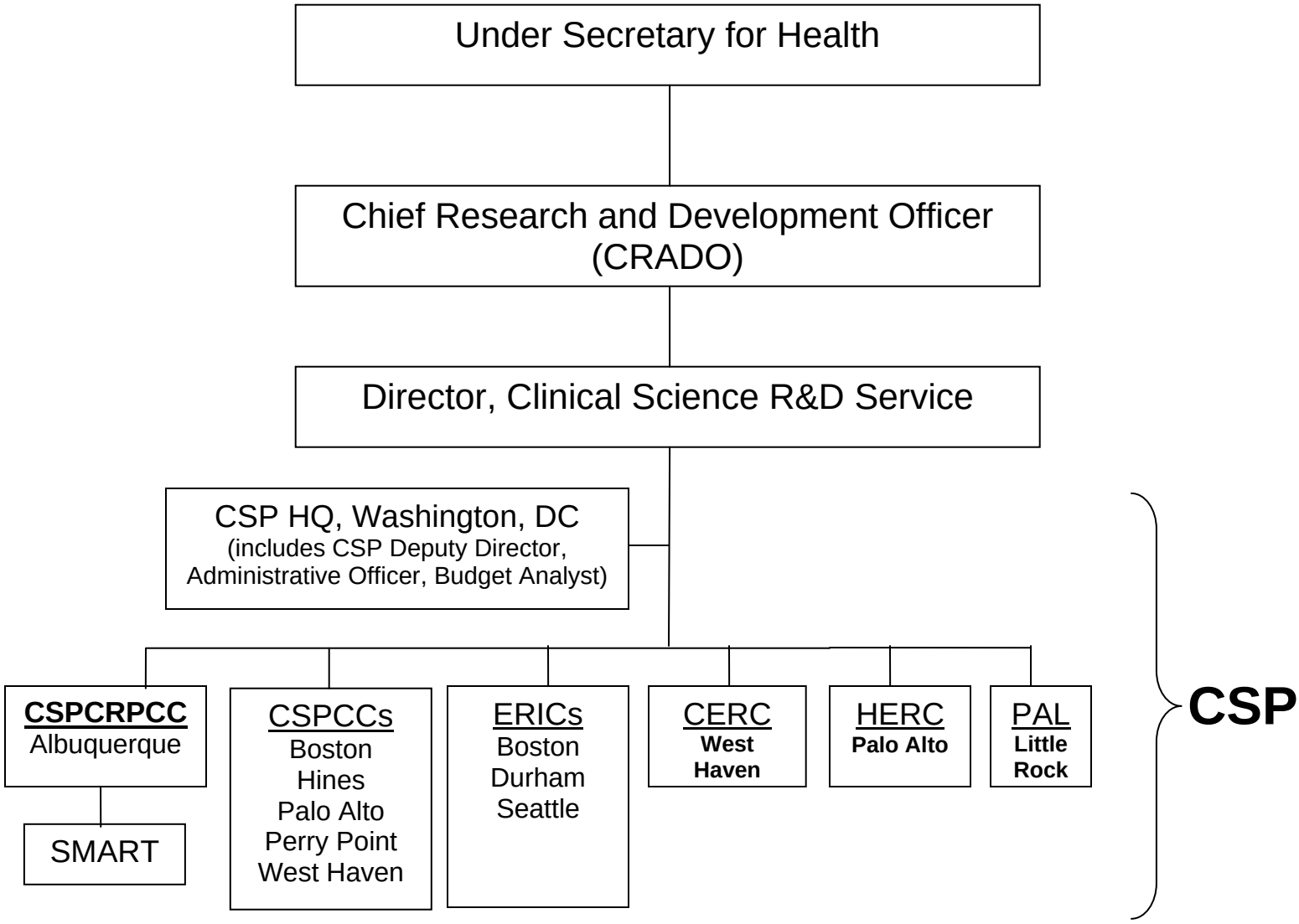
The three Epidemiological Research and Information Centers (ERICs) and the Clinical Epidemiology Research Center (CERC) were established to provide collaboration and guidance within the VA for epidemiological studies. Their mission is to enhance VA health care delivery by promoting VA-based population research and to disseminate epidemiologic research results in ways that help Veterans Health Administration providers improve patient care. The epidemiologic research centers are located at the VA Medical Centers in Boston, MA, Durham, NC, Seattle, WA, and West Haven, CT.

Another dimension of the CSP is the Health Economics Resource Center (HERC) at the VA Palo Alto Health Care System. Economists at HERC and the CSPCC's review all planning letters to determine whether an economic analysis is needed. The HERC provides design and analytical support in the conduct of CSP studies in instances where there are key cost effectiveness questions or other economic components.

A Pharmacogenomics Analysis Laboratory (PAL) has also recently been created at the Little Rock VA Medical Center. The PAL is dedicated to helping CSP investigators design studies aimed at evaluating the clinical utility of pharmacogenomic data and providing analytical expertise for such data collected in CSP studies.

In a cooperative study, certain persons and groups have specific responsibilities. These *Guidelines* highlight the most important tasks and responsibilities. They also reflect VA policy and provide CSP-specific policies for CSP activities. A successful cooperative study requires communication, cooperation, and a willingness to pursue a common goal. To help ensure these efforts, CSP personnel and investigators are expected to adhere to these Guidelines. If additional information is needed, the CSP Headquarters (HQ) in VA Central Office should be contacted.

FIGURE 1. Organization of the Cooperative Studies Program (CSP)



See Appendix A for names, addresses and telephone numbers.

II. DEVELOPING A CSP STUDY

A. Submission and Review of Planning Request

A CSP study begins with the submission of a Letter of Intent (LOI) by an eligible VA Investigator to the Director, CSR&D in VA Central Office. All correspondence pertaining to a CSP LOI should be sent to the following address:

ATTN: CSP LOI (Planning Request)
Cooperative Studies Program (125)
VA Office of Research & Development
810 Vermont Avenue, N.W.
Washington, D.C. 20420

The investigator who submits a LOI is designated as the Principal Proponent. A Co-Principal Proponent is named only when a clear and justifiable need exists; in general, this practice is discouraged. No more than two Principal Proponents may be named. A LOI should be no longer than 10 pages, and contain the following information:

- Completed Form 10-1313-13.
- Objectives of the proposed research.
- Importance of the study topic to the VA and its patients.
- Justification of the need for a multi-site study and the feasibility of conducting the study within the VA.
- Summary statement that the necessary preliminary research has been accomplished with data to support a large-scale evaluation.
- Acknowledgment of VA policy to include women and minorities in clinical research.
- Description of the proposed study design. Include the following items in the description as appropriate:
    - interventions/treatments/services to be compared
    - population to be studied
    - unit(s) of analysis
    - sampling strategy
    - data collection methods
    - research strategy (randomized study or observational study)
    - endpoints to be evaluated
    - logical links between questions, data, and endpoints
    - duration of the study
    - number of patients and participating medical centers

- resources (FTE and estimated total cost)
- other details as needed

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

- Statement of disclosure. A formal statement is required indicating that no financial or contractual relationship exists between the Principal Proponent(s) and any 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. (See Appendix B)

- Statement of eligibility. To be eligible for planning support, a Principal Proponent must either have at least a 5/8th's VA appointment or have applied for and received approval to submit from VA CSP HQ within the previous nine months if s/he does not have at least a 5/8ths VA appointment. In the latter case, a copy of the letter establishing eligibility to receive funds should be attached to the request.

- Cover letter from the Director and the ACOS for Research and Development at the Principal Proponent(s)' Medical Center(s) acknowledging and approving the submission.

- Curriculum Vitae (CV) of the Principal Proponent(s) with address, telephone and fax number(s) (not to exceed 10 pages).

- Names, addresses, telephone numbers and email addresses of five to seven unbiased experts in the field who might be suitable to review the proposal. LOIs will not be processed unless these names are included.

- Potential Planning Committee Members. Names, addresses and telephone numbers 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/Submitted Proposals. Indicate any on-going or submitted proposals that are directly related (e.g., pilot study, single-site/smaller clinical trial) to the study proposed in the LOI and the funding source.

Seven copies of the LOI and CVs should be submitted in addition to an electronic version of these documents on a floppy or compact disc (CD). Incomplete submissions will be delayed or returned to the investigator.

A preliminary protocol outline and 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.

Investigators who have questions about submission of an LOI are encouraged to contact the CSP HQ staff. When it appears advantageous, the Director, CSR&D may suggest a consultation with the staff

at one of the CSPCCs/ERICs. Similar support is available in the areas of cost effectiveness and decision analysis.

LOIs are sent to three or more reviewers to evaluate the merit of the proposal. The decision to fund planning efforts for the study will be made on the basis of the experts' recommendations, as well as at the discretion of the Director, CSR&D. Turnaround time for responses to planning requests is approximately two to three months depending on whether additional information is requested from the Principal Proponent and/or other situational factors.

Although most CSP studies are supported by CSP funds appropriated by VHA, occasionally studies are funded from other VA sources or by outside sources such as the National Institutes of Health or the pharmaceutical industry. Regardless of funding support, all VA and CSP rules and regulations must be followed both in the development of the protocol and the conduct of the study unless specifically waived by the Director, CSR&D. If industry support is anticipated, industry representatives may be included in the planning process (see Section V. U.).

B. Notification of Approval for Planning

When a study is funded for planning, the Principal Proponent is notified in writing by the Director, CSR&D. This letter indicates the CSPCC/ERIC to which the study has been assigned and the study number. The Director and the ACOS for Research and Development at the Principal Proponent's medical center are provided copies of the notification as well. Subsequent to these notifications, the Director of the CSPCC/ERIC will identify the Study Biostatistician/Epidemiologist and Project Manager with whom the Principal Proponent will work. The CSPCRPCC Director is also notified if the study involves drugs or devices, and he will assign a Clinical Research Pharmacist (CRP) to the study. If the study does not involve drugs or devices, he will assign a regulatory affairs manager to manage the adverse events aspects of the study. The HERC Director is 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. Finally, the CSP DNA Bank will be given notice to determine whether a genetic substudy can be developed in accordance to CSP genomic medicine efforts.

C. Planning a CSP Study: Participants

Planning and developing a CSP study requires close cooperation among several groups and individuals: the Principal Proponent, the CSPCC/ERIC (represented primarily by the Study Biostatistician/Epidemiologist and Project Manager), the CSPCRPCC (represented primarily by the Study CRP), the Study Health Economist and the other members of the Planning Committee.

1. Principal Proponent

The Principal Proponent provides leadership in the planning process with support from CSPCC and CSPCRPCC personnel. Working closely with the Study Biostatistician/Epidemiologist, the Principal Proponent will:

- Nominate the members of the Planning Committee for approval by the Director, CSR&D and choose a date for the first planning meeting.

- Develop an agenda and distribute relevant material prior to the first meeting.

- Serve as Chairperson at meetings.

- Coordinate the writing of the protocol.

- Present and defend the protocol before the Cooperative Studies Scientific Merit Review Board (CSSMRB).

- Contact industry or other federal agencies for possible support.

2. Cooperative Studies Program Coordinating Center / Epidemiology Research & Information Center (CSPCC/ERIC)

During the planning phase, the CSPCC/ERIC, represented primarily by the Study Biostatistician/Epidemiologist and Project Manager, 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 and operational aspects of the protocol, including statistical and experimental design, definition of end points and data to be collected, data flow and management, quality control methods, study monitoring plan, sample size determinations, planned interval and final statistical analyses and data summaries, forms design and budget estimation.

- Arrange for a protocol review by the CSPCC Human Rights Committee (HRC). For a "Just-In-Time" review, the HRC review could be deferred until after review by the CSSMRB.

- Arrange administrative support (e.g., word processing, copying and distributing the proposal to members of the Planning Committee, and preparing and submitting the final document to CSP HQ for review by CSSMRB).

- Assist CSP HQ in developing agreements/contracts with industry collaborators for supporting the study (e.g., with drugs and/or funds).

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

For studies involving drugs, biologicals or investigational devices, the CSPCRPCC, represented primarily by the Study CRP, will:

- Assist in the development of the study design, particularly with regard to drugs, dosage regimens, packaging, and randomization and blinding strategies, pharmacokinetics and pharmacoeconomics.

- 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 CSP HQ in developing an agreement/contract with industry.

- Provide comprehensive drug information to the CSPCC Human Rights Committee and study participants that include therapeutic category, pharmacology (mechanism of action and pharmacokinetics), approved uses, summary of clinical trials, dosage information, side effects/adverse reactions, drug interactions, and contraindications and precautions.

- Prepare a Drug/Device Information Report (DIR) for each primary study drug or device.

- Submit all DIRs to the CSPCC for review by the Human Rights Committee.

- Develop an adverse event reporting system for documenting and reporting routine and serious adverse events to assure compliance with FDA reporting regulations.

- SMART will evaluate monitoring needs and develop a plan for monitoring visits or GCP site visits as appropriate.

- SMART will develop source documentation guidance and other tools to promote adherence to GCP.

4. Health Economics Resource Center (HERC)

HERC coordinates the economics activities of the Cooperative Studies Program. 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

Shortly after the study is released for planning, the Principal Proponent and Study Biostatistician/Epidemiologist should submit a final list of Planning Committee member nominations with CVs to the Director, CSR&D for approval.

The Planning Committee is responsible for preparing a final study protocol, which should reflect a collaborative, in-depth effort in its development with agreement on all major issues of the proposed study.

The Committee includes the Principal Proponent, the CSPCC/ERIC Director, the Study Biostatistician/Epidemiologist, the Project Manager, the Study CRP (when appropriate), at least two potential site investigators and VA or non-VA consultants. A health economist, usually assigned by the HERC, will be included when this is an objective of the proposed study. If several disciplines are involved (e.g., medical and surgical), they should be reflected in the composition of the Committee. If systematic collection of blood or other specimens is anticipated as part of the study, then the Director of the Boston ERIC (MAVERIC) should be informed and invited to attend or to send a designee. The CSPCC/ERIC Project Manager also plays a major role on the Committee. The total planning group consists of eight to ten people. 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.

D. Planning a Cooperative Study: The Process

The planning will usually require two meetings typically lasting two days each. Under special circumstances, additional planning activities may be funded.

The Principal Proponent submits a list of proposed attendees to the CSPCC/ERIC Director as early as possible but no later than six weeks prior to a meeting. Clinical expertise other than the specialty of the Principal Proponent should be considered for representation on the Planning Committee.

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 CSPCC/ERIC to permit attendance of other relevant CSPCC/ERIC staff and, when desired, to facilitate the review of the proposal by the Coordinating Center's Human Rights Committee. Meetings will not be funded unless all major participants are able to attend.

If the first planning meeting is not held within three months of the notification that planning is authorized, or if subsequent planning meetings and activities do not occur within six months of the first meeting, it will be assumed that the planning activity has ceased, and no further support for planning will be provided. It is the responsibility of the CSPCC/ERIC Director to notify the Director, CSR&D to discontinue support for planning or, if the CSPCC/ERIC Director concurs that the circumstances in a

given situation are unusual and justify an exception from this practice, to petition the Director, CSR&D for an extension.

The CSPCC/ERIC is responsible for distributing specific materials to the Planning Committee prior to the first planning meeting to help with conducting a successful meeting. These materials include the original planning request, reviews, CSP documents, details on key scientific and methodological aspects of the study, and logistical documents. The CSPCC/ERIC has the full list of items for distribution. It is important that all Planning Committee members read all of these materials prior to the planning meeting.

If the Planning Committee decides that the study is not feasible, its clinical importance is questionable, or the study is untimely or irrelevant, this decision and its reason(s) will be communicated to the Director, CSR&D by the CSPCC/ERIC Director. Otherwise, there should be some preliminary discussion of potential participating medical centers and specific planning for a formal determination of patient availability. This determination consists of prospective (preferred) or retrospective screening of actual patient 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 study patients. This information should be available before the second planning meeting.

