COOPERATIVE STUDIES PROGRAM

GUIDELINES

FOR THE PLANNING AND CONDUCT OF

COOPERATIVE STUDIES

OFFICE OF RESEARCH AND DEVELOPMENT

DEPARTMENT OF VETERANS AFFAIRS

November 2001

Note: Changes from January 2001 versions highlighted in yellow

CSP

COOPERATIVE STUDIES PROGRAM

OFFICE OF RESEARCH AND DEVELOPMENT

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I. INTRODUCTION

The purpose of this manual is to describe practices and procedures 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 study collectively 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 multicenter 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.

The large number of medical centers within the VA presents an ideal environment for conducting multicenter cooperative studies. The VA has a large and relatively uniform patient base; this is especially appropriate for research that addresses medical problems and diseases prevalent in the veteran population. These characteristics facilitate the conduct of multicenter studies that require strict adherence to a common protocol. In this setting, it is more likely that the essential patient follow-up will be completed.

Successful cooperative studies require central administration to ensure uniformity of research methodology as well as fiscal control. The administrative structure of the VA contributes to this kind of coordination.

The Cooperative Studies Program, a division of the Department of Veterans Affairs Office of Research and Development, was established to provide coordination and collaboration for multicenter research studies that fall within the purview of the VA. When appropriate, CSP works with other divisions of the VA to promote cooperative studies.

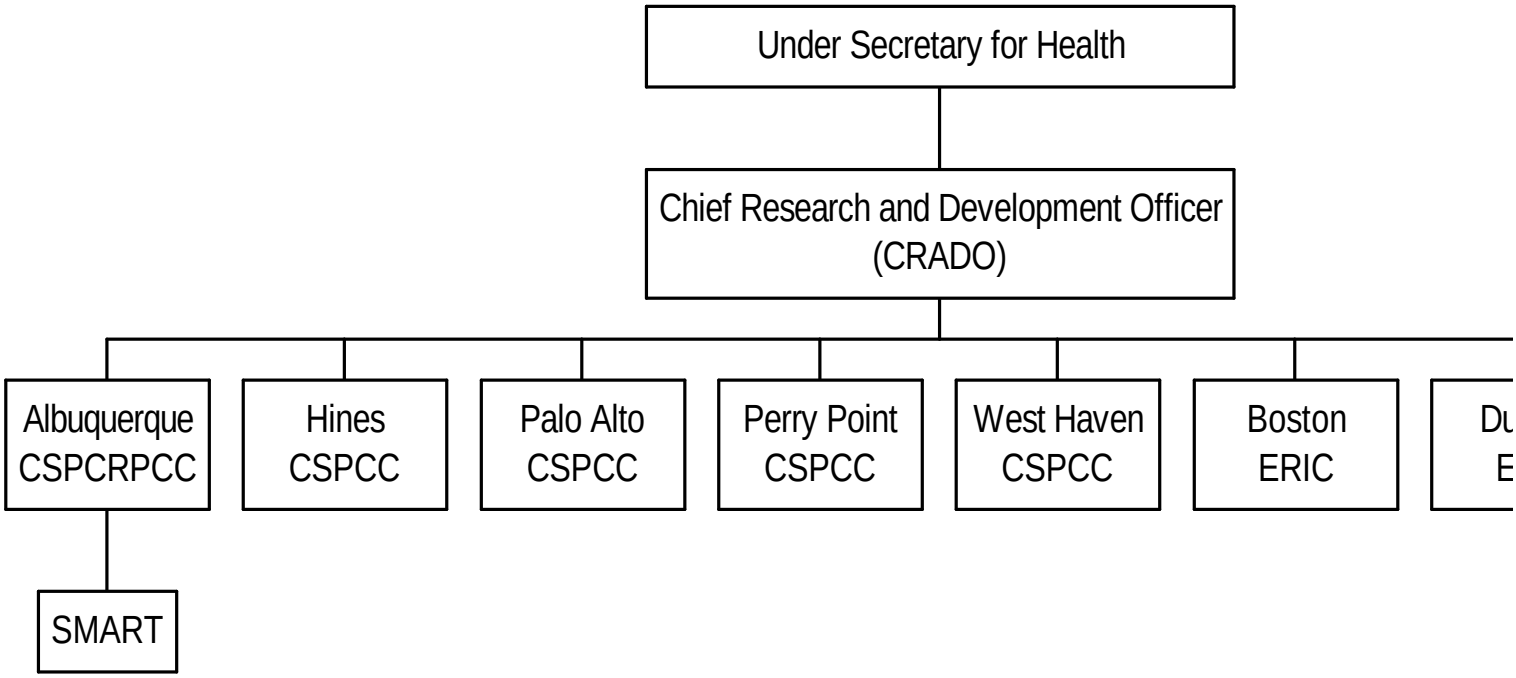
CSP has eight coordinating centers (see Figure 1): four statistical/administrative coordinating centers, one pharmacy coordinating center and three epidemiological research centers. The four Cooperative Studies Program Coordinating Centers (CSPCCs), located at the VA Medical Centers in Hines, IL, Palo Alto, CA, Perry Point, MD, and West Haven, CT, provide biostatistical collaboration, data processing and management and analyses for CSP studies and also ensure their compliance with Cooperative Studies Program guidelines. There is a Human Rights Committee established at each Coordinating Center that reviews the ethical aspects of proposed studies.

A fifth center, unique to CSP, is the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC), affiliated with the VAMC in Albuquerque, NM. 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 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 and Review Team (SMART), the quality assurance unit of CSP.

The three Epidemiological Research and Information Centers (ERICs) were established to provide collaboration and guidance within the VA for the increasingly important field of epidemiology. 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 three ERICs are located at the VA Medical Centers in Boston, MA, Durham, NC and Seattle, WA.

In a cooperative study, certain persons and groups have specific responsibilities. These *Guidelines* attempt to identify the most important tasks and responsibilities. A successful cooperative study requires communication, cooperation, and a willingness to pursue a common goal. We recommend that those interested in proposing a CSP study communicate with the CSP office in VA Headquarters if additional information is needed.

FIGURE 1. Organization of Cooperative Studies Program (CSP)



See Appendix A for names, addresses and FTS 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 Chief Research and Development Officer (CRADO) in VA Headquarters. All correspondence pertaining to a CSP LOI should be sent to the following address:

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

The investigator that 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:

?? 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 (FTEE and total cost)
- other

Other documents should accompany the LOI but are not included in the 10 page restriction:

?? 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, full disclosure must be provided by the Principal Proponent(s). (See Appendix D.)