Funding for the second planning meeting is contingent upon a satisfactory first meeting. To obtain funding for continuation of the planning process, the Principal Proponent is required to update his original planning request incorporating all changes that the Planning Committee has agreed upon. This request will then be sent to the CSPCC/ERIC Director. The CSPCC/ERIC 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. This package is then sent to the Director, CSR&D for the final decision on continued planning. 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.

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 clinical trial (see Section VI.C. of these *Guidelines*). Therefore, it is the responsibility of the Principal Proponent, the Coordinating Center and the Planning Committee to anticipate that product. At the Cooperative Studies Scientific Merit Review Board (CSSMRB) review, members will be instructed to pay particular attention to the publications plan.

Development of the protocol is a joint responsibility of the Planning Committee members. However, the primary responsibility lies with the Principal Proponent, the Study Biostatistician/Epidemiologist, the Study CRP, and the Study Health Economist.

The final planning meeting is spent refining the protocol and data collection forms, assessing preliminary patient availability estimates, formulating the final budget and, if applicable, conducting the Human Rights Committee review. “Just-In-Time” processes, which allow the Human Rights Committee Review to occur after the CSSMRB review, may be utilized after initial discussion between the CSPCC Director and Director, CSR&D (See Section III.A. for a description of the Human Rights Committee review.) To ensure that the goals of the final planning meeting are accomplished, the Principal Proponent

must mail an essentially complete protocol including research data forms and informed consent documents to each member of the Planning Committee and, if applicable, the Human Rights Committee at least three 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 CSPCC. If submission of this material is late or if it is substantially incomplete, as determined by the CSPCC Director, the final planning meeting will be rescheduled. After the final planning meeting, the CSPCC will prepare the final proposal for submission to the CSSMRB, through CSP HQ, by the required deadline.

If appropriate, the Study CRP begins negotiating with the pharmaceutical company early in planning to secure commitments for drug/device supplies for the study. The Principal Proponent usually makes the initial contact with the company, and the Study CRP follows up with CSP HQ personnel and completes the negotiations. The Director, CSR&D should be informed of all discussions. The Study CRP should attempt to secure a written commitment (e.g., Letter of Agreement (LOA)) from each involved company during planning or at least prior to CSSMRB review. The LOA will be generated by the Director, CSPCC/ERIC for signature by him, the Director, CSPCRPCC and the appropriate company officials. After all signatures have been obtained, a copy is forwarded to CSP HQ when possible. It is important that these negotiations be completed prior to CSSMRB review so that the start of the study will not be delayed once funding is approved. Industry representatives may participate in planning meetings, since they have detailed knowledge of the drugs involved (see Section V.U.). If the Principal Proponent is negotiating with the drug company to secure funds in support of the study, the CSPCC Director should be involved in these discussions and, if possible, a letter indicating this support should be obtained prior to CSSMRB review. Also at this time, consideration should be given to the potential need for additional intensive clinical site monitoring based on the company's intent to use the data to support a regulatory filing. The drug company would be expected to fund this monitoring activity. If it is anticipated that intellectual property must be included as part of any agreement with industry, a Cooperative Research and Development Agreement (CRADA) must be executed. CSP HQ will coordinate these efforts with the CSPCC and CSPCRPCC.

The Biopharmaceutics/Pharmacokinetics Laboratory at the Albuquerque CSPCRPCC must be considered first when planning a laboratory component for the study. If the Principal Proponent determines that a core lab is required, the Chief, Biopharmaceutics/Pharmacokinetics Laboratory Section at the CSPCRPCC should be consulted. If this laboratory will be used in the study, the Chief should be included in the planning of the study, although not necessarily as a member of the Planning Committee.

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

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. Protocols for such pilot studies are generally developed through the usual planning

process and presented to the Director, CSR&D who will determine if CSSMRB review is required. The completed pilot study may be reviewed by CSSMRB prior to the initiation of the full-scale trial. Limited GCP support will be provided by SMART for feasibility trials and must be provided for in the budget.

F. The CSP Study Proposal

The objective of the planning meetings is to produce the final proposal. The CSPCC will be responsible for ensuring the proposal is ready for submission to CSP HQ for CSSMRB review. To facilitate review, the proposal may be assembled into two volumes. This will be required when a proposal is voluminous, such as having a large number of forms or many large appendices.

The following specifies the contents of the proposal:

1. Protocol

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 CSSMRB, the CSPCC/ERIC Director will include them in the cover letter. The Director will also comment on the appropriateness of the statistical analysis plan, take note of the budget, and address any budget issues that CSSMRB should consider. Similarly, the CSPCRPCC Director will call the attention of CSSMRB to particular drug or device considerations that should be addressed during the review and plans for conducting quality assurance site visits based on regulatory needs, patient risks or unusual characteristics of the trial.

2) For a resubmission of a proposal:

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

- CSSMRB Report: A copy of the CSSMRB report, which contains the recommendations made by CSSMRB at the time of the first review.

- Letter from the Director, CSR&D to the Principal Proponent that summarizes the results of the first CSSMRB review.

- A statement by the Principal Proponent or the Study Biostatistician/Epidemiologist that summarizes the specific changes made in response to CSSMRB recommendations, including a point-by-point response to each concern listed in the CSSMRB 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 the VA, number of patients and participating sites, duration of patient intake and treatment (follow-up), definition of patient 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.

- Patient recruitment, patient selection criteria and method of assignment of patients to comparative groups.

- Intervention/methods of treatment including, if appropriate, provision for double-blinding (and procedures for breaking the blind).

- Methods of follow-up and methods of assuring uniformity of intervention.

- Outcome measurements including specialized rating scales.

- Schedule of observations and laboratory tests; 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 patients required, duration of patient intake period, and number of participating medical centers. Other studies that could compete for patients should be noted.

- Statistical analysis section which describes how the major hypotheses or research questions will be tested, including the specification of major end points.

- Plans for safety monitoring.

- 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 patients' medical records by CSP site visitors is a requirement for participation.

- Plans to assure security and confidentiality of study data.

- Recruitment strategies. Finding sufficient patients who meet all of the entry criteria is often difficult in clinical studies and requires diligence on the part of study personnel. Recruitment strategies must be discussed during the planning process and addressed in the study protocol and/or Operations Manual.

- Data security plans. Plans for how data will be maintained at the sites and how it will be transferred to the CSPCC/ERIC and other appropriate locations (e.g., the CSPCRPCC and Chairperson's Office) to ensure compliance with VA data security policies must be provided.

- Plans for dissemination of study results, including manuscript preparation and writing.

- Plans for notifying patients of study results; plans for transition of patients from study treatment to regular care after their participation in the study ends.

- Economic Analysis. The inclusion of an economic analysis in the proposal may be appropriate. Economic analysis has become an increasingly 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 CSSMRB. An appendix with the complete economic analysis plan should be included.

- Human Rights Considerations. Before preparing this section, VHA Handbook 1200.5 should be reviewed. This Handbook contains the agency position on these issues.

  There should be a brief description of the procedures that will be used in the study to obtain the patient's voluntary consent to participate. This description specifies who can solicit consent, when consent can be solicited, and under what circumstances. It specifies whether there must be a witness present throughout the entire consent

procedure or simply someone to witness the signature. The description can include details such as allowing the patient time to consider the issues or to consult others before giving consent, and providing the patient 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 might also be included as part of the discussion. The Principal Proponent 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 patients 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 patients. If surrogate or delayed consent is planned, this should be discussed and justified. The purpose of this discussion is to focus the attention of the Planning Committee on potential risks as well as to facilitate review by the Human Rights Committee, by CSSMRB and by the Subcommittee on Human Studies or the Institutional Review Board (IRB) at each of the participating medical centers.

One such issue that has both methodological and human rights implications is the CSP's responsibility for patients at the conclusion of their participation. In most treatment evaluations, particularly those that are double-blind, there should be consideration of the procedures that will be followed when a patient's participation in the study is completed, or terminated for other reasons. With some treatments, it may be necessary to break the code at this time in order to plan further treatment, and to inform the patient and/or the patient's physician. (See Section VI, "Concluding a CSP Study".)

Since there are special considerations for enrolling non-veterans into VA studies supported by appropriated funds, the use of non-veterans is discouraged. If the Principal Proponent believes that the use of non-veterans is essential, then s/he must provide adequate justification for their inclusion and obtain approval from the Director, CSR&D. This justification and a discussion of the use of non-veterans should be included in this section.

2. Appendices (Supporting Documents)

Appendices contain a variety of information that is of special interest to the primary reviewers. The following Appendices should be included:

a. Consent Documents and Human Rights Review

1) Consent Documents

Study subjects indicate their willingness to participate in a CSP study by signing VA Form 10-1086, "Agreement to Participate in Research By or Under the Direction of the Department of Veterans Affairs". (See VHA Handbook 1200.5, Appendix C.) This

document should describe the study in language that will be easily understood by the participant or his/her representatives so that a reasonable decision concerning participation can be made. It should include the following:

- A statement that the study involves research.

- A statement of the purpose of the investigation and a general statement as to its nature, i.e., how it relates to existing knowledge, what use may be made of the results obtained, and a description of any experimental procedures. The expected duration of a patient's participation must be stated.

- Information describing the procedures to be used, including invasive techniques, restrictions on normal activities, long-term follow-up examinations, or the possibility of receiving inactive material ("placebo") in a double-blind trial.

- Identification of any procedures which are experimental.

- A statement of any known risks, inconveniences, or side effects that could be expected and the measures that will be taken to minimize hazard or discomfort and, where applicable, a statement that the risks cannot be predicted.

- A statement of any benefits that the subject may receive as a result of participation in the trial, including therapeutic benefits, payments, or recognition. (An explanation will be provided as to whether compensation and medical treatment is available if physical injury occurs and, if so, the nature of the compensation or treatment, or where further information may be obtained).

- Information describing alternate courses of appropriate action, generally another accepted therapy, diagnostic procedure or health-related service, in lieu of participation in the study.

- A statement indicating that participation is voluntary and a decision not to participate in the study will not affect the subject's right to receive health care or any benefit to which he or she is entitled.

- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.

- When appropriate, a statement of the result to be anticipated if nothing is done, e.g., when neither an experimental nor a control drug is taken.

- An explanation of whom to contact for answers to pertinent questions about the study and patient's rights, and whom to contact in the event of a study-related injury to the patient.

- A statement that the subject may withdraw from participation at any time without prejudice.

- A statement that the patient will not be required to pay for treatment received as a participant in a VA research program although a co-payment may be required if so indicated by a means test.

- A statement that the provisions of the Privacy Act and Freedom of Information Act will be adhered to and that there is a possibility that the study's research records may be inspected and photocopied by regulatory agencies and by reviewers/monitors from the CSP or industry partner.

- Signatures of the subject or guardian, person obtaining consent, the Site Investigator and a witness. It is the policy of the Cooperative Studies Program that the witness to the signing of the consent document is not to be anyone directly involved in the conduct of the cooperative study.

- Dates of signature for each person signing the form.

Whenever they apply, the following elements are also included:

- Circumstances under which the patient's participation may be terminated without regard to his/her consent.

- Any additional costs to the patient that may result from participation in the study.

- Consequences of a patient's decision to withdraw from the study and procedures for orderly termination of participation.

- A statement that a particular treatment or procedure may involve risks to the patient (or embryo or fetus if patient is or becomes pregnant) which are currently unforeseeable.

- A statement that any significant new findings developed during the course of the study that relate to his/her willingness to continue will be provided to the patient.

- An approximate number of patients involved in the study.

- A statement regarding any payment that the patient is to receive.

This consent form also may be used to ask the patient for permission to use Social Security or VA claim numbers for identification for national database searches or

permission to use any biological samples collected in future, specified types of studies. Separate consent forms will usually be required for any substantial substudies such as genetic analyses. Requirements to be in compliance with Health Insurance Portability and Accountability Act (HIPAA) may be included in this consent or as a separate consent.

2) Human Rights Committee Report

The CSPCC/ERIC Human Rights Committee must review the protocol and consent form before the study can be funded. After discussion with the Director, CSR&D, this review may take place after the CSSMRB review. However, if the Director CSPCC/ERIC determines that there may be unique ethical issues to consider for the study, it is recommended that the HRC review be conducted prior to the CSSMRB review, optimally at the final planning meeting.

The report of the HRC review provides a description of the Human Rights Committee discussions of the protocol during its review and lists any conditions for approval that the Committee may have stipulated. It must be signed by the Human Rights Committee Chairperson. In this report or a subsequent report, the HRC Chairperson must document that all conditions have been satisfied.

b. Budget(s)

Every proposal contains a study budget including, costs for CSPCC and/or CSPCRPCC, study sites, 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 CSPCC will prepare the budget in the required format. Items to be included are the salaries of supporting personnel (including fringe benefits), capitation fees (if applicable), consultation fees, equipment, supplies, investigational or study articles and other medications and chemicals, and costs of patient travel if required by the study. The budget should also note the FTE required for the study. Supporting personnel are those hired solely for working on the study and are not existing personnel who work on the research as part of their regular duties. The Principal Proponent, with the assistance of the CSPCC, prepares position descriptions, including proposed grade levels, as part of the budget request. Positions should be filled at the grade level indicated in the study budget. Any exception must be justified. Study budgets should project a 5% increase annually to cover required step increases and/or COLA's. Personnel hired for the study work solely for the study and are not to have other responsibilities unless they have completed their study functions. Salaries of Site Investigators (SI) are supported by patient care funds rather than the CSP.

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. Patient travel is included only if the patient is required to travel for the sole purpose of being in the study. When medical services are furnished as part of an approved CSP study to a patient 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 patients to participate in research when the research is an integral part of the patient's medical care, under some circumstances such payments are permissible (see VHA Handbook 1200.5, Paragraph 12, Payment of Subjects). If such payments are deemed appropriate by the CSPCC/ERIC 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).

CSPCC, CSPCRPCC and 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. CSP centers are provided with guidance from CSP HQ on how such expenses are to be reported in the context of the overall study budget. In addition, the cost of Good Clinical Practice (GCP) monitoring, training and other GCP support services provided by the SMART unit must also be included.

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. Furthermore, 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 CSPCC approval. Transfer of funds from one CSP study to another at the same medical center requires prior CSP HQ approval. Unexpended CSP funds and FTE are not available locally for other research activities and shall be returned to CSP HQ on a quarterly basis (or more frequently, at the discretion of the CSP), unless a specific exception is granted.

2) Special Laboratory Budget

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

If a special 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. The totals will appear as a line item on the study budget.

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/Epidemiologist are required. If there is an economic analysis component, the CV of the person responsible for this part of the proposal should be included. Similarly, if the study's CRP is expected to attend the CSSMRB review, his/her CV should be included. Finally, if a consultant or other member of the Planning Committee will appear before CSSMRB, this CV should be included as well. Each CV should not exceed four pages. To remain within this limit, it may be necessary to include only those publications relevant to the study and indicate the additional number of publications.

d. Biostatistical and Research Data Processing Procedures (BRDP)

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 plan 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 may also include a summary of: case report form completion and data flow; data quality monitoring procedures; and computing software/hardware to be used.

e. Research Data Forms

A prototype set of research data forms is required when the proposal is submitted to CSSMRB for scientific evaluation. 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 CSSMRB review. However, the proposal should contain a representation of the important data items to be collected.

Properly designed data forms are required for the collection of complete and accurate data in a clinical trial. The forms contain all information essential to the study. They should include only data that will be needed in the analysis; it is important to practice parsimony in developing data forms. Forms should be designed to ensure that data collected would be unbiased. They should also be easy for the researcher to use so that errors can be minimized. The forms should be designed so that data can be efficiently entered into a computer for later retrieval and processing. Individual questions on the form should be constructed so that they are objective, single-dimensional and unambiguous. For these reasons, the data forms are designed jointly

by the clinicians, the Study Biostatistician/Epidemiologist, Study CRP, and data processing personnel. When there is an economic analysis, these researchers will work with the Study Health Economist to design forms for collecting economic data.