?? 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 from the Eligibility Panel in VA Headquarters (Circular 10-88-95) within the previous nine months. 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, and telephone numbers of five to seven unbiased experts in the field who might be suitable to review the proposal. LOI's 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. List should include potential VA site investigators.

Seven copies of the LOI and CVs should be submitted.

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 a planning request are encouraged to contact the CRADO. When it appears advantageous, the CRADO may suggest a consultation with the staff of one of the four CSPCCs. Similar support is available in the areas of cost effectiveness and decision analysis.

LOI's are sent to four or more reviewers to evaluate the merit of the proposal. The decision to fund the study for planning will be made on the basis of the experts' recommendations, as well as at the discretion of the CRADO. Turnaround time for responses to planning requests is four to six weeks unless additional information is requested from the Principal Proponent.

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 CRADO. If industry support is anticipated, industry representatives may be included in the planning process (see Section V. S.).

B. Administrative Approval

A limited number of proposals may be evaluated and approved by the CRADO. Such proposals are defined by the length of the research - less than two years, and the budget - less than $25,000. If approved, these proposals are assigned to a Coordinating Center and administratively reviewed midway through the course of the study. The planning and review process varies from that for a conventional CSP study in ways that are unique to each research plan.

C. Notification of Approval for Planning

When a study is funded for planning, the Principal Proponent is notified in writing by the CRADO, and informed as to which CSPCC the study will be assigned. The Director and the ACOS for Research and Development at the Principal Proponent's medical center are notified as well. The Director of the CSPCC will identify the Study Biostatistician with whom the Principal Proponent will work. If the study involves drugs or devices, the Director, CSPCRPCC will also be notified, and a Clinical Research Pharmacist (CRP) will be assigned to the study.

At the time a study is approved for planning, a TWX and/or e-mail are distributed by Office of R&D, VA Headquarters inviting expressions of interest in participation. Interested investigators are encouraged to contact the Principal Proponent or the Study Biostatistician.

D. Planning a CSP Study: Participants

Planning and developing a CSP study requires close cooperation among several groups and individuals: the Principal Proponent, the CSPCC (represented primarily by the Study Biostatistician), the CSPCRPCC (represented primarily by the Study CRP), 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, the Principal Proponent will:

?? Nominate the members of the Planning Committee for approval by the CRADO 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 Evaluation Committee (CSEC).

?? Contact industry for possible support.

2. Cooperative Studies Program Coordinating Center (CSPCC)

During the planning phase, the CSPCC, represented primarily by the Study Biostatistician, 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, sample size determinations, planned interval and final statistical analyses and data summaries, forms design and budget estimation.

?? Arrange for review by the CSPCC Human Rights Committee.

?? Arrange administrative support (e.g., typing, copying and distributing the proposal to members of the Planning Committee, and preparing and submitting the final document to CSP/VA Headquarters for review by CSEC).

?? Negotiate Letters of Agreement (LOAs) with industry sponsors for financial support.

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 develop a Letter of Agreement (LOA) 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.

?? For studies involving patient risk or confidentiality issues, SMART will evaluate the prototype informed consent and provide input to the Human Rights Committee. It will also evaluate monitoring needs and establish clinical research monitoring and/or review plans as appropriate.

4. Planning Committee

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 Study Biostatistician, the Study CRP (when appropriate), at least two potential site investigators and VA or non-VA consultants. An expert in economic analyses 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 total planning group consists of eight to ten people. Participation does not require VA affiliation. If industry support is planned, an industry representative may be invited to participate in the planning process.

E. 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 Director, CSPCC 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. Requests for travel should be submitted to CSP/VA Headquarters at least four weeks prior to scheduled meetings.

The first planning meeting is held in the Washington D.C. area to facilitate the attendance of the CRADO. The final planning meeting is held in the vicinity of the CSPCC to permit attendance of other relevant CSPCC staff and 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 Director, CSPCC to notify the CRADO to discontinue support for planning or, if the Director, CSPCC concurs that the circumstances in a given situation are unusual and justify an exception from this practice, to petition the CRADO for an extension.

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 Director. The CSPCC 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 CRADO for the final decision on continued planning. If the CRADO requests additional information to make this decision or the CRADO disapproves continued planning, the information or any appeal to the disapproval must be submitted to the CRADO within 30 days of notification.

The CSPCC is responsible for sending the following materials to the Planning Committee prior to the first planning meeting. Relevant material should be submitted to the CRADO as well.

- CSP *Guidelines*.
- CSP Brochure.
- Planning Request - including relevant publications submitted by Principal Proponent.
- Reviews of the preliminary proposal.
- Detailed analysis of reviewers' comments by Principal Proponent and/or Study Biostatistician, including a point-by-point response to the reviewers' criticisms.
- A review of the literature to provide the Planning Committee with a basis for design decisions (e.g., effect sizes, estimates of variability, outcome measures) and to provide evidence of the unique scientific contribution of the proposed study.
- List of Committee members.
- Agenda.
- Plans for collection, use, and storage of all centrally collected bloods, tissues and other body specimens.

At the first meeting, the Committee should consider and define, as appropriate:

? Literature review: Is literature sufficiently compelling to support need for a CSP trial?

?? The primary question(s) to be answered by the study.

?? Units of analysis.

?? Secondary questions of importance. Secondary objectives, if any, should be restricted to a minimum.

?? The population to be studied: inclusion/exclusion criteria. If women and/or minorities will be excluded, a compelling rationale for exclusion should be provided.

?? The therapeutic or prophylactic regimen(s), if applicable.

?? The variables to be measured and the outcomes of interest.

?? Schedule and frequency of observations, laboratory tests and/or data collection.

?? Comparisons of interventions/treatments/subgroups.

?? Anticipated magnitude of differences in outcome measures to be detected.

?? Logical links between questions, data, and endpoints.

?? The number of patients needed and how they will be assigned to regimen groups. Patient accrual is often a problem in cooperative studies.

?? Randomization procedures (if appropriate).

?? Other specifics of the experimental design, (e.g., blinding techniques).

?? Procedures to assure the scientific integrity of the study such as masking, independent endpoint assessment, quality assurance and monitoring procedures, and participating site performance standards.

?? The methods of interval and final analyses to be employed.

?? The need for core laboratories. These must be strongly justified.

?? The potential need for clinical monitoring.

?? Preliminary estimates of budgetary support (personnel, travel, and "all other") needed for the Chairperson's office, participating medical centers and central laboratories (if any).

?? The economic analysis component of the study, if relevant.

?? Patient rights and informed consent issues.

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 the reasons for it will be communicated to the CRADO by the Director, CSPCC. 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.

A plan for publications should be considered and incorporated in 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 CSEC 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 and the Study CRP.

The final planning meeting is spent refining the protocol and data collection forms, assessing preliminary patient availability estimates, formulating the final budget and conducting the Human Rights Committee review. (See Section III.A. for a description of the Human Rights Committee review.) To ensure that these goals are accomplished, and that there is a thorough human rights review, the Principal Proponent mails an essentially complete protocol including research data forms and informed consent documents to each member of the Planning Committee and 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. The Principal Proponent must brief the HRC concerning material changes made at the final planning meeting. If submission of this material is late or if it is substantially incomplete, as determined by the Director, CSPCC, the final planning meeting will be rescheduled. After the final planning meeting, the CSPCC will prepare the final proposal for submission to the Cooperative Studies Evaluation Committee, through CSP/VA Headquarters, 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 and completes the negotiations. The CRADO should be informed of <u>all</u> discussions. The Study CRP should attempt to secure a written commitment (LOA) from each involved company during planning or at least prior to CSEC review. The

LOA will be generated by the Director of the CSPCRPCC for signature by him, the appropriate CSPCC Director and the appropriate company officials. After all signatures have been obtained, a copy is forwarded to CSP/VA Headquarters. It is important that these negotiations be completed prior to CSEC 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.S.). If the Principal Proponent is negotiating with the drug company for securing funds in support of the study, the Director, CSPCC should be involved in these discussions and if possible a letter indicating this support should be obtained prior to CSEC review. Also at this time, consideration should be given to the potential need for 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.

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.

F. 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 CRADO who will determine if CSEC review is required. The completed pilot study may be reviewed by CSEC prior to the initiation of the full-scale trial.

G. 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.

H. The CSP Study Proposal

The objective of the planning meetings is to produce the final proposal. The CSPCC will be responsible for preparing the proposal for submission to CSP/VA Headquarters for CSEC 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. When two volumes are submitted, the first volume contains the study protocol, study budget material, selected human rights documents and CVs of the Principal Proponent(s), Study Biostatistician, and any other members of the

Planning Committee who will attend the CSEC meeting. When there is an economic analysis, the associated protocol, budget and CV are also included. All reviewers of the proposal are provided with this section. The second volume, containing a variety of supporting information, is provided to those individuals assigned as primary reviewers.

The following specifies the contents of each volume when two volumes are submitted. All material listed below, however, must be included in a proposal.

1. Volume I

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 CSEC, the CSPCC 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 CSEC should consider. Similarly, the CSPCRPCC Director will call the attention of CSEC to particular drug or device considerations that should be addressed during the review.

2) For a resubmission of a proposal:

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

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

?? Letter from the CRADO to the Principal Proponent that summarizes the results of the first CSEC review.

?? A statement by the Principal Proponent or the Study Biostatistician that summarizes the specific changes made in response to CSEC recommendations, including a point-by-point response to each concern listed in the CSEC report and notification letter.

c. Executive Summary/Abstract

The first page of the study protocol is a one-page abstract that succinctly states the research question(s) and the salient elements of the proposed study design including such information as the number of patients and participating sites, duration of patient intake and treatment (follow-up), definition of patient samples, treatment arms, 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 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 (if planned) of clinical site practices.

?? Recruitment strategies. Finding sufficient patients who meet all of the entry criteria is often difficult in clinical trials 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. 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 in Baltimore, Maryland. 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.

?? 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.

e. 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 CSEC. As in the study protocol, the first page is a concise abstract of the proposed economic analysis study.

f. Human Rights Considerations

Before preparing this section, it is wise to review M-3, Part I, Chapter 9 that contains the agency position on these issues. This section should include:

1) Procedures and Ethical 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 CSEC 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".)

2) 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 M-3, Part 1, Chapter 9, Appendix 9C.) 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.

?? 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.

The FDA further requires, for all projects that fall within its purview, that the following elements be included in the informed consent:

?? 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 the FDA or reviewers/monitors from the CSP or industry partner.

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.

3) Human Rights Committee Report

This report 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 CSPCC Human Rights Committee Chairperson.

In this report or a subsequent report, the HRC Chairperson must document that all conditions have been satisfied.

g. Budget(s)

Every proposal contains a study budget including, when appropriate, beyond-core costs for CSPCC or CSPCRPCC, 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), 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 FTEE 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 M-3, Part 1, Chapter 9, 9.13, Payment of Subjects). If such payments are deemed appropriate by the Director, CSPCC, 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).

Funds and FTEE 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/VA Headquarters approval. Unexpended CSP funds and FTEE are not available locally for other research activities and shall be returned to CSP/VA Headquarters on a quarterly basis (or more frequently, at the discretion of the CSP), unless a specific exception is granted.

2) CSPCC Beyond-Core Budget

If the study requires additional costs beyond that of the center's core support, a separate beyond-core budget with justification will be prepared, and the totals will be included in the study budget.

3) CSPCRPCC Beyond-Core Budget

When applicable, cost estimates and justification for resources beyond core costs will be prepared, and these totals will also appear on the study budget.

4) 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.

5) Economic Analysis Budget

A detailed budget should follow the economic analysis protocol. The yearly totals appear as a line item in the study budget.

h. Curricula Vitae

This will be the final item in the first volume of the proposal. The curricula vitae (CV) of the Principal Proponent and the Study Biostatistician are required. If there is an economic analysis component, the CV of the person responsible for this part of the proposal should be included. Finally, if a consultant or other member of the Planning Committee will appear before CSEC, 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.

2. Volume II -- Supporting Information

Volume II contains a variety of information that is of special interest to the primary reviewers. The following sections should be included:

?? Table of Contents.

?? Biostatistical and Research Data Processing Procedures (BRDP).

?? Research Data Forms.

?? Drug/Device Information Report (DIR).

?? Drug/Device Treatment and Handling Procedures (DTHP).

?? Tentative list of participating medical centers and a report of the patient availability survey.

?? Administrative issues, if any.

?? Other sections can be included as appropriate, e.g., description of training procedures, reliability studies, special laboratory procedures, definition of endpoints, central readings, etc.

a. Biostatistical and Research Data Processing Procedures (BRDP)

This section contains plans for analyses that are as complete as can be envisioned for both periodic (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.

b. Research Data Forms

A complete set of essentially final research data forms is required when the proposal is submitted to CSEC for scientific evaluation.

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 formatted 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 researchers including clinicians, the Study Biostatistician, Study CRP, and data processing personnel.

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 final approval of the data forms.

c. 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. 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.

d. 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.

e. 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.

f. 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.

I. 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/VA Headquarters. If the proposal is typed elsewhere, it should be provided on diskette to the CSPCC so that it can be reformatted according to CSP conventions.