The order of the data forms and the elements in each form should be arranged to follow the sequence of the procedures required for conduct of the study. In addition to clear instructions for completion of the forms, self-explanatory codes and criteria should be available on the data forms for immediate reference.

Deficiencies in data forms can often be uncovered by a preliminary field trial so that revision can be made before the forms are distributed for use in all the participating sites. The CSPCC has responsibility for approval of the data forms before submission to OMB for final approval, if needed.

f. Drug/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 be distributed to investigators after the study begins. Besides use by the CSSMRB, this section is useful for Site Investigators and their R&D Committees and Subcommittees on Human Subjects or their local IRBs, as well as the CSPCC's HRCs.

g. Drug/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.

h. Medical Center Participation and Patient Availability

This section contains a list of medical centers that have expressed interest in participation in the study and describes the methodology and results of the assessment of patient availability.

i. 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, evaluating results and transmitting data. Other material might include descriptions of training procedures, reliability studies, definitions of endpoints, or plans for on-site monitoring.

G. Submitting the Proposal

All CSP proposals are submitted through the assigned CSPCC. After the final planning meeting and review by the CSPCC Human Rights Committee, the Principal Proponent sends the final version of the proposal to the CSPCC, where it is reviewed, typed in the required format and duplicated for submission to CSP HQ. If the proposal is typed elsewhere, it should be provided on appropriate electronic media (e.g., compact disc) to the CSPCC so that it can be reformatted according to CSP conventions.

CSSMRB meets twice each year in the Spring and Fall. The deadline for submission of completed proposals to the CSP HQ and to CSSMRB members is six weeks prior to the scheduled date of the CSSMRB review meeting unless otherwise specified.

To allow sufficient time for review, typing, duplication, binding and distribution of the proposal, a complete final draft must reach the CSPCC at least four weeks before the deadline for submission to CSP HQ/CSSMRB members. These deadlines must be observed or the review will be deferred to the next meeting. A protocol that is deficient in any important aspect will be returned to the Principal Proponent for appropriate action before it is submitted to CSSMRB.

III. CSP REVIEW PROCEDURES

Ethical, scientific, professional, manuscript preparation and administrative aspects of the proposal are evaluated by the CSPCC Human Rights Committee (HRC) and the Cooperative Studies Scientific Merit Review Board (CSSMRB - formerly known as the Cooperative Studies Evaluation Committee (CSEC)). In addition, each proposal is reviewed prior to the CSSMRB meeting by at least three independent reviewers who provide written critiques. Finally, after CSSMRB scientific approval and CSP funding approval, the proposal is submitted for review by the R&D Committee and Subcommittee on Human Studies/Institutional Review Board at each medical center being considered for inclusion in the study. If non-VA centers are participating, the proposal is submitted to the local Institutional Review Board (IRB) for review.

A. The CSPCC Human Rights Committee

Any study involving the use of human subjects requires consideration of the protection of the rights and welfare of the person volunteering to participate in the study. A Human Rights Committee (HRC) has been established at each CSPCC to provide these safeguards.

1. Composition

The Committee is composed of individuals from the community and VHA who have the interest and background required to consider the ethical and legal issues involved in the participation of human subjects in research. The Committee is chaired by a person who currently holds a VA appointment. At least two members are non-VA appointees who have no direct connection with research within a VA facility. At least one practicing physician from the community and one non-physician scientist will be on the Committee. Additional representation usually includes a member of the clergy, an attorney, a veteran and/or a member of a recognized minority group. Membership and procedures are consistent with appropriate sections of VHA Handbook 1200.5, Paragraph 6.

2. Responsibilities

The responsibility of the HRC at the planning stage of the study is to determine if the protection of the patient's rights and welfare in the proposed study is adequate. Assessment can be done prior to submission for CSSMRB review. “Just-In-Time” processes may be utilized if the CSPCC Director determines it is appropriate after discussion with CSP HQ so that HRC review occurs after CSSMRB review, but prior to study initiation. The Committee must ensure that the patient (or guardian, if the patient is judged incompetent) will be fully informed of the meaning of and any risk in participation. This review should include an in-depth consideration of the protocol and the informed consent procedures and documents. If the study involves the use of a medical device, the HRC must make a determination (based on current FDA guidelines) as to the degree of risk inherent to the device.

The HRC may, on consideration of human rights issues only, recommend to approve the study as proposed, approve it with conditions, or reject it outright. If the study is rejected, the revised protocol must be approved by the HRC before it is submitted for CSSMRB review, or in the case of a “Just-In-Time” review, prior to study initiation. A recommendation by a HRC may not be reversed

except by its own action. Therefore, no study can be fully approved for funding until it has been approved by the HRC. If the study is accepted with conditions, the Study Biostatistician/Epidemiologist is responsible for ensuring that the conditions have been met before it is initiated. A letter to this effect signed by the Chairperson, HRC is required.

The HRC provides a general assessment of the human rights aspects of the proposal. Neither this review nor the general assessment of feasibility, scientific merit, relevance and professional ethics by CSSMRB is a substitute for review by the local participating centers' R&D Committees and the Subcommittees on Human Studies or local IRBs.

B. Written Reviews for Cooperative Studies Scientific Merit Review Board

When the CSPCC completes the final proposal and ensures that all required information is included, copies are sent to CSP HQ. Upon receipt, CSP HQ distributes the proposal to the CSSMRB members and ad hoc reviewer(s). Clinical and biostatistical written critiques are prepared by CSSMRB members and ad hoc reviewers, as needed. These written critiques are usually made available to the Principal Proponent, Study Biostatistician/Epidemiologist, and Study CRP prior to the meeting without any identifying information.

Reviewers are asked to comment on the 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 patients 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, frequency of observations, sample size, plans for data processing and analysis and any other relevant features.

C. The Cooperative Studies Scientific Merit Review Board

The Cooperative Studies Scientific Merit Review Board (CSSMRB) reviews new CSP studies and makes recommendations to the Director, CSR&D regarding the scientific merit of the studies. Ongoing studies may be reviewed by CSSMRB if there are major protocol changes, significant increases in the budget, or if the study is not meeting initial projected recruitment goals.

1. Committee Members

Members of CSSMRB are appointed by the Department of Veterans Affairs Under Secretary for Health upon recommendation by the Chief Research & Development Officer. Members represent many medical specialties, the fields of epidemiology and biostatistics, and health services research. Some members may also have affiliations with other federal agencies. All members have extensive experience in clinical research and in the conduct of clinical trials. Members are appointed for a four-year term. Two members of CSSMRB, usually a biostatistician and a clinician, are assigned primary responsibility for reviewing each protocol. In addition, for new proposals, the Board may be augmented by *ad hoc* member(s) knowledgeable in the particular subject matter of the protocol(s) being reviewed. The Chairperson of CSSMRB is nominated by the Director, CSR&D. The responsibilities of the Chairperson are to conduct the meeting and to summarize the deliberations of

the Board. The Director, CSR&D and his staff serve as coordinators for the meetings. Appendix C lists CSSMRB members as of the publication date of these *Guidelines*.

2. The CSSMRB Review Process

For a given proposal, the CSSMRB first holds a closed session to summarize and discuss the key critiques from the written reviews. After this briefing session, the Principal Proponent and the Study Biostatistician/Epidemiologist appear before the CSSMRB. If the proposal includes an economic analysis component, the health economist appears as well. 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 petition the Director, CSR&D, in writing, to allow an additional consultant(s) to attend the CSSMRB review to help defend those areas where he lacks appropriate expertise.

Once before the CSSMRB, the Principal Proponent will be provided with a summary of the main critiques discussed in the closed session. The Principal Proponent and study team will be given fifteen minutes to provide a concise summary of the research problem, state why it should be supported by VA and to address critiques. If there is an economic component, the individual responsible for preparing that protocol will also be given five-minutes to address any questions on this matter. Following this presentation, the proponents defend the protocol in an interactive discussion. with the CSSMRB on additional problems and issues they have identified during the course of the discussion.

The Principal Proponent and the Study Biostatistician/Epidemiologist should take relevant notes at the meeting since in-depth reports of the CSSMRB proceedings are usually not provided.

After the interactive review, the proponents are excused for the CSSMRB Executive Session. The *ad hoc* reviewer remains and participates as a voting member in this closed session, during which the CSSMRB formulates recommendations.

3. CSSMRB Recommendations

Generally one of four actions is taken:

- Unconditional approval. The study is approved without changes and is recommended for funding.

- Conditional approval. The CSSMRB approves the study with the understanding that the Principal Proponent and the Study Biostatistician/Epidemiologist will make certain changes or additions to the protocol. When the changes are made and are approved by the Director, CSR&D, the Chairperson of CSSMRB, and the CSSMRB primary reviewers, the study will be recommended for funding.

- Reject or defer consideration of the study with recommendation for resubmittal. The CSSMRB 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 CSSMRB 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.

The Principal Proponent(s), the CSPCC Director, and the Study Biostatistician/Epidemiologist are informed of the CSSMRB recommendation immediately after the close of the Executive Session.

For new studies that are approved, CSSMRB assigns a numeric rating of the scientific merit of the proposal. This rating is from 10 to 50 with 10 as the best rating. Approval of a proposal by CSSMRB does not ensure funding. Action by the CSSMRB constitutes a recommendation to the Director, CSR&D. Written notification by the Director, CSR&D constitutes the official action on the proposed study. Studies approved but not funded are reviewed on a continuing basis and will be dropped from the awaiting funding list if the Director, CSR&D determines that funding will not become available within 18 months after CSSMRB approval. If the Principal Proponent then chooses to resubmit a proposal, a new request for planning must be sent to the Director, CSR&D.

IV. INITIATING A CSP COOPERATIVE STUDY

A. Study Chairperson

Once a study is funded, the Principal Proponent is designated as the Study Chairperson. The Chairperson is responsible to the Director, CSR&D, through the CSPCC/ERIC Director, for the conduct of the study. The appointment of a Co-Chairperson may be considered (e.g., when a study involves two major disciplines). However, there must be a clear and justifiable need, and the request for a Co-Chairperson 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 CSSMRB reviews the protocol. The Study Chairperson should not be a member of VA Central Office staff, a current chairperson of another CSP study (unless granted a waiver by VACO), nor function as the Study Biostatistician/Epidemiologist. It is not advisable to be concurrently Study Chairperson and Site Investigator of another CSP study. The Study Chairperson may not serve as the Site Investigator at his/her own facility and should not be the director of a designated study central laboratory.

There are a number of steps to be taken before patient intake can begin. These should be done in a timely fashion or there will be delay in funding and/or patient intake. These steps include:

- Revision of study protocol incorporating changes suggested by CSSMRB.
- Final selection of participating medical centers.
- Final review and approval of study data forms, and submission for OMB approval.
- Collaboration with CSPCC/ERIC on development of an Operations Manual.
- Collaboration with CSPCRPCC on pharmaceutical and FDA issues and on SMART GCP support services.
- Nomination of members of the Executive Committee.
- Nomination of members of the Data Monitoring Committee.
- Hiring support staff at the Chairperson's Office.
- Selection of core labs, if required.
- Planning for acquisition of equipment and/or supplies.
- Planning of organizational meeting.
- Printing and distribution of the study data forms.
- Planning for study newsletter.
- If applicable, any agreements and/or contracts with industry and/or other federal agencies need to be finalized prior to the organizational meeting.

B. Selecting the Participating VA Medical Centers

Selection is based on indication of patient availability and other information. When the medical centers are identified, the Study Chairperson sends the list of nominations to the CSPCC/ERIC Director. The CSPCC/ERIC Director will ensure that all potential participating VA centers have a Federal Wide Assurance (FWA) from the Office for Human Research Protections after review by the VA's Office of Research Oversight (ORO). Only VA centers having a FWA will be allowed to participate.

C. Review by Participating Medical Centers

When the Principal Proponent has been notified that funding is available, the CSPCC/ERIC will then send the study protocol to the selected medical centers for their review. In order to avoid delay, the Site Investigator (SI) should schedule the Research and Development (R&D) Committee and Subcommittee on Human Studies/IRB reviews (or, for non-VA centers, the IRB review) as soon as possible.

Comments, criticisms and/or suggestions for improvement of the proposal by the local R&D Committees are welcomed by the Cooperative Studies Program and will be seriously considered by study staff in preparing the Operations Manual (the primary procedural guideline for the study). Although some changes may be made, all participating centers must conform to the final protocol requirements as well as the standard policies of the Cooperative Studies Program. In addition to the scientific aspects, the R&D Committee should address questions of feasibility. There must be an individual who is willing to serve as SI and who is eligible to receive research funding (i.e., at least 5/8 VA time or approved by the VA Central Office Eligibility Committee). Usually, the SI will require active support from the SI's service and other services (e.g., Pharmacy, Clinical Laboratory). There must be ready access to patient medical records by CSP representatives to verify data and proper study conduct. There may be a need for space. R&D Committee approval to participate implies that adequate staff, space, and other resources are available and that the medical center is willing to make a commitment to the study.

Recruitment of a sufficient number of patients is often a chronic problem in conducting cooperative studies. If the R&D Committee is aware of any circumstances that would seriously compromise the medical center's ability to contribute their quota of patients, these limitations should be taken into consideration in the review of the proposal (e.g., if there is another CSP study or a local study involving identical or very similar patients).

Although it is the preference of the CSP that a single standard consent form is used at all participating centers, the ultimate responsibility for the welfare of the patient resides at the individual center. The consent form document, developed by the Principal Proponent and approved by the CSPCC /ERIC Human Rights Committee during the planning phase, should be considered as a prototype. If the Subcommittee on Human Studies/IRB from a participating medical center makes suggestions for changes, they will be seriously considered. Similarly, local variations can be incorporated into the prototype document with the approval of the CSPCC/ERIC Director. Major changes must have the approval of the CSPCC/ERIC Human Rights Committee.

Medical centers that approve participation in the study must submit a copy of the minutes indicating approval by their R&D Committee and Subcommittee on Human Studies or local IRB to the CSPCC/ERIC

as soon as they are available. VA Form 10-1223 should be used for reporting approval by the Subcommittee on Human Studies. If the study involves drugs/devices, a copy of these minutes must be sent to the CSPCRPCC Director by the CSPCC/ERIC before any study agents can be distributed to the participating medical centers. A VA Form 10-9012 (Investigational Drug Information Record) must be completed and forwarded to the local Pharmacy Service by the SI prior to dispensing study drugs. Additionally, if the study is conducted under an IND, completion of VA Form 1572 (Statement of Investigator) will be required. In the case of an IDE, a signed agreement from the SI is required.

If there has been a significant delay (more than 12 months) between approval by the local R&D Committee and the Subcommittee on Human Studies/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. In these instances, the CSPCC/ERIC Human Rights Committee will also need to conduct a re-review.

After a medical center 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 CSPCC/ERIC Director that is signed by the Medical Center Director. Any deviation from the approved budget requires the endorsement of the CSPCC/ERIC Director and the approval of the Director, CSR&D.

Enrolling patients from VAMCs that are not a primary study site (i.e., satellite sites) may be approved by the Director, CSR&D, under special circumstances. However, in general, consideration of new patients from satellite sites is discouraged. The Director, CSPCC/ERIC must submit a written request with justification for considering satellite patients to the Director, CSR&D for approval. If approved, the CSPCC/ERIC must ensure that the satellite site has a valid FWA. No study-related activities can occur at sites without a valid FWA. If the proposed satellite site has a valid FWA, then the CSPCC/ERIC must ensure that both the primary and satellite IRB and R&D Committees approve the study protocol and plan for sharing the research-related activities. A satellite site investigator must be identified as the responsible party at the satellite site and must complete all GCP and human subjects research training. The informed consent must also be modified to reflect the role of the satellite site in the study. For FDA-registered trials, the names of the satellite site and its investigator(s) must be added to the FDA Form 1572 or Investigator's Signed Agreement of the primary site.