CSEC meets twice each year in April/May and October/November. The associated deadlines for submission of completed proposals to the CSP/VA Headquarters for CSEC review are outlined in the following table:

PROPOSAL SUBMISSION DEADLINES		
	Deadlines for Submissions to:	
CSEC Meeting	CSPCC	CSP/VA Headquarters
April/May	Dec. 15	Feb. 1
October/November	June 15	Aug. 1

To allow sufficient time for review, typing, duplication, binding and distribution of the proposal, a complete final draft must reach the CSPCC at least six weeks before the deadline for submission to CSP/VA Headquarters. 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 CSEC.

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 Evaluation Committee (CSEC). In addition, each proposal is reviewed prior to the CSEC meeting by at least three independent reviewers who provide written critiques. Finally, after CSEC 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 M-3, Part I.

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 is usually done at the final planning meeting but always prior to submission for CSEC review. 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. To assist the HRC in this review, the SMART at the CSPCRPCC will review the consent document and provide its findings to the HRC.

The HRC may, on consideration of human rights issues only, accept the study as proposed, accept 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 CSEC review. A recommendation by a HRC may not be reversed except by its own action. Therefore, no study can be submitted to CSEC for evaluation until it has been approved by the HRC. If the study is accepted with conditions, the Study

Biostatistician is responsible for ensuring that the conditions have been met before it is submitted for CSEC evaluation. 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 CSEC is a substitute for review by the local participating centers' R&D Committees and the Subcommittees on Human Studies or local IRBs.

B. Drug Information

When a study involves drugs, the Study CRP develops a Drug Information Report (DIR) on each primary study drug that provides comprehensive information including known side effects, adverse effects, contraindications and precautions. This report(s) is sent to the Director, CSPCC who will distribute it to the Human Rights Committee, the Planning Committee and others as appropriate. A Drug Information Section containing all DIRs for a given study is incorporated into Volume II of the CSEC submission. This information is provided for use by CSEC, the Site Investigators, and their R&D Committees and Subcommittees on Human Studies or their local IRBs.

C. Written Reviews for Cooperative Studies Evaluation Committee

Once CSP/VA Headquarters receives the proposal, it is reviewed to ensure that all the required information is included. Copies of the proposal are then sent to *ad hoc* reviewers who provide written critiques to the Cooperative Studies Evaluation Committee. These written critiques are available to the Principal Proponent, Study Biostatistician, and Study CRP prior to the meeting. The reviewers may request anonymity.

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.

D. The Cooperative Studies Evaluation Committee

The Cooperative Studies Evaluation Committee (CSEC) reviews new and ongoing CSP studies and makes recommendations to the CRADO regarding the scientific merit of the studies.

1. Committee Members

Members of CSEC are appointed by the Secretary of the Department of Veterans Affairs upon recommendation by the CRADO. There are members representing many medical specialties as well as representatives from the FDA, the fields of epidemiology and biostatistics, and from health services research. All members have had extensive experience in clinical research and in the conduct of clinical trials. Members are appointed for a four-year term. Two members of CSEC,

usually a biostatistician and a clinician, are assigned primary responsibility for reviewing each protocol. In addition, for new proposals, the Committee is augmented by an *ad hoc* member knowledgeable in the particular subject matter of the protocol being reviewed. The Chairperson of CSEC is nominated by the CRADO. The responsibilities of the Chairperson are to conduct the meeting and to summarize the deliberations of the Committee. The CRADO and his staff serve as coordinators for the meetings. Appendix B lists CSEC members as of the publication date of these *Guidelines*.

2. The CSEC Review Process

The Principal Proponent and the Study Biostatistician appear before the Committee. If the proposal includes an economic analysis component, the consultant appears as well.

At the meeting, the Principal Proponent will be asked to make an opening statement not to exceed ten minutes, followed by a five-minute statement from the Study Biostatistician. If there are Co-Proponents present, only one will make a formal statement. If there is an economic component, the individual responsible for preparing that protocol will also be expected to make a five-minute statement. At the request of the Principal Proponent and with the concurrence of the CRADO, additional consultants may be available to answer questions and may make a five-minute statement. These statements should be based on written documents that are distributed to CSEC members prior to the meeting. They should provide a concise summary of the research problem and state why it should be supported by VA.

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

After the formal statements, the *ad hoc* reviewer, the CSEC primary reviewers and the remaining CSEC members question the proponents on problems and issues they have identified. The proponents defend the protocol in an interactive discussion.

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

3. CSEC Recommendations

Generally one of four actions is taken:

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

?? Conditional approval. The Committee approves the study with the understanding that the Principal Proponent and the Study Biostatistician will make certain changes or additions to the protocol. When the changes are made and are approved by the CRADO, the

Chairperson of CSEC, and the CSEC primary reviewers, the study will be recommended for funding.

?? Reject or defer consideration of the study with recommendation for resubmittal. In unusual circumstances the Committee finds the study worthwhile, but in need of major revisions. In this case, should the investigator choose to submit a revised protocol, the CRADO may waive the requirement for an initial planning request and review.

?? Reject the study. The Principal Proponent will have an opportunity to review the CSEC report. If the Principal Proponent wants to resubmit the proposal to the CSP, a new request for planning must be sent to the CRADO.

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

For new studies that are approved, CSEC 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 CSEC does not ensure funding. Action by this Committee constitutes a recommendation to the CRADO. Written notification by the CRADO 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 CRADO determines that funding will not become available within 18 months after CSEC approval. If the Principal Proponent then chooses to resubmit a proposal, a new request for planning must be sent to the CRADO.

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 CRADO, through the Director, CSPCC, 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 CRADO. This decision is made most appropriately at the time of the initial planning meeting, but may occur after CSEC reviews the protocol. The Study Chairperson should not be a member of VA Headquarters staff, a current chairperson of a CSP study, nor function as the Study Biostatistician. 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.

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 CSEC.

?? Final selection of participating medical centers.

?? Final review and approval of study data forms, and submission for OMB approval.

?? Collaboration with CSPCC on development of an Operations Manual.

?? Collaboration with CSPCRPCC on pharmaceutical and FDA issues.

?? Nomination of members of the Executive Committee.

?? Nomination of members of the Data and Safety Monitoring Board.

?? Hiring support staff at the Chairperson's Office.

?? Selection of core labs.

?? 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 with industry 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 Director, CSPCC. The Director, CSPCC will ensure that all potential participating VA centers have a Multiple Project Assurance (MPA) issued by the VA's Office of Research Compliance and Assurance (ORCA). Only VA centers having a MPA will be allowed to participate. 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 Human Rights Committee will also conduct a re-review.