D. Forms Approval and Printing

Forms approval and printing are initiated soon after the CSPCC is advised that a study is likely to be funded. A final review of the forms should be conducted before they are sent to VA Central Office for approval. The Study Biostatistician/Epidemiologist will initiate this review with the Study Chairperson, the Study CRP, and relevant members of the CSPCC/ERIC. The Study Chairperson may visit the CSPCC/ERIC for the review. A one page abstract will always need to be submitted to CSP HQ. CSP HQ will make a determination on whether OMB review is required based on guidance/instructions provided by the VHA OMB liaison. If OMB requires a full review of the forms, the Study Biostatistician/Epidemiologist prepares the request for VA and OMB approval. If time permits, prospective Site Investigators should be asked to review the forms prior to the approval and printing stage, since it becomes progressively more difficult to make changes later.

Some studies may use electronic forms in an electronic data capture system. In this case, the CSPCC will develop the system and provide the appropriate equipment and training to the participating centers.

E. The Study Operations Manual and Training Materials

After funding is approved, the Study Chairperson, Study Biostatistician/Epidemiologist, Study CRP, and other study members prepare an Operations Manual. This manual is used by the study team at each participating medical center and is intended to ensure that the study procedures are followed as uniformly as possible. 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 should be included, as should a section on complying with Good Clinical Practices. In addition, the SI's responsibilities to the Pharmacy Service concerning prescription writing or drug ordering, the Pharmacy Service's responsibility to the SI and other items germane to the conduct of the study are clearly defined. If appropriate, the Operations Manual should also include instructions for using investigational or study supplies. The manual frequently consists of two volumes: Volume I is typed, assembled and distributed by the CSPCC; Volume II is typed, assembled and distributed by the CSPCRPCC. Other training materials may need to be prepared for the Organizational Meeting; e.g., videotapes or demonstrations.

F. Equipment-Intensive Studies

Studies that are equipment-intensive will be conducted in three phases:

- Install equipment in Study Chairperson's office. Evaluate equipment.
- Install equipment at two to three additional medical centers. Continue evaluation of equipment and monitor patient recruitment.
- Install equipment in all remaining centers.

G. Hiring and Training of Study Personnel

CSP study personnel are generally hired on term appointments. When an emergency situation arises concerning FTE shortages or cuts, use of an Intergovernmental Personnel Act (IPA) (through a non-profit organization or a service contract through the Acquisition & Materiel Management Service) will be used. The CSPCC needs to be fully informed of all IPA agreements. Approval authority for IPA agreements is delegated at the local VA medical facility level.

Training sessions for study personnel must take place before patient entry begins, usually at the time of the initial organizational meeting. Good Clinical Practice training will be provided at the organizational meeting by SMART. All SIs and Site Study Coordinators must document training in human ethics in clinical trials and HIPAA prior to study start-up at their site. SIs and study coordinators must meet the VA-mandated training requirements to participate in CSP trials, i.e., annual training in Human Subject Protections, Good Clinical Practices and VHA Privacy training. Additionally, site study coordinators are required to attend the live GCP course presented by SMART. This course is offered at the organizational

meeting, but any coordinator unable to attend the meeting or joining the trial after the meeting must take the GCP course available on the ORD website (http://www1.va.gov/resdev/programs/pride/training/gcp-hsp.cfm) and must attend the SMART training within 90 days of joining the trial.

During the patient recruitment phase of the study, staffing will vary depending on estimated workload. Generally, many participating centers 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.

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

The CSPCRPCC will determine if an IND or IDE is required and provide the necessary guidance regarding required FDA approvals and submissions. In almost all instances, the VA CSP is designated as the sponsor of the IND/IDE. In addition, the Study Chairperson and every investigator who will be participating in the study must be registered with the FDA and meet specific requirements. The CSPCRPCC will coordinate the preparation and submission of the IND or IDE in accordance with FDA requirements. The Study CRP will be the CSP representative to the FDA and will work closely with the Study Chairperson to resolve FDA-related issues and problems regarding the study. All correspondence with the FDA from study personnel is directed through the Study CRP.

The FDA will notify the sponsor in writing of the date they receive 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 on file at the CSPCRPCC before study articles can be distributed to participating medical centers. The CSPCRPCC will obtain a signed FDA Form 1572 (Statement of Investigator) or device agreement from the Study Chairperson and each SI as soon as the participating medical centers are selected. Drugs/devices cannot be shipped until the signed documents have been received by the CSPCRPCC. Routine updating of FDA Form 1572 will be coordinated on behalf of the sponsor by the CSPCRPCC at required intervals.

When a pharmaceutical company or device manufacturer acts as a sponsor of a study, the company accepts the responsibility for filing the IND or IDE with the FDA. In these cases, CSP requires a letter from the pharmaceutical company or manufacturer identifying their FDA assigned IND or IDE number. In such cases, a Cooperative Research and Development Agreement is also advisable to delineate all requirements of the CSP that are necessary to enable the company to meet its obligations as sponsor of the IND or IDE.

I. Organizational/Training Meeting

Prior to the recruitment of patients, all studies will be funded for at least one organizational/training meeting. These meetings are generally two to four days, but can be longer for more complicated studies. All study personnel, including Site Investigators, Site Study Coordinators, the Study Chairperson and his/her staff, CSPCC/ERIC Study staff, CSPCRPCC Study staff, a SMART representative, and Executive Committee members, will attend the meeting. The primary purposes of the meeting are: 1) to ensure that everyone knows the protocol and what is expected of them, 2) to review the study forms to ensure that everyone knows how to complete them, 3) to review VA and CSP policies on conducting research, and 4)

to discuss what SIs and Research/Study Coordinators need to do to be in compliance with Good Clinical Practices. If special medical techniques or data collection forms are to be used, training on these techniques or use of the forms will be done at this meeting.

The CSPCC/ERIC Director, or Study Biostatistician/Epidemiologist will review VA CSP policies and regulations while a SMART representative will review GCP. The majority of the time, however, will be spent in reviewing the protocol and forms and providing necessary training. The Study Chairperson, his/her National Study Coordinator, the Study Biostatistician/Epidemiologist and CSPCC/ERIC staff, and the Study CRP and CSPCRPCC staff will generally provide this review and training. When there is an economic analysis component, the health economics staff will provide review and training concerning economics data forms.

Also, held in conjunction with this meeting will be a one-day training course on Good Clinical Practices presented by SMART. Coordinators will be required to attend this course. SIs should attend the course but may be excused from attending if they submit documentation of equivalent training obtained elsewhere.

Meeting/travel arrangements are the same as those described in Section V.C.

J. Recruitment Strategies

One strategy that has worked in the past is to develop a publicity campaign. These campaigns may be limited to the local hospital using posters and pamphlets to remind physicians and staff of the study and to make potential subjects aware of the study or they may include advertising in the local media such as radio and newspapers. Assistance in developing publicity materials required can be obtained from VA R&D Communications Office through VA HQ. It is important that the appropriate authorities in the local medical center have approved the publicity plan and that all advertisements have R&D Committee and Human Subjects Subcommittee/Institutional Review Board approval and that such approvals are clearly documented in the investigators' files. The publicity plan must also be reviewed and approved by the Study Chairperson and the appropriate CSPCC/ERIC. Study personnel may not contact veterans directly by phone.

V. CONDUCTING A CSP STUDY

A. CSP Study Management and Monitoring

The Director, CSR&D delegates responsibility for each CSP study to the respective Directors, CSPCC/ERIC who will in turn keep him fully informed and will forward to him those actions or recommendations that require his approval. Each study will be considered in a probationary status for the first year. Towards the end of this period, the CSPCC/ERIC Director will provide a detailed report of progress to the Director, CSR&D with special attention to patient accrual and/or problems that might affect the successful completion of the study. The Director, CSR&D may discuss the contents of this report with the Study Chairperson and the CSPCC/ERIC Director in writing or by telephone 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.

Five groups, in addition to the SMART Review and Monitoring Teams, share the responsibility for conducting and/or monitoring a CSP Study: the Study Group, the Executive Committee, the Data Monitoring Committee, the CSPCC Human Rights Committee and the Cooperative Studies Scientific Merit Review Board. Before patient 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 patient intake begins, appropriate progress reports are distributed to these committees by the CSPCC at least three weeks before regularly scheduled meetings, and interim updates are provided between meetings. Studies experiencing major problems or requesting major changes are reviewed by CSSMRB as needed.

The standard schedule of meetings for the Study Group, Executive Committee and Data Monitoring Committee consists of an initial meeting for organizational, informational and training purposes prior to patient intake, a meeting approximately nine months after the initiation of patient 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 patient follow-up is less than six months.

1. Study Group

The Study Group is chaired by the Study Chairperson and includes the Study Biostatistician/Epidemiologist, the Study CRP, the Study Health Economist, the CSP Project Manager, the National Study Coordinator, all Site Investigators and any permanent consultants to the study. At the Organizational Meeting, the Study Biostatistician/Epidemiologist or CSPCC/ERIC Director will make a presentation on research ethics and inform the group of routine procedures that are required by the CSP such as HRC site visits. Two to three weeks prior to Study Group meetings, the Study Biostatistician/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 the study. Results of blinded data related to study endpoints are not discussed with this group. The Study Coordinator(s) from each center and other CSP personnel may also attend these meetings. It is the Study Chairperson's responsibility to write a report of each Study Group meeting within three weeks of the meeting, and send it to the CSPCC/ERIC Director for distribution. All SIs and study consultants will be required to submit a Statement of Disclosure (Appendix B). Site Investigators will also be required to submit an Agreement to Participate which clearly states what is expected from them as a study participant.

2. Executive Committee

The Executive Committee, chaired by the Study Chairperson, consists of six to ten members and includes the Study Chairperson, the Study Biostatistician/Epidemiologist, the CSPCC/ERIC Project Manager, the Study Health Economist (if any), the Study CRP, the head(s) of any special central support unit(s) related to the study, the National Study Coordinator, study coordinator from the Chairperson's Office, two or three Site Investigators, and selected consultants when necessary. If there are no more than five investigators, 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. It decides on all proposed changes in the study and on any subprotocols/substudies or use of the study data, 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 numbers five to eight members: experts in the subject matter of the study, one or two independent biostatisticians, and other appropriate technical or scientific specialists. Any study that involves patient intervention will have a DMC. When there is an economic analysis component, the Board will include an expert in health economics. The Study Chairperson and the Study Biostatistician/Epidemiologist are nonvoting study representatives and the Director, CSR&D and the CSPCC/ERIC Director are nonvoting CSP representatives. Meetings of the DMC are closed meetings so that additional attendees, such as pharmaceutical representatives, may not attend these sessions unless specifically invited by the DMC for the purpose of clarifying specific issues for the DMC. The Study Chairperson 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 Director, CSPCC/ERIC, and/or Director, CSR&D.

It is the responsibility of the Study Chairperson to nominate members for this Board to the CSPCC/ERIC Director. The Study Biostatistician/Epidemiologist and/or the CSPCC/ERIC Director usually will assist the Study Chairperson in selecting biostatistician nominations. Alternate nominations for any of the members may be suggested by the Director, CSR&D.

The Study Chairperson and the Study Biostatistician/Epidemiologist should not personally contact the nominees. The CSPCC/ERIC Director will write or call those nominated to determine their willingness to serve on the Board and request a CV before forwarding the list to CSP HQ. The Director, CSR&D will make the final selection and issue a formal letter of appointment. A complete copy of the study protocol and a copy of the CSP *Guidelines* will be provided to each member by the CSPCC/ERIC Director. The term of appointment will extend through the last day of patient follow-up or as specified in the protocol. If the services of Board members are required after that time, it may be on an *ad hoc* basis.

Data Monitoring Committee members are highly qualified by background, training, experience and knowledge in relevant disciplines and are responsible for monitoring, evaluating and making recommendations concerning all aspects of the ongoing study. Members should be informed of the CSP policy regarding conflict of interest. Conflict of interest may exist if a member has a substantial financial interest in an organization that could be significantly affected by the conduct or conclusion of the study; if the member serves as an officer of such an organization; or if the member has a consultancy or similar contractual relationship with such an organization. It is important to recognize that conflict of interest applies if these interests or relationships exist or appear to exist. A person who participated in the planning of the study or who is from the same institution as those playing key roles in the study should not be nominated. Persons from industry should not be nominated for studies involving the evaluations of industrial products of potential commercial value. It is the direct responsibility of the CSPCC/ERIC Director to see that nominations put forth are in accordance with the true spirit and intent of CSP policy. DMC members must submit a statement of disclosure (see Appendix B).

The Data Monitoring Committee 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 thereafter. 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 Board maintains the confidentiality of interim results that are presented at scheduled meetings.

The major responsibilities of the Data Monitoring Committee are:

- To consider the question of whether the study should continue. Inherent in this question are considerations such as patient accrual, overall study progress, treatment efficacy, adverse effects and patient safety, futility, and proper monitoring and reporting by the CSPCC or other support units in the study.

- To assess the performance of each participating center and make appropriate recommendations regarding continuation, probationary status or termination.

- To review and provide recommendations regarding protocol changes and subprotocols/substudies.

As part of the study proposal, the Study Biostatistician/Epidemiologist prepares an outline of reporting procedures including prototype tables and graphs that will be used to present study data of various kinds (Appendix BRDP of the study protocol). The Data Monitoring Committee is encouraged to provide a critical review of these proposed biostatistical monitoring procedures at their first meeting and to make recommendations or suggestions for improvement. At subsequent meetings, they may request new or different data displays. The Study Biostatistician/Epidemiologist prepares and distributes a report two-three weeks prior to meetings and at least one interim report between meetings. If data provided to the DMC are unblinded, tables containing these data will not be provided to the Study Chairperson, who must remain blinded. At the discretion of the DMC, the Study Chairperson may be provided with unblinded baseline data. The Study Chairperson reviews the progress of the study and informs the Board of all proposed changes in the protocol, data collection forms or in plans for analyses. After a full discussion of all study issues, the Board meets in Executive (closed) Session (with the Study Biostatistician/Epidemiologist and CSP representatives) to review unblinded data and formulate recommendations. The DMC may choose to meet in an Executive Session without study/CSP representatives to formulate recommendations.

At their first meeting, the members of the Data Monitoring Committee select a Chairperson with the assistance of the CSPCC/ERIC Director. In addition to chairing each meeting, it will be this individual's responsibility to prepare a brief report of each meeting and send it to the CSPCC Director within three weeks. The report states those actions that the Board believes are necessary or highly desirable. These are phrased as recommendations to the Director, CSR&D. The DMC may also make suggestions that are not intended to be binding but are to be considered by the study representatives. When the report is received at the CSPCC, the Study Biostatistician/Epidemiologist will be asked to consult with the Study Chairperson and indicate how the recommendations will be implemented. The CSPCC/ERIC Director will concur or add whatever comments s/he wishes, and forward the report to the Director, CSR&D with additional distribution to the Study Chairperson (deleting sections reporting unblinded data), the Data Monitoring Committee and the CSPCRPCC Director. After the meeting, the Study Biostatistician/Epidemiologist should telephone the Director, CSR&D's office in order to make an informal report. DMC reports are confidential and will not be distributed to industry collaborators, SIs, local Human Subjects Subcommittees/IRBs, etc.

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/IRBs of the participating centers informing them of any safety issues or lack of safety issues in the study. Since the Human Subject Subcommittees/IRBs will not have access to unblinded data results, the report will provide them some assurance that the DMC is monitoring the safety of study patients 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.

During the course of the study, the Study Chairperson and other members of the Study Group, including the Study Biostatistician/Epidemiologist, may not consult with DMC members without the approval of the CSPCC/ERIC Director.

An Office of the General Counsel (OGC) memorandum dated July 7, 1975 indicated that DMC members, when meeting on a study, are considered VA employees and, as such, are entitled to

liability coverage under either 38 U.S.C. 4116 or the Doctrine of Official Immunity. This decision also covers the liability of non-VA members of the Executive Committee, the Human Rights Committee and the Study Group. Efforts are currently underway to determine whether policies or statutes have since changed which may affect liability coverage.

4. Human Rights Committee

In addition to reviewing the protocol for human rights issues prior to study funding, this Committee is responsible for ensuring that patients' rights and welfare are protected during the course of the study. At least once a year during the course of the study, the Human Rights Committee meets with the Data Monitoring Committee to participate in that part of the meeting that deals with patients' rights and welfare. Alternatively, if the DMC and Human Rights Committee do not meet at the same time, a HRC representative may attend the DMC meeting or the Study Chairperson can attend the annual HRC review to provide an update of study progress. It is the responsibility of the Study Biostatistician/Epidemiologist and the Study Chairperson to provide the Committee with the appropriate information, including some or all of the data provided to the Data Monitoring Committee and a summary of the progress of the study written in lay language. The Human Rights Committee Chairperson is responsible for writing a report of the meeting within three weeks of the meeting. This report should be sent to the CSPCC/ERIC Director who will make the proper distribution. In rare instances where the HRC is blinded and the DMC is not (such as agreements between CSP and other agencies in interagency agreement funded studies), a member of the HRC may be appointed to the DMC.

Each fiscal year, three site visits to participating medical centers are conducted by members of the CSPCC Human Rights Committee, accompanied by a member of the CSPCC. The purpose of these visits is to determine whether the human rights aspects of the studies are receiving proper attention. If possible, the Human Rights Committee member will observe at least one informed consent being given and will talk with study patients about their participation in that study. Upon returning from the site visit, the member will write a report of the visit and send it to the CSPCC Director. The report should <u>not</u> identify the patient(s) by name. Since each CSPCC has more than three ongoing studies, a medical center in each study may not be visited each year. However, at least one Human Rights Committee 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 requires the active cooperation of many individuals. Since participation in a VA 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 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 medical center is prepared to provide the necessary and appropriate support. Involvement in a CSP study is demanding. A Study Chairperson and the Site Investigators must be willing and able to devote time and energy to its success.

Participants should recognize from the outset of a CSP study that funding of an approved study would not be continued in the absence of objectively demonstrated satisfactory performance (e.g., number of patients enrolled, quality of data acquisition, adherence to Good Clinical Practices, etc.). The Study Chairperson and Study Biostatistician/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 Data Monitoring Committee 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 he determines that the study is not achieving its objective.

It is the responsibility of the CSPCC/ERIC through the SI to inform patients if similar studies conducted by other agencies have been stopped prematurely, and the Data Monitoring Committee has recommended continuation of the CSP study. In this situation, patients should be notified, by written communication, of the most recent information that has been made available to the public. Site Investigators and study personnel at each participating medical center will be sent a letter to distribute to study patients after obtaining IRB approval.

C. Meeting/Travel Arrangements

To initiate one of the regularly scheduled Study Group/Executive Committee meetings, the Study Chairperson should contact the Study Biostatistician/Epidemiologist at least six to eight weeks in advance of the proposed meeting date. However, as much as three to six months advance planning may be necessary to schedule hotel availability. The CSPCC Administrative Officer or study team will select three sites with reasonable accommodations that minimize the cost of travel and per diem and which are convenient for travelers to reach, and calculate travel costs for each of them. The selected location, the estimated travel budget must be within the limit of the study budget and have the concurrence of the CSPCC/ERIC Director. Exceptions to these rules for selecting meeting sites will only be granted if there are unique and valid reasons to do so, such as availability of special laboratory facilities for training purposes. If plans are to have more than two participants per site attend or costs exceed original budget projections, special written approval of the Director, CSR&D is required. Meeting attendees may be allowed to attend a national meeting in conjunction with a study meeting under the following conditions: the CSP meeting must be scheduled immediately before or after the national meeting (not concurrent with); the national meeting must occur reasonably close to the regularly scheduled meeting time of the study; the CSP will not be responsible for extra per diem or fees associated with attending the national meeting; costs in excess of those projected for the selected site will need to be assumed by the participants.

The Data Monitoring Committee meets either in the vicinity of the CSPCC in order to facilitate the Human Rights Committee review or at a convenient location. However, the initial meeting of the DMC may be held in Washington, D.C. if the Director, CSR&D is to attend. If the DMC and Human Rights Committee do not meet at the same time, a HRC representative may attend the DMC meeting or the Study Chairperson may attend a full meeting of the HRC.

Funding for travel to meetings of the Study Group, Executive Committee, Data Monitoring Committee, and other authorized CSP study activities will be provided from CSP HQ centrally directed travel funds in accordance with the study budget. When the meeting has been approved, the CSPCC will notify all expected attendees and the appropriate ACOS/R&D offices and give them the necessary details. A scheduled meeting will be postponed if the expected attendance falls below 80% of those that are authorized to attend. Attendees should receive the agenda and any materials to be reviewed at the meeting two to three weeks prior to the scheduled meeting date.

It should be emphasized that all participants, including the Data Monitoring Committee and CSPCC personnel, are dealing with privileged information and that confidentiality must be maintained.

D. Protocol Changes

Subsequent to CSSMRB approval, no person or group including the Study Chairperson, Study Biostatistician/Epidemiologist, the Study Group, the Study Health Economist, the Executive Committee, the Data Monitoring Committee and the Study CRP (if the study involves drugs or devices), may unilaterally or collectively make study protocol changes without the appropriate approvals. Authorizations from the Study Chairperson to deviate from protocol in justifiable instances do not constitute protocol changes and do not imply authorization beyond the immediate instances of exception.

The Study Chairperson, Study Biostatistician/Epidemiologist, Study CRP, and the Study Health Economist should discuss proposed study protocol changes among themselves before presenting such changes for approval. The Study Biostatistician/Epidemiologist, Study CRP, and the Study Health Economist must prepare an "Executive Summary of Proposed Study Protocol Change" form for their respective Centers that delineates 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, the HRC, and the Data Monitoring Committee. In all cases, the involved Center Directors (CSPCC/ERIC and CSPCRPCC) and the Director, CSR&D must approve proposed study protocol changes. The Director, CSR&D will make the decision whether or not the proposed study protocol changes require the approval of CSSMRB.

After the Director, CSR&D or CSSMRB (when required) approves the proposed change, the ACOS/R&D at each participating medical center is informed, since the protocol changes may require resubmission to the local R&D and Human Subjects Subcommittee/IRBs. If the study is being conducted under an IND/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 the Director, CSR&D. Major changes may require another CSSMRB review. Requests for additional funding at participating centers must be initiated by the SI through the office of the ACOS/R&D at the center, with the appropriate justification and delineation of needs including personnel (FTE, GS grade, dollar costs), equipment and operating costs. This request should be forwarded to the Study Chairperson for approval and then to the CSPCC/ERIC Director. If the CSPCC/ERIC Director recommends approval and the Director, CSR&D concurs, the office

of the ACOS/R&D and the SI of the participating medical center will be informed that an official request may be initiated through the Medical Center Director and the VISN Director.

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. Unused funds and FTE are to be returned to CSP HQ on an annual (or quarterly if determined necessary) basis.

Study extensions that require less than a 5% increase in the approved study budget and the lesser of a one year increase or 25% increase in the originally planned study duration will be reviewed administratively by the Director, CSR&D for approval. Requests for extensions that do not meet these criteria will require review by CSSMRB and final approval by the Director, CSR&D.

F. Ethical Considerations

1. Informed Consent

All patients must sign and date an informed consent form to participate in a CSP study. Each patient must be permitted to read (or have read to him/her) the informed consent form in order to have an understanding of the study before discussing it with the investigator or his/her designee. In discussing the study with the patient, the investigator may provide additional details beyond those contained in the consent forms, but no substantive addition, deletion, or modification to these statements is allowed. This document is the tangible evidence of what the investigator tells a patient. A copy is given to the patient when he or she signs the forms. If anesthesia, surgery, or other procedures are to be used, consent must also be obtained on an SF 522. The consent form may include the HIPAA authorization. If it does not, then a separate signed and dated HIPAA authorization form must also be completed. For policy regarding who may consent to the participation of patients with impaired decision-making capacity, refer to VHA Handbook 1200.5 (11) – Research Involving Human Subjects with Surrogate Consent.

Failure to obtain informed consent will result in disciplinary sanctions by the Director, CSR&D and could result in the dismissal of the SI. Data from patients without a properly signed and dated informed consent form will be excluded from all study reports. The consent form must be discussed with the patient by the SI or his/her designee and signatures must be witnessed by a person unrelated to the study. This is a face-to-face discussion unless other provisions are specified in the protocol. While the SI need not be present while the 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. A dated progress note in the patient's medical chart indicating that the patient has given informed consent and by whom and that the patient has entered the study must also be completed.

A copy of each patient's signed informed consent document must be sent to the CSPCC to verify that every patient has given consent. A copy of the signed consent form must be provided to the patient. Copies of each consent must also be sent to the local VAMC pharmacy in the case of studies involving pharmaceuticals. The original consent form is retained in the investigator study file. When non-VA centers are participating in a CSP coordinated study and the non-VA center's Institutional Review Board has a policy of not allowing informed consent forms to be sent off station, a letter signed by the Site Investigator stating that the patient has signed a consent form and giving the date of the signing will be acceptable in place of the actual signed informed consent form.

Several elements MUST be included in the consent document according to FDA and/or VA regulations. They are included in the consent form checklist that CSP centers can provide. Although local or central IRBs may require additional requirements, the checklist elements must remain in the consent. The minimal requirements for consent signatures as outlined by FDA and VA are: patient or patient representative witness (two if subject can only sign by mark: VHA 1004.1 7C) and person obtaining consent. Site Investigator signature is no longer required, however, if it is on the consent signature list, it must be completed and should be done so within a reasonable timeframe (CSP recommends within 72 hours of patient signature).

2. Patient Confidentiality

It is CSP policy to protect the confidentiality of patient study data to the extent permitted by law. In order to protect patient confidentiality, patient identifiers, such as names or social security numbers, will not routinely be placed on study data forms. A unique study generated patient identifier number will be assigned to each patient. This unique number will be placed on each study form to allow different forms for a patient to be identified as belonging to him/her. In addition, some type of name code (e.g., initial of first name and last three letters of last name) may be entered on each form to provide a means of checking that the patient's study number on the form is correct. That is, a data form will be accepted as being from a specific patient only if the unique patient study number and the name code (if used) match.

Patient identifying information will be maintained at the participating sites. However, in many studies, it may be necessary for the CSPCC/ERIC to have patient identifying information such as addresses or social security numbers. Examples of such circumstances include the need to obtain data from VA central data bases, long-term follow-up of patients by the CSPCC/ERIC or letters/surveys that are mailed to patients from the CSPCC/ERIC. When such information is required by the CSPCC/ERIC, it must be provided on a separate form or recorded on VA Form 10-1086 (Informed Consent), which is submitted to the CSPCC/ERIC. This information must be provided to the CSPCC/ERIC according to the protocol's data security plan and/or the local medical center's data security policy, if the medical center has additional requirements. At the CSPCC/ERIC, patient identifier information, both paper and electronic versions, will be kept in separate files away from the main data files in order to make it more difficult for non-authorized personnel to link patient identifiers to patient study data.

When CSP representatives visit participating sites, access to patient medical records must be provided for quality assurance purposes. Permission for ready access to health information must be included in the consent form in accordance with HIPAA provisions so as not to violate patient confidentiality.

3. Yearly Medical Center Reviews

It is VA policy that all studies involving humans must be reviewed at least annually by the medical center's R&D Committee and Human Subjects Subcommittee/Institutional Review Board. These annual reviews are to be done by the anniversary of the initial reviews by these committees and not necessarily by the anniversary of the start of patient recruitment. Reviews may be conducted more frequently than yearly at the discretion of the various committees. It is both the Site Investigator's and the R&D

Committee/Human Subjects Subcommittee/Institutional Review Board's responsibility to ensure that these yearly reviews occur.

For VA Cooperative Studies, the CSPCC/ERIC will notify the Site Investigators, with a copy to the ACOS for R&D, of an impending review in advance to facilitate scheduling with the appropriate committee. The CSPCC/ERIC will also provide the Investigators with any material requested for this yearly review, except for unblinded outcome data. The CSPCC/ERIC 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., Institutional Review Board 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 of the review and the outcome of the review, will be acceptable. If the written notification (minutes or Chairperson letter) of the review is not received at the CSPCC/ERIC by the anniversary date, the participating center will be placed on probation. Probation in this instance will mean that the center's participation including the ability to randomize patients will be suspended until the appropriate documentation of the yearly review has been received at the CSPCC/ERIC. Sites will need to care for patients already randomized to ensure patient safety. If the written notification is not received within 10 days of the anniversary date, then CSP HQ will be notified that the center is delinquent with their review.

G. Data Collection, Editing and Patient Entry Policy

Data are to be collected only on VA (and if necessary, OMB) approved data forms supplied by the CSPCC/ERIC or the CSPCRPCC. The SI is responsible for assuring the accuracy and completeness of all data submitted to the CSPCC/ERIC. In general, data reported on the forms should be reviewed by the SI at each medical center before being sent to the CSPCC/ERIC for data processing review and assessment. 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 Chairperson for medical review. Some studies may utilize electronic forms and distributed data entry. In these cases, data are entered at the participating hospital and submitted to the CSPCC/ERIC electronically using appropriate data security measures. Review processes for such data will vary depending on individual study requirements.

It is the CSP policy that a patient be enrolled in only one drug/device intervention, randomized clinical trial at any one time. It is permissible for patients to be in other non-interventional trials while participating in a CSP trial (e.g., surveys, long-term follow-up cohort studies, etc.). Exemptions to the policy of patients participating in only one intervention trial will be allowed for individual patients on a case-by-case or a study-by-study basis. Exemptions require the agreement in writing of all of the following individuals or groups: (1) the Site Investigators of both studies; (2) the Study Chairmen of the involved studies; (3) the appropriate CSPCC/ERIC Director(s); and (4) the local R&D Committee and Human Subjects Subcommittee/Institutional Review Board. Once all of the signed letters have been obtained, the CSPCC/ERIC Director(s) will prepare a cover letter to the Director, CSR&D certifying that all of the appropriate signatures have been obtained. Only after the Director, CSR&D has given final approval, will the patient be allowed to participate in both studies. The guiding principles for granting an exemption should be (1) to do what is best for the patient and (2) to protect the integrity of the involved studies.

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

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

1. Definitions:

- Adverse Device Effect (ADE) - Any adverse effect/event caused by or associated with the use of a device.
- Adverse Event (AE) - Any untoward medical occurrence in a study patient administered a pharmacological product or participating in a clinical trial. The AE does not necessarily have to have a causal relationship with the pharmacological product, study intervention or assessment. An AE can, therefore, be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medicinal investigational) product.
- Serious Adverse Event (SAE) - Any adverse event or reaction in study patients that results in 1) death, 2) a life threatening experience, 3) an inpatient hospitalization or prolongation of an existing hospitalization, 4) a persistent or significant disability/incapacity, 5) a congenital anomaly/birth defect, or 6) any other condition that, based on medical judgment, may jeopardize the patient and requires medical or surgical treatment to prevent one of the above outcomes.
- Unanticipated Adverse Device Effect (UADE) - Any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, or problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of patients.