When a medical center is informed that it has been chosen to participate, the SI, with the assistance of the ACOS/R&D, prepares a formal request for funds to the CRADO that is signed by the Medical Center Director. This request duplicates the budgetary estimates provided by the CSPCC. Any deviation from the approved budget requires the endorsement of the Director, CSPCC and the approval of the CRADO.

C. Review by Participating Medical Centers

When the Principal Proponent has been notified that funding is available, the CSPCC 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 Headquarters Eligibility Committee). Usually, the SI will require active support from the SI's service and other services, e.g., Pharmacy, Clinical Laboratory. 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 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 a standard document for use in all or most medical centers. When necessary and appropriate, variations across centers will be permitted with the approval of the Director, CSPCC. Major changes must have the approval of the CSPCC 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 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 Director, CSPCRPCC by the CSPCC 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.

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. Although the forms were reviewed by CSEC, there should be another review before they are sent to VA Headquarters for approval. The Study Biostatistician will initiate this review with the Study Chairperson, the Study CRP, and relevant members of the CSPCC. The Study Chairperson may visit the CSPCC for the review. The Study Biostatistician prepares the request for VA and Office of Management and Budget (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 a distributed data entry 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, Study CRP, and other study members prepare an Operations Manual. This manual is used by the data collectors at each participating medical center and is intended to ensure that the study procedures are followed as uniformly as possible. It includes details of data collection, flow, recording 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 that will be prepared by SMART. 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. Hiring and Training of Study Personnel

CSP study personnel are generally hired on term appointments. When an emergency situation arises concerning FTEE shortages or cuts, use of an 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. In addition, all SIs and Site Study Assistants must document human ethics in clinical trials training prior to study start-up at their site.

During the patient recruitment phase of the study, staffing will vary depending on estimated workload. Generally, many participating centers will employ full-time research assistants, though less than full-time may be sufficient. During follow-up, a part-time appointment is generally sufficient.

G. 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 most 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 Letter of Understanding 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.

H. 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 one to two days, but can be longer for more complicated studies. All study personnel, including Site Investigators, Site Study Assistants, the Study Chairperson and his/her staff, CSPCC Study staff, CSPCRPCC Study staff, a SMART representative, and Executive Committee members, will attend the meeting. If the study is to be monitored, a SMART monitor will also attend. 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 SI's 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 Director, CSPCC, or Study Biostatistician will review VA CSP policies and regulations while a SMART monitor 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 Project Director, the Study Biostatistician and CSPCC staff, and the Study CRP and CSPCRPCC staff will generally provide this review and training.

Also, held in conjunction with this meeting will be a one-day training course on Good Clinical Practices presented by SMART. Coordinators and SI's will be required to attend this course or submit documentation of equivalent training obtained elsewhere.

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

V. CONDUCTING A CSP STUDY

A. CSP Study Management and Monitoring

The CRADO delegates responsibility for each CSP study to the respective Directors, CSPCC 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 Director, CSPCC will provide a detailed report of progress to the CRADO with special attention to patient accrual and/or problems that might affect the successful completion of the study. The CRADO may discuss the contents of this report with the Study Chairperson and the Director, CSPCC in writing or by telephone and recommend appropriate actions. Any study that does not reach at least 90% of the targeted accrual for the first year will be at risk for termination. The decision to continue a study is at the discretion of the CRADO.

Five groups, in addition to the SMART unit, share the responsibility for conducting and/or monitoring a CSP Study: the Study Group, the Executive Committee, the Data and Safety Monitoring Board, the CSPCC Human Rights Committee and the Cooperative Studies Evaluation Committee. The first three committees meet to review the operational and monitoring aspects of the study before patient intake begins. 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 lasting more than four years are reviewed by CSEC at three-year intervals or more often, should a specific need arise. Studies lasting four years or less are reviewed by CSEC at the halfway point of the study.

The standard schedule of meetings for the Study Group, Executive Committee and Data and Safety Monitoring Board consists of an initial meeting for organizational, informational and training purposes prior to patient intake, a meeting six to nine months after the initiation of patient intake, and annual meetings thereafter. After the first year, meetings will be scheduled as needed. 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, the Study CRP, all Site Investigators and any permanent consultants to the study. At the Organizational Meeting, the Study Biostatistician or Director, CSPCC will make a presentation on research ethics and inform the group that site visits routinely take place. Two to three weeks prior to Study Group meetings, the Study Biostatistician prepares and distributes a report to the Study 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. When appropriate, the Research Assistant(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 Director, CSPCC for distribution. As is the case with the Principal Proponents, all SIs and permanent consultants to the study will be required to submit a

Statement of Disclosure (Appendix D). 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 four to eight members and includes the Study Chairperson, the Study Biostatistician, the Study CRP, the head(s) of any special central support unit(s) related to the study, 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 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 and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) usually numbers six to eight members: experts in the subject matter of the study, two independent biostatisticians, and other appropriate technical or scientific specialists. Any study that involves patient intervention will have a DSMB. When there is an economic analysis component, the Board will include an expert in health economics. The Study Chairperson and the Study Biostatistician are nonvoting study representatives and the CRADO and the Director, CSPCC are nonvoting CSP representatives. Meetings of the DSMB are closed meetings so that additional attendees, such as pharmaceutical representatives, may not attend these sessions unless specifically invited by the DSMB for the purpose of clarifying specific issues for the DSMB.

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

The Study Chairperson and the Study Biostatistician should not personally contact the nominees. The Director, CSPCC 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/VA Headquarters. The CRADO 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 Director, CSPCC. The term of appointment will extend through the last day of patient follow-up. If the services of Board members are required after that time, it will be on an *ad hoc* basis.

Data and Safety Monitoring Board 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 Director, CSPCC to see that nominations put forth are in accordance with the true spirit and intent of CSP policy. As is the case with Principal Proponents, DSMB members should submit a statement of disclosure (see Appendix D).

The Data and Safety Monitoring Board 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 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 and Safety Monitoring Board 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.

As part of the study proposal, the Study Biostatistician 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 and Safety Monitoring Board 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 prepares and distributes a report two-three weeks prior to meetings and at least one interim report between meetings. If data provided to the DSMB are unblinded, tables containing these data will not be provided to the Study Chairperson, who must remain blinded. 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 can, if it wishes, meet in Executive Session (with the Study Biostatistician and CSP representatives) to formulate recommendations.

At their first meeting, the members of the Data and Safety Monitoring Board select a Chairperson with the assistance of the Director, CSPCC. 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 Director, CSPCC within three weeks. The report states those actions that the Board believes are necessary or highly desirable. These are phrased as recommendations to the CRADO. The DSMB 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 will be asked to consult with the Study Chairperson and indicate how the recommendations will be implemented. The Director, CSPCC will concur or add whatever comments he/she wishes, and forward the report to the CRADO with additional distribution to the Study Chairperson, the Data and Safety Monitoring Board and the Director, CSPCRPCC. After the meeting, the Study Biostatistician should telephone the CRADO's office in order to make an informal report.

In addition to the report of the DSMB meeting, the DSMB 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 blinded data results, the report will provide them some assurance that the DSMB is monitoring the safety of study patients and will make them aware of any safety issues. The report needs to be worded such that blinded study results are not revealed unless absolutely necessary.

During the course of the study, the Study Chairperson and other members of the Study Group may not consult with DSMB members without the approval of the Director, CSPCC.

In regard to the question of liability, the decision of General Counsel was announced in a memorandum dated July 7, 1975. The Counsel stated that DSMB 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.

4. Human Rights Committee

In addition to reviewing the protocol for human rights issues prior to submission to CSEC, 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 and Safety Monitoring Board to participate in that part of the meeting that deals with patients' rights and welfare. Alternatively, if the DSMB and Human Rights Committee do not meet at the same time, a HRC representative may attend the DSMB meeting. It is the responsibility of the Study Biostatistician and the Study Chairperson to provide the Committee with the appropriate information, including some or all of the data provided to the Data and Safety Monitoring Board 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 Director, CSPCC who will make the proper distribution. In rare instances where the HRC is blinded and the DSMB is not (such as agreements

between CSP and other agencies in interagency agreement funded studies), a member of the HRC, usually the HRC Chairperson, will be appointed to the DSMB.

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 Director, CSPCC. The report should not 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 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 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 and Safety Monitoring Board 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 CRADO may decide to terminate the study if he determines that the study is not achieving its objective.

It is the responsibility of the CSPCC to inform patients if similar studies conducted by other agencies have been stopped prematurely, and the Data and Safety Monitoring Board 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 copies of the letter(s).

C. Meeting/Travel Arrangements

To initiate one of the regularly scheduled Study Group/Executive Committee meetings, the Study Chairperson should contact the Study Biostatistician 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. If the cost projections for the three sites are comparable, the Study Chairperson may choose one. However, if the differences are significant, the site will be selected by the Director, CSPCC. If the Study Chairperson wants to schedule a meeting at a more costly location, the attendees (excluding those from the CSPCC and CSPCRPCC) must obtain the additional funds from sources other than locally or centrally directed VA research travel funds. 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 CRADO is required. Committee members 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.

When these details have been settled, the Study Biostatistician informs the Director, CSPCC of the dates and place of the meeting, the names of the attendees and the addresses of any non-VA personnel who will be traveling on letters of agreement. An agenda indicating meeting times is attached. This letter, with appropriate justification, is forwarded to CSP/VA Headquarters as early as possible but no later than four weeks prior to the scheduled meeting date. Non-routine meetings of any of the groups necessitated by unusual problems arising during the study may be arranged on shorter notice by contact with the Director, CSPCC.

The Data and Safety Monitoring Board generally meets in the vicinity of the CSPCC in order to facilitate the Human Rights Committee review. However, the initial meeting of the DSMB may be held in Washington, D.C. if the CRADO is to attend. Alternatively, if the DSMB and Human Rights Committee do not meet at the same time, a HRC representative may attend the DSMB meeting.

Funding for travel to meetings of the Study Group, Executive Committee, Data and Safety Monitoring Board, and other authorized CSP study activities will be provided from CSP/VA Headquarters centrally directed travel funds. When the meeting has been approved, the CSPCC will notify all expected attendees and the associated ACOS 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 and Safety Monitoring Board and CSPCC personnel, are dealing with privileged information and that confidentiality must be maintained.

D. Protocol Changes

Subsequent to CSEC approval, no person or group including the Study Chairperson, Study Biostatistician, the Study Group, the Executive Committee, the Data and Safety Monitoring Board and the Study CRP (if the study involves drugs or devices), may unilaterally or collectively make study protocol changes without the appropriate approvals.

The Study Chairperson, Study Biostatistician, and Study CRP should discuss proposed study protocol changes among themselves before presenting such changes for approval. The Study Biostatistician and Study CRP 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 and the Data and Safety Monitoring Board. In all cases, the involved Center Directors (CSPCC and CSPCRPCC) and the CRADO must approve proposed study protocol changes. The CRADO will make the decision whether or not the proposed study protocol changes require the approval of CSEC.

After the CRADO or CSEC (when the CRADO requires that CSEC reviews the change(s)) approves the proposed change, the ACOS/R&D at each participating medical center is informed, since major changes in the protocol 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 CRADO. Major changes may require another CSEC 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 Director, CSPCC. If the Director, CSPCC recommends approval and the CRADO concurs, the office of the ACOS/R&D of the participating medical center will be informed that an official request may be initiated through the Medical Center Director and the VISN Director.

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/VA Headquarters on a quarterly basis.

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 allowed to read (or have read to him/her) the informed consent form in order to have some understanding of the study before discussing it with the investigator. 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. These sheets are 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. For policy regarding who may consent to the participation of incompetent patients in VA research, refer to VA Circular 10-90-052, Subject: Research with Surrogate Consent.

Failure to obtain informed consent will result in disciplinary sanctions by the CRADO and could result in the dismissal of the SI. The data from patients not having an informed consent form will not be used in any study report. This form must be administered by the SI or his/her designee and signatures must be witnessed by a person unrelated to the study. While the SI need not be present during the actual informed consent signing, he/she 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. Original copies of VA 10-1086 are sent to the Research Office at each participating medical center for placement in the IRB file. A copy of the signed consent form must be given to the patient for his/her own use. Copies of each consent must also be sent to the local VAMC pharmacy in the case of studies involving pharmaceuticals. 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.

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) will 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 match.

Patient identifying information will be maintained at the participating sites. However, in many studies, it may be necessary for the CSPCC 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, or letters/surveys that are mailed to patients from the CSPCC. When such information is required by the CSPCC, it must be provided on a separate form or recorded on VA Form 10-1086 (Informed Consent), which is submitted to the CSPCC. At the CSPCC, 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.

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 reviews are to be done on the anniversary of the initial reviews by these committees and not necessarily on 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 will notify the Site Investigators, with a copy to the ACOS for R&D, of an impending review two or three months in advance to facilitate scheduling with the appropriate committee. The CSPCC will also provide the Investigators with any material requested for this yearly review, except for blinded outcome data. The CSPCC 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 yearly reviews are not done in a timely fashion or the CSPCC does not receive the minutes or chairperson's letter in a timely fashion, the participating center will be placed on probation. Probation in this instance will mean that the center's participation including the funding and ability to randomize patients will be suspended until the appropriate documentation of the yearly review has been received at the CSPCC.