2. Procedures

Procedures for collecting and reporting of all AEs/ADEs are determined by the study planning committee and outlined in the study protocol. Exact procedures for reporting AEs/ADEs are to be specified in the study Operations Manual. For studies with an IND or IDE, annual reports of AEs/SAEs/ADEs/UADEs are provided to the Food and Drug Administration.

The Site Investigator must report all SAEs/UADEs to the appropriate study office(s) (CSPCRPCC, CSPCC/ERIC, Study Chairman's Office, ACOS/R&D, and/or Medical Monitor's Office) using the format of communication (FDA Form 3500A or study specific SAE/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/UADE. Exceptions to this policy will be those SAEs/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 for following local IRB/R&D Committee requirements for reporting SAEs/UADEs or other adverse events and notifying all appropriate individuals at their facility. Documentation of such communications shall be kept in the Investigator Study File.

The CSPCC/ERIC is responsible for summary reporting of SAEs/UADEs to the DMC and Human Rights Committee as part of the study progress reports, as well as those individual SAEs/UADEs that the DMC and HRC have decided that they want to be notified of. The CSPCRPCC Director will work with the CSPCC/ERIC Director to inform the Director, CSR&D of SAEs/UADEs reported to FDA or other sensitive adverse events that the Director, CSR&D needs made to be aware of. The CSPCRPCC Director or CSPCC/ERIC Director, as appropriate, should also verify with the SI that the local administration (ACOS for R&D, Chief of Staff, Hospital Administration) has also been notified. Events reported to the Director, CSR&D will usually be done after consultation with the Study Chairperson. Notification to the Director, CSR&D should occur within 72 hours of the CSPCC/ERIC and CSPCRPCC Directors being notified.

When SAEs/UADEs or other sensitive adverse events are reported to the CSR&D, the SI is responsible for notifying all appropriate individuals at their facility according to local guidelines and timeframes for reporting adverse events in research (cf. VHA Handbook 1200.5). The SI shall cooperate with individuals at the local institution to determine responsibilities for reporting to the Office of Research Oversight (cf. VHA Handbook 1058.1).

I. Breaking Study Blind

Many CSP studies involving drugs are double-blind studies in which neither the patient nor the SI knows which drug the patient is receiving. Emergency drug code envelopes are prepared by the CSPCC/ERIC or CSPCRPCC and shipped with the study drugs to the Pharmacy Service of the participating medical center prior to the study starting. Each envelope is numbered with a unique patient randomization number and contains the treatment assignment for that patient. These envelopes are placed in the custody of the Pharmacy Service 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 medical management of the patient. In such an emergency, the Pharmacy Service may open the envelope and reveal the treatment assignment for a given patient to the SI. However, before doing so, the SI and the Pharmacy Service must comply with protocol procedures. Such procedures often include contacting the Study Chairperson or Study CRP before breaking the code.

The Pharmacy Service at the participating medical center must notify the Study CRP at the CSPCRPCC 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 CSPCRPCC within 72 hours of the code break. Upon receipt of the code envelope, the CSPCRPCC will immediately inform the Study Biostatistician/Epidemiologist via telephone and send a copy of the envelope, which is filed with the study documents at the CSPCC/ERIC. When the study has been completed (or terminated early), the unopened envelopes must be returned to the CSPCRPCC. The CSPCRPCC will verify that the

envelopes were or were not intact and notify the Study Biostatistician/Epidemiologist of their condition. Drug code envelopes should not be confused with the randomization code envelopes (if used).

J. Release of Information and Data to the Site Investigators/Executive Committee During Study

In order to protect the integrity of the study, to prevent bias in decision making due to knowledge of what has happened with patients already in the study, and to ensure that study results are not prematurely released, the CSPCCs/ERICs with the advice and/or consent of the DMC and Director, CSR&D, strictly control the release of study information and data outside of the CSPCC/ERIC. The CSPCC/ERIC will typically provide Study Chairpersons, Executive Committees, and site investigators 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 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 Chairperson be unblinded to study outcomes in order that the DMC can have a more meaningful discussion with the Chairperson when it is 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.

Data sets will also not be released to requesting individuals until the database is locked. This ensures that all reports of study results will be consistent since investigators will all be using the exact same database. Exceptions to this policy require a DMC recommendation of approval with approval by the Director, CSR&D, or need to be included in the original CSSMRB approved study protocol. Examples of such exceptions include the need to send data outside the CSPCC/ERIC in order to have tests centrally scored, such as a neuropsychological test battery; data from an approved subprotocol that is completed well 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-ups, the use of background variables (after this section of the database has been locked) to prepare manuscripts that are not related to study outcomes.

K. Subprotocols / Substudies

Subprotocols (or substudies) to VA CSP studies are generally discouraged since they add burden to the participating clinic personnel, the CSPCC/ERIC, the patients in the study, and to the Cooperative Studies Program costs. Subprotocols need to be proposed at the time of planning and included in the original proposal and budget reviewed by CSSMRB. In exceptional circumstances, subprotocols requiring the collection of additional data, tests, procedures or biologic samples that are proposed after CSSMRB review will only be entertained by CSP when the entire study is on target with respect to expected accrual and budget. It is important to note that investigators who do not obtain CSP approval prior to the submission of a substudy for outside funding (e.g., NIH and industry) will not be supported by

CSP, and a formal complaint of scientific misconduct may be filed against the investigator by the Program.

However, if a Study Chairperson or SI insists on proposing a subprotocol, the following steps are taken:

1) A formal protocol is written that includes background and justification, objectives, patient selection, informed consent documents, methods, data to be collected, sample size determination, and budget.

2) The subprotocol is reviewed and approved by a majority vote of the study's Executive Committee and Data Monitoring Committee, and the CSPCC Human Rights Committee.

3) The committees reviewing the subprotocol determine if a patient's participation in the subprotocol will interfere with participation in the main CSP study. If it will, the subprotocol must be disapproved because the primary study must always take precedence.

4) If funding is required, non-CSP sources such as National Institutes of Health (NIH), the Agency for Healthcare Research and Quality (AHRQ), VA Research Service's Merit Review Program, private foundations or pharmaceutical companies should first be contacted. Funding requests to CSP should be submitted only when other sources are not available. The Biomedical Laboratory Research & Development Service in conjunction with the Clinical Science Research & Development Services (formerly the Medical Research Service) may review the subprotocols of investigators in CSP trials who want to perform Merit Review Studies related to the CSP trial. Review will be conducted even if the investigator has a separate Merit Review funded study.

5) If non-CSP sources are unavailable and funding is ultimately requested from CSP, the subprotocol will be sent out for scientific review.

6) All oversight committee approvals are conveyed to the Director, CSR&D as recommendations for action. Final approval must be obtained from the Director, CSR&D.

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

8) If approved by the Director, CSR&D, the subprotocol must be reviewed and approved by the R&D and Human Subjects Subcommittee/IRB at each anticipated participating center.

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

L. Newsletter

Study newsletters are prepared and issued regularly by the Study Chairperson, Study Biostatistician/Epidemiologist, CSPCC/ERIC Project Manager and/or the National Study Coordinator. The newsletter is a primary means of keeping participants informed between meetings. The newsletter should contain items of general interest to the participants, progress and performance reports, drug-related issues, and discussion of any problems that arise. The newsletter should not include unblinded data or study results. Distribution will be made by the CSPCC/ERIC and/or Study Chairperson.

M. Site Visits

Site visits by the Study Chairperson, the Study Biostatistician/Epidemiologist, the Study CRP, or other technical experts are not a routine part of CSP studies, but 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 medical center, a site visit may be funded if endorsed by the CSPCC/ERIC Director, approved by the Director, CSR&D, and travel funds are available.

A site visit report should be sent within ten days to the Study Chairperson, who may simply endorse the report, add recommendations or conclusions, or, if necessary, attach a summary of the specific actions recommended by the Executive Committee to correct deficiencies that may have been discovered. The report is then mailed to the CSPCC/ERIC Director for appropriate action.

On occasion, the FDA, as a part of their biomedical compliance monitoring program for sponsor, monitors, and clinical investigators, will visit a CSPCC/ERIC or participating CSP facility. When the FDA announces their impending visit, the SMART is responsible for working closely with the Study Chairperson, the Study CRP, and the individuals being visited to prepare them for the FDA visit. Occasionally, collaborating pharmaceutical companies, whether sponsoring the IND/IDE or not, will wish to conduct site visits to assure compliance with FDA regulations. Such visits must be approved and coordinated by the CSPCC/ERIC.

N. GCP Review/Monitoring Visits/Audits

SMART conducts three types of visits to sites participating in CSP trials, i.e., monitoring visits, GCP site reviews and for-cause audits. The type and frequency of visits conducted for a trial are dependent on the nature of the trial as determined during planning. Each trial is budgeted to receive a program of routine site visits consisting of either monitoring visits or GCP site reviews. CSP trials that are 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., NIDA or an industry partner. Trials not intended to produce data for a FDA submission receive GCP site reviews rather than monitoring visits. These reviews are typically conducted annually, but frequency may be modified based on the patient risk and other characteristics of the trial. At a minimum, each site is visited at the start of the trial to set up GCP tools and practices. A third type of visit is a for-cause audit. For-cause audits are requested by study management when problems in study conduct are known or suspected. The request is made to the Director, CSPCRPCC.

O. Replacement of a SI or Study Chairperson During the Course of a Study

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

If a SI cannot conduct the study until its completion, s/he should give as much advance notice as possible to the Study Chairperson and, if possible, suggest an appropriate replacement. The Study Chairperson should then inform the CSPCC/ERIC Director of the proposed change. If the study involves drugs or devices, the CSPCC/ERIC Director will inform the CSPCRPCC. The local ACOS/R&D should obtain endorsement of the center's R&D Committee for this change and inform the CSPCC/ERIC Director, forwarding the R&D minutes when they are available. IRB approval is also needed. In cases of "emergency," with little or no advance notice, temporary assignment of an investigator by the local center is permissible until the formal replacement process is completed. If no suitable or available replacement for the departing SI exists, the center's participation in the study will be terminated. The CSPCC/ERIC will notify the CSPCRPCC of all SI changes.

If the Study Chairperson cannot continue to direct the study, s/he should inform the CSPCC/ERIC 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 center as the original Chairperson. If the individual accepts the nomination, his/her medical center will be contacted to obtain the approval and support of the 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 Chairperson until the formal process is accomplished. However, if no suitable or available replacement Chairperson exists, the study may be terminated prematurely.

If an IND has been filed for the study, new SIs and/or new participating medical centers will be required to sign FDA Form 1572 for submission to the FDA. In the case of a significant risk device, addition of new participants may not be instituted until approved by the FDA.

P. Putting a Medical Center on Probation

If a participating center is not performing at the expected level, negotiations should take place between the Study Chairperson and the SI. If these discussions fail to correct the problem, the Executive Committee, with an endorsement from the Data Monitoring Committee when possible, can propose to place a participating site on probation. The proposal should be sent to the CSPCC/ERIC Director for a decision. If the CSPCC/ERIC Director concurs, the Study Chairperson should issue a probationary letter which states the reason(s) why the center 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 CSPCC/ERIC, which will forward the letter with a copy to the local ACOS/R&D and to the CSPCRPCC.

After the probationary period has elapsed, the Study Chairperson should issue a follow-up letter to the SI evaluating the performance during the period. The letter should clearly state that the site 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 site from the study. In either case, a letter should be written to the CSPCC/ERIC Director stating the rationale and the proposed action. The CSPCC/ERIC 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 should contact the local ACOS/R&D or write to the Study Chairperson with a copy to the local ACOS/R&D acknowledging the lack of performance and the desire to be dropped.

Q. Early Termination of a Medical Center

During the course of a study, it is sometimes necessary to drop one or more medical centers from the study. Such action may be approved by the CSPCC/ERIC Director, who will then notify CSP HQ. Early termination is usually based on recommendations from the Executive Committee and the Data Monitoring Committee and most often reflects inadequate patient intake or serious noncompliance with Good Clinical Practices. This action will always be taken in response to what is considered the best interests of the study and does not necessarily imply poor performance on the part of the SI or the medical center. The recommendation should be sent to the CSPCC/ERIC Director who will make the final decision and will notify the Director, CSR&D of his decision. The CSPCC/ERIC Director will inform the ACOS/R&D of the medical center and the CSPCRPCC. After that contact, the CSPCC/ERIC Director will write to the SI through the Director and the ACOS/R&D of the participating medical center. The letter will include the date of termination and information to the effect that funding not to exceed 45 days will be provided for the placement of study personnel. In unusual circumstances, a request for extension can be submitted to the Director, CSR&D. Funding for up to an additional 45 days (no more than 90 days total) may be provided if the need is documented and justified. In either case, accumulated annual leave must be included within the limits of salary support. If the study is being conducted under an IND and the early termination is due to non-compliance with regulations, then FDA must also be notified.

Sites who lose their FWA during the course of a study must also be terminated. For patients at sites who lose their FWA during the course of a study, the CSPCC/ERIC must immediately either submit a request to CSP HQ to continue the patients in the study at a participating site that has a valid FWA, IRB approval, and a site investigator who has agreed to assume all study related activities for these patients or develop a plan to safely transition the patients out of the study. The transition plan may be to have no further contact with the patients after informing them that they are being terminated, or amending the protocol to allow the patients to transition out of the study while giving permission only for medical record review at the end of the study.

If equipment purchased for the study is needed at another medical center, the CSPCC/ERIC Director will notify the ACOS/R&D at the terminated center that the equipment is to be transferred. If funds are not available for shipment, a request should be made to the CSPCC/ERIC Director for such purpose. In the event that a new center is not yet identified, the Study Chairperson or Study Biostatistician/Epidemiologist

may wish to have the equipment transferred to his/her center. In the event that the equipment is not needed by the CSP, it will be made available for other use.

Some medical centers are supported by a capitation plan instead of recurring salary and all other funds. If the medical center has not received equipment, medical devices, or supplies to be used for the study, then there would be little or no reason to terminate early. But, if the medical centers involved in a study have equipment, medical devices, or supplies that could be reallocated to a more promising center, then these resources should be reallocated. In this case, the Executive Committee should set the criteria for terminating a capitated center. Once the criteria are established, the process would be the same as a center that receives recurring funds (see above).

R. CSSMRB Reviews of Ongoing Studies

CSP studies will not usually be reviewed by CSSMRB after the original approval phase. However, for those studies experiencing difficulties identified by the DMC or studies that require major protocol changes (e.g., extension of patient recruitment period) or a significant change in the study budget, special reviews can be scheduled as required during the ongoing phase of the study. The Study Biostatistician/Epidemiologist and the Study Chairperson are responsible for scheduling these reviews through CSP HQ. Submission deadlines are the same as for new proposals.

The CSPCC/ERIC will be responsible for preparing the submission to CSP HQ in the following format:

- Table of Contents.

- Executive Summary or Abstract of the study.

- CSPCC/ERIC Director's Summary of Progress: The CSPCC/ERIC Director is required to conduct an in-depth review of the entire study and prepare an evaluative summary statement covering progress, performance and probability of successful conclusion of the study. S/he also presents a concise review of the budgetary aspects of the study.

- Letters of Understanding (if necessary): a letter from CSPCRPCC may be required to acknowledge requests for extension of patient intake or follow-up that affect supplies of drugs/devices.

- Study Progress Report: This section, jointly prepared by the Study Chairperson and the Study Biostatistician/Epidemiologist, includes a history of the study to date and a statement of current status. The latter includes the number of patients entered into the study (by time and medical center) and a comparison with the projected number; losses to the study, (such as dropouts and changes of therapy due to failure or toxicity) and a statement of when and why these occurred; comparison with study objectives; and estimates of the prospects of success. The report should include aggregated outcome data, and it should compare overall event rates with the rate predicted in the original protocol. At their discretion, CSSMRB may request outcome data by

blinded treatment assignment (e.g., groups A and B), or, in unusual circumstances, unblinded outcome data. Reconsideration of the power/sample size issues may be necessary. In the case of a request for extension of patient intake or follow-up duration, this report should also contain a justification for the request. When investigators request an extension and/or an increase in budget, or if there is any problem with the conduct of the trial, the calculation of conditional probability must be provided to CSSMRB. In these cases, a letter from the Chair of the DMC should also be included in the mid-term report.