G. Data Collection, Editing and Patient Entry Policy

Data are to be collected only on VA and OMB approved data forms supplied by the CSPCC or the CSPCRPCC. In general, data reported on the forms should be reviewed by the SI at each medical center before being sent to the CSPCC for biostatistical and 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 is entered at the participating hospital and submitted to the CSPCC electronically. 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 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 Director(s) will prepare a cover letter to the CRADO certifying that all of the appropriate signatures have been obtained. Only after the CRADO 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 is 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, Study Chairman's Office 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 is notified or 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 Site Investigator also has the responsibility to follow local IRB requirements for reporting SAEs/UADEs and other adverse events and to include documentation of such communications in the Investigator Study File.

The CSPCC is responsible for reporting all SAEs/UADEs to the DSMB and Human Rights Committee as part of the study progress reports. The Director, CSPCRPCC or the Director, CSPCC, as appropriate, will inform the CRADO of SAEs/UADEs that, in their judgment, the CRADO needs to be aware of. For studies in which the CSPCRPCC is involved, the Director, CSPCRPCC will be responsible for notifying the CRADO. In these studies, the SAEs/UADEs reported to the CRADO will be those that the CSPCRPCC reports to FDA for studies with IND/IDEs or, for studies without an IND/IDE, ones that they would have reported to FDA if there had been an IND/IDE. For studies in which the CSPCRPCC is not involved (e.g., surgical trials, trials of psychotherapy), the CSPCC Director will be responsible for notifying the CRADO. This will usually be done after consultation with the Study Chairperson. For SAEs/UADEs reported to the CRADO, notification should usually occur within 72 hours of the Director, CSPCC/CSPCRPCC being notified. The CRADO will be responsible for reporting SAEs/UADEs to the Office of Research Compliance and Assurance (ORCA).

I. Breaking Study Blind

Most 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 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 via telephone and send a copy of the envelope, which is filed with the study documents at the CSPCC. 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 of their condition. Drug code envelopes should not be confused with the randomization code envelopes.

J. Subprotocols

Subprotocols to VA CSP studies are generally discouraged since they add burden to the participating clinic personnel, the CSPCC, the patients in the study, and to the Cooperative Studies Program costs. 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 and Safety Monitoring Board, and the CSPCC Human Rights Committee.

3) The subprotocol must be reviewed and approved by the R&D and Human Subjects Subcommittee/IRB at each anticipated participating center.

4) 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.

5) If funding is required, non-CSP sources such as National Institutes of Health (NIH), the Agency for Health Care Policy and Research (AHCPR), 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 Director of the MRS has agreed to 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.

6) All oversight committee approvals are conveyed to the CRADO as <u>recommendations</u> for action. Final approval must be obtained from the CRADO.

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

All policies that govern CSP projects also apply to subprotocols. For example, manuscripts must be approved by the Executive Committee and the Director, CSPCC.

K. Newsletter

Study newsletters are prepared and issued regularly by the Study Chairperson and/or Study Biostatistician. 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 and/or Study Chairperson.

L. Site Visits

Site visits by the Study Chairperson, the Study Biostatistician, 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 Director, CSPCC, approved by the CRADO, 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 Director, CSPCC 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 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.

M. GCP Review/Monitoring Visits

All VA centers participating in the CSP studies will be visited at least once during the course of the study by GCP reviewers from the Site Monitoring and Review Team (SMART). The purpose of these visits is to assess compliance with Good Clinical Practice requirements. GCP reviewers will review patient study files and source documents in both clinic files and patients' official VA medical records and will also review regulatory/essential documents such as IRB correspondence and FDA regulatory documents. Areas of particular concern will be patient consent issues, protocol adherence, safety

monitoring, IRB reviews and approvals, regulatory documents, patient records, drug or device accountability and handling, and site operations/investigator involvement.

In trials intended to provide data for a regulatory submission, clinical monitors may periodically visit each site. These monitors will ensure that sites are strictly adhering to the protocol and that the data being submitted are accurate. These monitors can either be provided by the Good Clinical Practice Monitoring Group of SMART or by an industry sponsor. If provided by an industry sponsor, these monitors will be under the direction of SMART. Unlike the SMART unit, which will be provided funding for all VA CSP studies, funding for the monitoring of studies must be obtained from non-VA CSP sources.

N. 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 it impossible to 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, he/she 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 Director, CSPCC of the proposed change. If the study involves drugs or devices, the CSPCC 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 Director, CSPCC, forwarding the R&D minutes when they are available. 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 will notify the CSPCRPCC of all SI changes.

If the Study Chairperson cannot continue to direct the study, he/she should inform the Director, CSPCC as early as possible so that nominations can be made to the CRADO. 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 should initiate a letter endorsing the nominee as described previously. In cases of an "emergency," where there is little or no advance notice, the CRADO 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.

O. 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 and Safety Monitoring Board, can propose to place a participating site on probation. The proposal should be sent to the Director, CSPCC for a decision. If the

Director, CSPCC 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, 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 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 Director, CSPCC stating the rationale and the proposed action. The Director, CSPCC will then seek the approval of the CRADO for the action.

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 performance and the desire to be dropped.

P. 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 must have the prior approval of the CRADO. Early termination is usually based on recommendations from the Executive Committee and the Data and Safety Monitoring Board 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 Director, CSPCC who will make comments and forward the recommendation to the CRADO for decision. If the CRADO concurs, he will inform the Director, CSPCC, who will inform the ACOS/R&D of the medical center and the CSPCRPCC. After that contact, the Director, CSPCC 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 CRADO. 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 study is being conducted under an IND and the early termination is due to non-compliance with regulations, then FDA must also be notified.

If equipment purchased for the study is needed at another medical center, the Director, CSPCC 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 Director, CSPCC for such purpose. In the event that a new center is not yet identified, the Study Chairperson or Study Biostatistician 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 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 the center may be terminated early. In this case, the Executive Committee should set the criteria for terminating a capitation center. Once the criteria are established, the process would be the same as a center that receives recurring funds (see above).

Q. CSEC Reviews of Ongoing Studies

All CSP studies are reviewed by CSEC at least once during their active phase. For studies lasting four years or less, this review will take place at the study's midpoint. For studies lasting more than four years, these reviews take place at three-year intervals. For these studies the first review is scheduled for the CSEC meeting nearest to the three-year anniversary of the first funding unless there has been an intervening CSEC review for another purpose. In the latter case, CSEC determines the date of the next review. Ordinarily, a three-year review will not be scheduled if fewer than 6 months remain until patient follow-up is ended.