- Previous CSSMRB Reports.
- Data Monitoring Committee Reports or Minutes if they are needed to support study request(s).
- Human Rights Committee Minutes (including site visit reports).
- Bibliography of Study Publications.
- Budgets: The original budget approved by CSSMRB; a budget showing actual costs to date; the difference between the two; and projected costs for the completion of the study.
- Original study protocol and/or research data forms (only if significant modifications are being requested).
- Other supplemental material.

S. CSP Study Files

The sponsor files on CSP studies are maintained at the CSPCC/ERIC, the CSPCRPCC, and the SMART office (not necessarily all at any one site) and include copies of consent and data forms, protocols, committee reports, drug accountability data, and other documentation related to the review and conduct of the studies. The Study Chairperson, SI and laboratories should also maintain copies of all data forms and study related correspondence until the study is completed.

T. Periodic Reports

1. Research and Development Information System (RDIS)

The Office of Research and Development requires certain information annually from every VA medical center that conducts research (VHA Handbook 1200.5, Paragraph 7(g)). The local R&D office at each medical center is responsible for compiling this information and will initiate the reporting process and provide current instructions. Each Study Chairperson and SI will be asked to provide information. Questions about reporting are best directed to the local R&D office.

Within 15 working days after the funding of the Study Chairperson's office in a CSP study, the Study Chairperson should complete a Project Data Sheet (VA Form 10-1436). This form will be

completed annually during the course of the study and at termination. Complete instructions can be found in M-3, Part I, and the local R&D office can provide necessary assistance. Project Data Sheets must be reviewed for confidential data and thus should be submitted through the appropriate CSPCC/ERIC with a copy to the ACOS/R&D. If the Study Chairperson has not previously been reported in the RDIS database, a VA Form 10-5368 should also be completed.

2. Annual Progress Report to FDA

The sponsor of an IND/IDE is required to submit an Annual Progress Report to the FDA; the CSPCRPCC will coordinate this activity on behalf of the CSP as the sponsor.

U. Collaboration with Industry

The following are general guidelines that should be followed in collaborations with industry:

- VA and Industry should establish the concept of mutual but not identical interests and distinguish principles from practice.
- Agreements involving intellectual property must utilize a Cooperative Research and Development Agreement (CRADA).
- Industry funds must be contributed to a VA non-profit corporation (NPC), and funds must be under the control of NPC - not industry or the investigator.
- Industry representatives may participate in planning meetings, Study Group meetings, Executive Committee meetings and Publication Committee meetings.
- Industry representatives cannot participate in Data Monitoring Committee meetings (unless requested by DMC), nor have access to DMC minutes.
- Industry representatives cannot have access to unblinded data prior to the end of patient follow-up.
- Industry representatives may receive courtesy pre-publication manuscript 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.
- CSP should help in FDA preparations and be reimbursed for extra effort.
- If industry representatives are to provide site monitoring, their visits and reports will be coordinated and distributed through SMART.

VI. CONCLUDING A CSP STUDY

A. Closing Down

In some instances, patients will still require treatment after their participation in a CSP study. The patient's treating physician should plan the transition from study treatment to whatever continued treatment is appropriate. If a patient has done well on a drug that is still investigational and the physician would like to continue its use, a new source of the drug must be found. Final results of the study will ordinarily not be immediately available for the physician's guidance. When the final results do become available upon publication of the major manuscript, letters reporting the study results should be sent to all study patients through the SI with IRB approval. These should describe the results in lay language, and must be reviewed by the Human Rights Committee. Specific plans for handling the closeout phase, unblinding, and notifying investigators and patients of study results should be included in the original protocol (see Section II.G.1.d.).

When follow-up on all patients enrolled in the study has ended, the CSPCC/ERIC has the responsibility for final data summaries and analyses of the study, which should be completed within a reasonable time after receipt of the last data forms at the CSPCC/ERIC. The Executive Committee is responsible for approving the publication and presentation of all data and results of the study. Six months prior to the end of the study, the Executive Committee should submit a publication plan to the CSPCC/ERIC Director, who will forward it to CSP HQ. Material for publication should ordinarily be submitted within one year of receipt of all data at the CSPCC/ERIC. Normally the Executive Committee will be funded for one meeting during this year to prepare the manuscript(s) for final publication.

At the close of the study, the CSPCC/ERIC should have physical possession of all study data. The CSPCC/ERIC will maintain readily accessible files on the study for five years after its completion, at which time the data will be evaluated for archiving. If it is not appropriate to archive at that time, the data files will be reevaluated periodically. Participating medical centers can, after consultation with the CSPCC/ERIC, discard files five years after the study is completed. However, local policies may require a longer period. For trials of investigational products, study files will be retained until at least two years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These files can be retained for a longer period if required by applicable regulatory requirements or as agreed with an industry sponsor/partner, or if needed by the CSP. CSPCRPCC will advise the CSPCC/ERIC if such requirements apply, extending the standard 5-year retention period. The CSPCC/ERIC will ensure that all study related files, including electronic files, are archived and maintained appropriately.

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

The sponsor of an IND/IDE is required to submit a Termination Report to the FDA shortly after completion of the study. The CSPCRPCC will coordinate this activity on behalf of the CSP as the sponsor. Each investigator is required to notify the Human Studies Subcommittee/IRB that the study has ended at the site.

At the completion of the study, the CSPCC/ERIC Administrative Officer or Project Manager will call the other coordinating centers to determine if equipment purchased specifically for the study can be usefully deployed to other studies and if so, will arrange for its transfer through the appropriate Acquisition & Materiel Management Service. Otherwise, such equipment will be disposed of in accordance with the regulations of the Regional Research Equipment Program (RREP) (Reference: VA Manual MP-2, Subchapter H, page 43.3-4, dated May 23, 1988).

Subsequent to final analysis, if data are used for meta analysis, the CSPCC/ERIC Director should be informed. Questions of appropriate use of CSP data will be referred to the Director, CSR&D.

B. Final Study Meeting

The Study Group and the Data Monitoring Committee, 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 takes place after the manuscript writing meeting of the Executive Committee or its designated writing subcommittee(s). At this meeting, the Study Chairperson 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. CSP considers the publication and dissemination of study findings to be of utmost importance.

Publications are to be made in a timely fashion. In collaboration with the Study Chairperson, Study Biostatistician/Epidemiologist, and the Director, CSR&D, the CSPCC/ERIC Director will establish a date for submission of the major manuscript. This date will usually be **six months** after funding for the last study personnel has terminated. If the major manuscript is not submitted on time, the CSPCC/ERIC Director and Director, CSR&D will designate other study participants to write the manuscript.

The presentation or publication of any or all data collected by SIs is under the direct control of the study's Executive Committee. This control applies to whether the publication or presentation provides the results of the principal undertaking or the results of an ancillary analysis. The CSPCC/ERIC Director must approve a manuscript with concurrence from the Director, CSR&D prior to submission The CSPCC/ERIC Director will notify CSP HQ when a manuscript is accepted for publication.

Submission of manuscripts must follow VA policy. All publications must give proper recognition to VA CSP. Additionally, authors with VA appointments must list their VA affiliation first. Ideally, a subtitle is

used stating, "A VA Cooperative Study," or, for example, in the case of shared funding, "A VA-NHLBI Cooperative Study." An alternative method is to list the study group as the final author, e.g. "The Veterans Affairs Cooperative Study Group on (study topic)". A footnote or acknowledgment should state: "Supported by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development" or "Supported by the Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development and the NHLBI by interagency agreement No. XXX." CSPCC/ERIC Directors are required to ensure that this policy is carried out for all study publications.

When a major manuscript has been submitted, a copy of the manuscript should be sent to CSP HQ. When any manuscript is accepted for publication, the Study Chairperson and the Study Biostatistician/Epidemiologist should write a summary of the results and send it (along with a copy of the revised manuscript) to CSP HQ. This summary should be a brief statement, no longer than a page, in direct and informal language, describing the results of the study and its importance. When the date of publication and the journal is known, that information should be sent to CSP HQ. After CSP HQ has received and approved the summary, guidance on working with the Office of Research & Development's Communications Division will be provided. CSP HQ will work with the appropriate offices to coordinate publicity efforts for major publications.

When reprints are available, copies will be distributed to other CSP centers and CSP HQ. Electronic versions of the paper will be sent when available.

D. Custodianship of Data

The policy regarding custodianship of data should be communicated to investigators in the planning and organizational stages by the Study Chairperson and CSPCC/ERIC. The CSP is the custodian of all data collected as part of a cooperative study. All site investigators must release their data to the participating CSPCC/ERIC at the appropriate time. While most data should be submitted to the CSPCC/ERIC shortly after it is collected, there may be special circumstances when a site investigator or a central laboratory investigator may legitimately keep the data for longer periods of time. In these circumstances, the Director of the CSPCC/ERIC will determine when the appropriate time is to submit the data to the CSPCC/ERIC.

All analyses related to the objectives of the study and publication plan as specified in the study protocol, except for economic analyses, will be performed by the CSPCC/ERIC. Economic analyses will be carried out by the health economics staff. All raw study data will reside at the CSPCC/ERIC and will not be released until objectives as stated in the protocol and manuscripts in the protocol publication plan have been completed. The CSPCC/ERIC will act as the repository of all study data from a completed cooperative study. Raw data may be released to other investigators after all planned objectives and manuscripts are completed and upon approval of the Study Chairman, Executive Committee (if it still exists), CSPCC/ERIC Director and Director, CSR&D (see next section). Data use agreements, including assurance that all VA data security policies will be strictly adhered to, will be instituted prior to any data being released.

The Study Executive Committee has the authority to determine all uses of the data, provided that these uses do not conflict with the study protocol, 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.

If, in the judgment of the CSPCC/ERIC Director, the Study Chairperson ceases to exercise this authority in an appropriate manner, the CSPCC/ERIC will take over the management of access to the study data. Requests for release of data to VA or other investigators will be reviewed by the CSPCC/ERIC and, where appropriate, sent to the Director, CSR&D for final review. If a study dataset is released to anyone outside the CSPCC/ERIC, the recipient inherits the responsibilities of stewardship, and may not redistribute the data to anyone else and must follow HIPAA guidelines.

E. Release of Study Data Sets

While the 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 appropriately used scientifically and ethically and that the rights and welfare of study participants are protected. Site investigators are encouraged to submit proposals to the Executive Committee for use of the data and these will be approved if scientifically and ethically sound. Data sets will not be released before the study database is locked. Site investigators should be aware, however, that the CSPCC/ERIC's main responsibility is to prepare the needed analyses for the primary manuscript(s) and secondary manuscripts as spelled out in the protocol or planned by the Executive Committee. Secondary analyses by the CSPCC/ERIC may be delayed until the primary analyses and manuscripts are completed. Alternatively, the CSPCC/ERIC may provide the site investigators 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 make exceptions.

The Director, CSPCC/ERIC has the authority to release data sets to site investigators/Executive Committee members, who have been given approval for access to these data sets by the Executive Committee or Study Chairperson, if the Executive Committee is no longer functioning. Investigators outside of the study, both VA and non-VA, must obtain approval for release of data by the Executive Committee (if still functioning), the Director, CSPCC/ERIC, and the Director, CSR&D. All recipients of CSP databases must sign a data use agreement that they will only use the data for the stated purposes, that they will give proper credit to the study and the CSP and VA in all presentations and publications, that they will not give this data to other investigators without consent of the Directors, CSPCC/ERIC and CSR&D, that they will destroy or return the data when they have completed their work, that they will not try to identify any study participant, and that they will consider the data sets as confidential information and will keep the data sets in a secure location. The CSPCC/ERIC for its part will provide the investigator requesting the data with a de-identified database, making identification of study participants as difficult as possible. HIPAA guidelines for de-identified data sets will be used, when possible. Investigators will not

usually be provided with full study databases, but rather just with the information that they will need to do their research.

F. Continuing Analytic Activities

In general, the CSR&D Merit Review mechanism 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 CSSMRB submission/budget. Supplemental funds from CSP may be available for low cost continuing analytic activities at the discretion of the Director, CSR&D.

G. Administrative Repercussions

The CSP policies for data analysis and dissemination of results apply to all members of the study team (Study Chairperson, SIs, Study Biostatistician/Epidemiologist, etc.). If a Study Chairperson or Site Investigator 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 one to five years, commensurate with the seriousness of the infraction (at the discretion of the CSR&D & Biomedical Laboratory R&D Directors).

Individuals may also be subject to civil or criminal penalties or fines.

VII. CONCLUSION

The planning, review, initiation and completion of a CSP study are complex processes requiring close communication among all participants. This document provides policies and procedures for these efforts, but the need for flexibility in the conduct of Cooperative Studies is recognized. Exemptions to items stated in this document guidelines may be granted by the Director, CSR&D. Requests for exemptions should be made through the Director of the appropriate CSPCC/ERIC. Suggestions for inclusion in subsequent editions of this document are welcome.

APPENDIX A - CSP ADDRESSES

STAFF PHONE/FAX NUMBERS

VA CENTRAL OFFICE

Cooperative Studies Program (125)
VA Office of Research & Development
810 Vermont Ave., N.W.
Washington, DC 20420

Timothy J. O'Leary, M.D., Ph.D., Acting Director, CSR&D — COM: (202) 254-0192
Grant Huang, M.P.H., Ph.D., Deputy Director, CSP — FAX: (202) 254-0471
Karen Hood, Management Analyst – Finance — EMAIL: csp@va.gov
Bridgett Baer, Administrative Officer, CSR&D
Blythe Ferguson, Program Analyst, CSP
Kelli Potter, Program Specialist, CSP

COOPERATIVE STUDIES PROGRAM COORDINATING CENTERS

Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (151-I)
2401 Centre Avenue, SE
Albuquerque, NM 87106-4180

Mike R. Sather, Ph.D., F.A.S.H.P., Center Director — COM: (505) 248-3200
Dennis W. Raisch, R.Ph., Ph.D., Associate Center Director — FAX: (505) 248-3202
Thelma P. Salazar, B.S., Assistant Center Director for Administrative Operations
Mark S. Jones, M.B.A., Assistant Center Director for Technical Operations
Kathy D. Boardman, B.S., R.Ph., Asst. Center Director for Pharmaceutical Management and Research
Julia E. Vertrees, Pharm.D., BCPP, Asst. Center Director for Pharmaceutical Management and Research
Stuart R. Warren, J.D., Pharm.D., Asst. Center Director for Pharmaceutical Management and Research
Crystal L. Harris, Pharm.D., Asst. Center Director for Pharmaceutical Management and Research
Robert J. Ringer, Pharm.D., BCNP, Asst. Center Director for Pharmaceutical Management and Research
Kathleen M. Swanson, R.Ph., M.S., Chief, Regulatory Affairs Clinical Compliance Group
Cindy Colling, R.Ph., M.S., Quality Assurance Specialist
Clair Haakenson, M.S., CCRA, Chief, SMART Good Clinical Practices Standards and Resources Group
Carol L. Fye, R.Ph., M.S., CCRP, Chief, SMART Good Clinical Practices Review Group
Julia M. Buckelew, B.S., CCRA, Chief, SMART Good Clinical Practices Monitoring Group

Cooperative Studies Program Coordinating Center (151 MAV)
Boston VA Health Care System
150 S. Huntington Ave.
Boston, MA 02130

Louis Fiore, M.D., MPH, Director — COM: (617) 232-9500 x 4201
J. Michael Gaziano, M.D., MPH, Co-Director — FAX: (617) 278-4424
Gregory Muldoon, Administrative Officer
Ryan Ferguson, MPH, Quality Assurance Specialist

Cooperative Studies Program Coordinating Center (151K)
Edward Hines Jr. VA Hospital
Hines, IL 60141-5151

Domenic J. Reda, Ph.D., Acting Director — COM: (708) 202-5350
Joyce Jimenez, Administrative Officer — FAX: (708) 202-2116
Mary Ellen Vitek, Quality Assurance Specialist

Cooperative Studies Program Coordinating Center (151K)
VA Health Care System
795 Willow Road Bldg 205
Menlo Park, CA 94025

Mark Holodniy, M.D., Acting Director — COM: (650) 617-2719
Kelvin K. Lee, Ph.D., Associate Director — FAX: (650) 617-2605
Lori Planting, Senior Project Manager
Jennifer Cockroft, Quality Assurance Specialist

Cooperative Studies Program Coordinating Center (151E)
VA Maryland Health Care System
P.O. Box 1010
Perry Point, MD 21902

Joseph F. Collins, Sc.D., Director — COM: (410) 642-1007
David G. Weiss, Ph.D., Assistant Director for Scientific Management — FAX (410) 642-1860
Susan C. Stinnett, Assistant Director for Administration
Tara Burke, Quality Assurance Specialist

Cooperative Studies Program Coordinating Center (151A)
VA Connecticut Health Care System
950 Campbell Avenue
West Haven, CT 06516

Peter Peduzzi, Ph.D., Director — COM: (203) 937-3440
Gary Johnson, M.S., Assistant Director — FAX: (203) 937-3858
Margaret R. Antonelli, Assistant Director (Operations)
Lynn Durant, Quality Assurance Specialist

EPIDEMIOLOGICAL RESEARCH AND INFORMATION CENTERS

Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC)
Boston VA Healthcare System (151 MAV)
150 S. Huntington Ave.
Boston, MA 02130

J. Michael Gaziano, M.D., MPH, Director — COM: (856) 364-4201
Louis Fiore, M.D., MPH, Co-Director — FAX: (857) 364-4424
Mercedes Andino, Acting Administrative Officer
Ryan Ferguson, MPH, Quality Assurance Specialist

Epidemiological Research and Information Center (152)
Building 6, HSR&D
VA Medical Center
508 Fulton Street
Durham, NC 27705

Dawn Provenzale, M.D., MS, Director — COM: (919) 286-0411 x5745
Eugene Oddone, M.D., MHSc, Associate Director — FAX: (919) 416-5836
Jane Kolimaga, Assistant Director - Operations

Epidemiological Research and Information Center (S-152E)
VA Medical Center
1660 S. Columbian Way
Seattle, WA 98108

Nicholas Smith, Ph.D., Interim Director — COM: (206) 764-2773
Thomas D. Koepsell, M.D., MPH, Co-Director — FAX: (206) 764-2563
Phillip Terry, MHA, Assistant Director
Jen Sporleder, Quality Assurance Specialist

Clinical Epidemiology Research Center
VA Connecticut HCS
950 Campbell Avenue – Bldg. 35A (151B)
West Haven, CT 06516

John Concato, MD, MPH, Director, CERC — (203) 932-5711 ext. 2993
Mihaela Aslan, Ph.D., Associate Director, CERC — FAX: (203) 937-3425
Nancy Cummings, R.N., M.A., Program Manager
Lynn Durant, Quality Assurance Specialist

Health Economics Resource Center
VA Palo Alto HCS
795 Willow Road (152MPD)
Menlo Park, CA 94025-2595

Paul G. Barnett, Ph.D., Director — (650) 493-5000 x22475
Mark W. Smith, Ph.D., Associate Director — FAX (650) 617-2639
Yoko Ogawa, Administrative Officer

Pharmacogenomics Analysis Laboratory
Central Arkansas Veterans Healthcare System
Pathology and Laboratory Medicine Service, 113/LR
4300 West 7th Street
Little Rock, AR 72205-5484

Steven A. Schichman, M.D., Ph.D., Director — (501)257-6445
FAX (501) 257-6441

APPENDIX B - STATEMENT OF DISCLOSURE

STATEMENT FOR THE PRINCIPAL PROPONENT, THOSE SERVING IN AN *AD HOC* REVIEW OR ADVISORY CAPACITY, SITE INVESTIGATORS AND MEMBERS OF DATA MONITORING COMMITTEES

CSP #___
(name of study)

Except as noted below, I am not an employee (part or full-time, paid or unpaid) of any organization(s) either involved in the study(s) under review or whose products or services would be clearly and directly affected in a major way by the outcome of the study(s), nor am I an officer, member, owner, trustee, director, expert, advisor or consultant of such an organization. It is important to recognize that conflict of interest applies if these interests or relationships exist or appear to exist.

Except as noted below, I do not have any financial interest in any organization meeting the above criteria, nor does my spouse, minor child, nor an organization with which I am connected.
(State "None" or identify any exceptions)

I will notify the Director of the CSPCC promptly if (a) a change occurs in any of the above during the tenure of my responsibilities or (b) if I discover that an organization with which I have a relationship meets the criteria.

I am aware of my responsibilities for the maintenance of confidentiality of any non-public information that I receive or become aware of through this activity and for the avoidance of using any such information for my personal benefit or for the benefit of my associates or of an organization with which I am connected or with which I have a financial involvement.

Signature

Date

APPENDIX C – COOPERATIVE STUDIES SCIENTIFIC MERIT REVIEW BOARD MEMBERS

George Machiedo, M.D. (6/10) - Chair
Chief of Surgery
VA Medical Center
East Orange, NJ

Warren S. Browner, M.D., MPH (12/08)
Vice President Academic Affairs
Scientific Director, Research Institute
California Pacific Medical Center
San Francisco, CA

David Cohen, M.D. (6/07)
Director, Cardiovascular Research
Mid-American Heart Institute
Kansas City, MO

Barry R. Davis, M.D., Ph.D. (6/09)
Executive Director, Biostatistics
Amgen, Inc.
Thousand Oaks, CA

Michael Domanski, M.D. (6/09)
National Heart, Lung, & Blood Institute
Bethesda, MD

Theodore Karrison, PhD (6/09)
Associate Professor
Department of Health Studies
University of Chicago
Chicago, IL

Sheryl F. Kelsey, Ph.D (6/09)
Professor
Department of Epidemiology
University of Pittsburgh
Pittsburgh, PA 15261

Term end date noted in parentheses

WORKSHEET FOR VERIFYING REQUIRED ELEMENTS OF INFORMED CONSENT

CONSENT FORM CHECKLIST

Protocol: _____ Sponsor: _____
Protocol Version (No. and/or Date): _____
Consent Form Version (No. and/or Date): _____
Participating Site: _____

I. ELEMENTS OF INFORMED CONSENT REQUIRED IN VA RESEARCH*

PRESENT			
YES	NO		
☐	☐	1.	Name of the Study.
☐	☐	2.	Name of the Principal Investigator.
☐	☐	3.	Statement that the study involves research.
☐	☐	4.	Explanation of the purpose of the research.
☐	☐	5.	Expected duration of the subject's participation.
☐	☐	6.	Description of the procedures to be followed. *For VA: Identify which procedures are done for research purposes.*
☐	☐	7.	Identification of any procedures, which are experimental.
☐	☐	8.	Description of any reasonably foreseeable risks or discomforts. *For VA: this also includes privacy risks (legal, employment, and social).*
☐	☐	9.	Description of any benefits to the subject or others, which may reasonably be expected from the research.
☐	☐	10.	Disclosure of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the subject.
☐	☐	11.	Statement describing the extent to which confidentiality of records identifying the subject will be maintained and noting the possibility that the sponsor (e.g., VA Cooperative Studies Program), the FDA [if applicable] and other Federal agencies; e.g., the Office for Human Research Protection (OHRP) and the Government Accounting Office (GAO), may inspect records;
☐	☐	12.	For research involving more than minimal risk, an explanation as to whether any compensation is available and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

**All of these requirements apply to both VHA and CSP. CSP has one additional requirement concerning witnessing consent (see page 3).*

Compliments of:
SMART
Site Monitoring, Auditing and Review Team
VA Cooperative Studies Program, Albuquerque, NM 4/13/06

PRESENT
YES NO

☐ ☐ 13. An explanation of whom to contact for answers to questions about research and research subject's rights and whom to contact in case of research-related injury to subject. *For VA: At least one contact's name and phone number other than investigator or study personnel is required.*

☐ ☐ 14. Statement that participation is voluntary.

☐ ☐ 15. Statement that refusal to participate will involve no penalty or loss of benefits to which subject is otherwise entitled.

☐ ☐ 16. Statement that subject may discontinue participation at anytime without penalty or loss of benefits to which subject is otherwise entitled.

II. ADDITIONAL ELEMENTS REQUIRED WHEN APPLICABLE
(Note: Seldom are these elements not applicable to a clinical trial)

PRESENT
YES NO NA

☐ ☐ ☐ 1. Statement that the particular treatment or procedure may involve risks to the subject (or to embryo or fetus, if subject is or may become pregnant), which are currently unforeseeable.

☐ ☐ ☐ 2. Anticipated circumstances under which subject's participation may be terminated by the investigator without regard to subject's consent.

☐ ☐ ☐ 3. Any additional costs to the subject that may result from participation in the research.

☐ ☐ ☐ 4. Consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

☐ ☐ ☐ 5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to subject.

☐ ☐ ☐ 6. Approximate number of subjects involved in the study.

☐ ☐ ☐ 7. If an FDA-regulated test article is involved, the FDA requires a statement that the FDA may choose to inspect research records that include the subject's individual medical records.

☐ ☐ ☐ 8. As appropriate, a statement regarding any payment the subject is to receive and how payment will be made.

☐ ☐ ☐ 9. A statement that a veteran-subject will not be required to pay for care received as a subject in a VA research project except as follows:

a. Certain veterans who are required to pay co-payments for medical care and services provided by VA. Suggested wording: "Some Veterans are required to pay co-payments for medical care and services provided by VA. These co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this study."
b. Investigators need to note that charges will not be made for medical services, including transportation, furnished as part of a VA-approved research study.

PRESENT				
YES	NO	NA		
☐	☐	☐	10.	If the investigators believe that the human biologic specimens obtained could be part of, or lead to the development of a commercially valuable product, or if the specimens are to be retained after the end of the study, current VA policy and Veterans Health Administration (VHA) regulations must be followed. NOTE: *If genetic testing is to be done, VA requirements pertaining to genetic testing must also be met.*

III. ADDITIONAL ELEMENTS REQUIRED BY LOCAL IRB

PRESENT			
YES	**NO**		
☐	☐	1.	_____.
☐	☐	2.	_____.
☐	☐	3.	_____.
☐	☐	4.	_____.
☐	☐	5.	_____.
☐	☐	6.	_____.
☐	☐	7.	_____.

IV. OTHER VHA REQUIREMENTS CONCERNING CONSENT FORMS

1. VA Form 10-1086 must be used to prepare the consent form.
   VA Form 10-1086 has been used. ☐ YES ☐ NO
2. IRB Stamp or pre-printed box on each page of the consent form indicating date of most recent IRB approval. ☐ YES ☐ NO
3. Signature lines provided on the form are to be consistent with VHA and CSP policy.
   VHA and CSP require that current forms be signed and dated by the subject (or subject's legally-authorized representative), a witness and the person obtaining the informed consent.
   IRBs and Sponsors may have additional requirements for signatures, but at the minimum, VHA & CSP consent forms must provide:

☐ YES ☐ NO Line for signature and date of patient or representative.
☐ YES ☐ NO Line for signature and date of person obtaining consent.
☐ YES ☐ NO Line for signature and date of witness*.

*CSP requires that the witness not be part of the study team; VHA does not.

V. ELEMENTS OF PATIENT AUTHORIZATION REQUIRED BY THE HEALTH INSURANCE PORTABILITY & ACCOUNTABILITY ACT (HIPAA) OF 1996:

The following elements are required, either as part of an IRB-approved consent form or as a stand-alone HIPAA authorization document.

PRESENT				
YES	NO	NA		
☐	☐	☐	1.	A description of the information to be used or disclosed,
☐	☐	☐	2.	The identification of the persons or class of persons authorized to make the use or disclosure of the protected health information,
☐	☐	☐	3.	The identification of the persons or class of persons to whom the covered entity is authorized to make the use or disclosure,
☐	☐	☐	4.	A description of each purpose of the use or disclosure,
☐	☐	☐	5.	An expiration date or expiration-triggering event,
☐	☐	☐	6.	The individual's signature and date, and
☐	☐	☐	7.	If signed by a personal representative, a description of his or her authority to act for the individual.
☐	☐	☐	8.	A statement about the potential for the protected health information (PHI) to be subsequently disclosed by the recipient (disclosure of PHI to FDA is permitted under the rule, disclosure to business associates requires a written contract).
☐	☐	☐	9.	A statement that the individual may revoke the authorization in writing (except to the extent that VHA has taken action in reliance on the consent), and either a statement regarding the right to revoke, and instructions on how to exercise such right.
☐	☐	☐	10.	A statement that treatment, payment, enrollment, or eligibility for benefits may not be conditioned on obtaining the authorization if such conditioning is prohibited by the Privacy Rule, or if conditioning is permitted by the Privacy Rule, a statement about the consequences of refusing to sign the authorization.

The HIPPA authorization elements listed above are:

☐ incorporated into the informed consent form.

☐ presented in a stand-alone HIPAA authorization form or addendum.

_____ _____

Reviewer Date

APPENDIX E - GLOSSARY OF ABBREVIATIONS

ACOS	Associate Chief of Staff
ADE	Adverse Device Effect
AE	Adverse Event
AHCPR	Agency for Health Care Policy and Research
AMM	Acquisition and Material Management Service
BECC	Biomedical Engineering and Computing Center
BLRD	Biomedical Laboratory Research & Development Service
BPLS	Biopharmaceutics/Pharmacokinetics Laboratory Section
BRDP	Biostatistical and Research Data Processing Procedure
CRADA	Clinical Research and Development Agreement
CRADO	Chief Research & Development Officer
CERC	Clinical Epidemiology Research Center
CRP	Clinical Research Pharmacist
CSEC	Cooperative Studies Evaluation Committee
CSP	Cooperative Studies Program
CSPCC	Cooperative Studies Program Coordinating Center
CSPCRPCC	Cooperative Studies Program Clinical Research Pharmacy Coordinating Center
CSR&D	Clinical Sciences Research & Development Service
CSSMRB	Cooperative Studies Scientific Merit Review Board
CV	Curriculum Vitae
DIR	Drug Information Report
DMC	Data Monitoring Committee
DTHP	Drug Treatment and Handling Procedures
DVA	Department of Veterans Affairs
EEG	Electroencephalogram
EKG	Electrocardiogram
ERIC	Epidemiological Research and Information Centers
FDA	Food & Drug Administration
FTE	Full Time Equivalent
FTEE	Full Time Equivalent Employee
FTS	Federal Telecommunications System
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 and Development
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
MPA	Multiple Project Assurance
MRS	Medical Research Service
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OMB	Office of Management and Budget
ORD	Office of Research & Development (VA)
ORO	Office of Research Oversight

R&D	Research and Development
RDIS	Research and Development Information System
RR&D	Rehabilitation Research and Development
RREP	Regional Research Equipment Program
SAE	Serious Adverse Event
SI	Site Investigator
SMART	Site Monitoring and Review Team
UADE	Unanticipated Adverse Device Effect
VA	Veterans Affairs
VA HQ	VA Headquarters
VAMC	Veterans Affairs Medical Center
VHA	Veterans Health Administration