Special reviews, e.g., requests for extensions of patient intake duration, are scheduled as required during the ongoing phase of the study. The Study Biostatistician and the Study Chairperson are responsible for scheduling these reviews through CSP/VA Headquarters. Submission deadlines are the same as for new proposals.

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

?? Table of Contents.

?? Executive Summary or Abstract of the study.

?? CSPCC Director's Summary of Progress: The Director, CSPCC 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. He/she 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, 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, CSEC may request outcome data by blinded treatment assignment, 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 CSEC. In these cases, a letter from the Chair of the DSMB should also be included in the mid-term report.

?? Previous CSEC Reports.

?? Data and Safety Monitoring Board Reports or Minutes.

?? Executive Committee Reports or Minutes.

?? Human Rights Committee Minutes (including site visit reports).

?? Bibliography of Study Publications.

?? Budgets: The original budget approved by CSEC; 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.

R. CSP Study Files

Complete files are maintained on CSP studies at the CSPCC, the CSPCRPCC, and the SMART office 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.

S. 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 (M-3, Part I, Chapter 4). 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 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.

A new system, VA-STAR (System to Track and Advance Research) will be introduced during the Spring 2000. The objective of the VA-STAR project is to develop an enterprise wide information management system that incorporates the functions of the current system, as well as enhancements to meet other user needs.

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 sponsor.

T. 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.
- Industry funds must be contributed to an independent foundation, and funds must be under the control of CSP - not industry or investigator.
- Industry may participate in planning meetings, Study Group meetings, Executive Committee meetings and Publication Committee meetings.
- Industry cannot participate in Data and Safety Monitoring Board meetings.
- Industry cannot have access to unblinded data prior to the end of patient follow-up.
- Industry should receive courtesy pre-publication manuscript for comments and receive acknowledgment for funding in study publications.
- Industry should not have any veto over publication.
- Industry should not release pre-publication data in any form.
- CSP should help in FDA preparations and be reimbursed for extra effort.
- If industry is to provide site monitoring, their visits and reports will be coordinated and distributed through SMART.

Detailed information regarding collaborative agreements with industry can be found in the document “Understanding the Contracting Practices in VA Cooperative Studies Program”.

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. 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.H.1.d.).

When follow-up on all patients enrolled in the study has ended, the CSPCC 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. The Executive Committee is responsible for the publication 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 Director, CSPCC, who will forward it to CSP/VA Headquarters. Material for publication should ordinarily be submitted within one year of receipt of all data at the CSPCC. 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 should have physical possession of all study data. The CSPCC 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, 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. The CSPCC 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 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 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 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 Director should be informed. Questions of appropriate use of CSP data will be referred to the CRADO.

B. Final Study Meeting

The Study Group and the Data and Safety Monitoring Board, 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.E.), 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, and the CRADO, the Director, CSPCC 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 Director, CSPCC may request that the CRADO 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 is true whether the publication or presentation presents the results of the principal undertaking or the results of an ancillary analysis. The Director, CSPCC must approve a manuscript prior to submission. The CRADO must approve a manuscript submission prior to publication.

All publications must give proper recognition to VA CSP. It is obligatory to list the VA as the primary institutional affiliation. Submission of manuscripts must follow the usual VA policy. 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 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/VA Headquarters. When any manuscript is accepted for publication, the Study Chairperson and the Study Biostatistician should write a summary of the results and send it (along with a copy of the revised manuscript) to CSP/VA Headquarters. 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/VA Headquarters. After CSP/VA Headquarters has received and approved the summary, it should be forwarded to the Office of Research Communications. CSP/VA Headquarters will work with the appropriate offices to coordinate publicity efforts for major publications.

A copy of the abstract from the published paper (including the complete journal reference and a brief lay-language summary of the study and the paper), should be sent to the Perry Point CSPCC for inclusion in the next *Cooperative Studies Update*. If the published paper does not include an abstract, the Study Chairperson or Study Biostatistician should write one. When reprints are available, the Study Chairperson should send 15 copies to the Director, CSPCC. Five of these will be forwarded to CSP/VA Headquarters and a courtesy copy will be sent to other CSPCCs, the CSPCRPCC and the ERICs.

D. Custodianship of Data

The policy regarding custodianship of data should be communicated to investigators in the planning and organizational stages. 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 at the appropriate time. While most data should be submitted to the CSPCC 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 will determine when the appropriate time is to submit the data to the CSPCC.

All analyses related to the objectives of the study and publication plan as specified in the study protocol will be performed by the CSPCC. All raw study data will reside at the CSPCC and will not be released until objectives as stated in the protocol and manuscripts in the protocol publication plan have been completed. The CSPCC will act as the repository of all study data from a completed cooperative study. Under certain circumstances, 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 Director and CSP Director.

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 guidelines, 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 Director, the Study Chairperson ceases to exercise this authority in an appropriate manner, the CSPCC 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 and, where appropriate, sent to the CRADO for final review. If a study dataset is released to anyone outside the CSPCC, the recipient inherits the responsibilities of stewardship, and may not redistribute the data to anyone else.

E. Administrative Repercussions

The CSP policies for data analysis and publications of results apply to all members of the study team (Study Chairperson, SIs, Study Biostatistician, etc.). If a Study Chairperson or Site Investigator has been discovered to be misusing study data or has submitted unauthorized manuscripts for publication, the following administrative actions may be taken (at the discretion of the CRADO):

- 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 CRADO).

VII. CONCLUSION

The planning, review, initiation and completion of a CSP study are a complex process requiring close communication among all participants. We have prepared this document as a guideline, but we recognize the need for flexibility in the conduct of Cooperative Studies. Exemptions to these guidelines may be granted by the CRADO. Requests for exemptions should be made through the Director of the appropriate CSPCC. We welcome suggestions from study participants for inclusion in subsequent editions of these guidelines.

APPENDIX A - CSP ADDRESSES

STAFF PHONE/FAX NUMBERS

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Thelma Salazar, Assistant Director for Administration	
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*Members as of September 18, 2001

**Member serves through this date

APPENDIX C - 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
BPLS	Biopharmaceutics/Pharmacokinetics Laboratory Section
BRDP	Biostatistical and Research Data Processing Procedure
CRADO	Chief Research and Development Officer
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
CV	Curriculum Vitae
DIR	Drug Information Report
DTHP	Drug Treatment and Handling Procedures
DSMB	Data and Safety Monitoring Board
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
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
OMB	Office of Management and Budget
ORCA	Office of Research Compliance and Assurance
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
VAMC	Veterans Affairs Medical Center
VHA	Veterans Health Administration

APPENDIX D - STATEMENT OF DISCLOSURE

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

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