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GUIDELINES

FOR

VA COOPERATIVE STUDIES

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IMPORTANT EVENTS IN A VA COOPERATIVE STUDY

I. INTRODUCTION

The purpose of this manual is to describe policies and procedures for the organization and operation of VA cooperative studies, including the required laboratory and other technical support functions. Cooperative studies are those in which investigators from two or more VA medical centers voluntarily agree to study collectively a selected problem in a uniform manner, under a common protocol with central coordination.

Cooperative studies are particularly advantageous for certain problems in the Medical Research Service (MRS) as well as for selected problems in the Health Services Research and Development Service (HSR&DS), and the Rehabilitative Engineering Research and Development Service (RER&DS). For the more common medical conditions, they can deal with the problems of diverse approaches, local bias, work load, duration of study, and differences in clinical setting. For medical conditions which are relatively rare so that one medical center may admit only a few patients a year, knowledge can be accumulated more rapidly by the pooling of observations of several facilities. With few exceptions, however, a cooperative study is not the place for the development and refinement of therapeutic techniques. Instead, clinical trial cooperative studies should be performed to evaluate the safety, efficacy, and cost effectiveness of health care intervention measures that have been developed and refined by preliminary trials in humans. Some epidemiological issues, however, may also be appropriate topics for cooperative studies. When such an approach is considered appropriate and advantageous, cooperative studies are encouraged by the Veterans Administration.

Because of the importance attributed to this type of study, the VA has established the Cooperative Studies Program within the Medical Research Service to administer and coordinate them regardless of whether they fall within MRS, HSR&DS, or RER&DS. The Chief, Cooperative Studies Program (CSP), has in turn established four Cooperative Studies Program Coordinating Centers (CSPCCs), located at the VA Medical Centers, Hines, IL, Palo Alto, CA, Perry Point, MD, and West Haven, CT, and a Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC), located at the VAMC, Albuquerque, NM. (Appendix A).

The primary responsibilities of the CSPCCs are to provide biostatistical and data processing support and administrative coordination for VA cooperative studies and to ensure that they are conducted according to the guidelines set forth in this manual. Although it is expected that the CSPCCs will be responsible for the biostatistical and data processing needs of most cooperative studies, in certain situations these responsibilities may be performed by an outside contractor. In such cases, a CSPCC will monitor the study to ensure that these guidelines are followed and that the outside contractor is performing adequately.

The primary responsibilities of the CSPCRPCC, in those studies where they are involved, are to assist in developing the study design and to acquire, assure the quality, distribute, monitor usage and adverse reactions, provide accountability and direct the disposition of all study articles (drugs, medical devices, diagnostic agents, biologicals, electronic devices, etc. for human use) under inventory in VA cooperative studies. The CSPCRPCC acts as a liaison between the pharmaceutical industry or manufacturers and the Study Chairperson and the related study committees, solves study article-related problems, provides guidance on and monitors compliance with FDA regulations governing clinical investigations and provides a comprehensive drug information service to study participants. The drug information service includes information on pharmacological mechanisms, absorption, half-lives, steady-state levels, distribution, metabolism, excretion, adverse and toxic effects, drug-drug, drug-laboratory and drug-food interactions, stability data, and assay methods of drugs in biological fluids.

In a cooperative study most responsibilities are shared. However, certain persons and groups will have primary or major responsibilities. It is the purpose of these guidelines to identify the responsibilities and the means of providing for them.

II. DEVELOPING A COOPERATIVE STUDY

A. Submission of Ideas

An individual or someone representing a group (the Principal Proponent), interested in developing a cooperative study, sends a request for funds to plan a protocol to the Chief of the Cooperative Studies Program in VACO through his/her medical center's ACOS for Research and Development. This individual must either (a) be at least a 5/8 time employee of the VA or (b) if less than a 5/8 time employee, must have applied for and received approval for eligibility to receive Research and Development (R&D) funds from the Eligibility Panel of the VACO, R&D Service. In the latter case, a copy of the letter establishing eligibility to receive funds must be attached to the request.

The request for planning funds should be a one or two page statement indicating the objectives of the proposed research, the importance of the study topic to the VA and its patients, and why it requires a cooperative study within the VA. A paragraph which provides a firm summary statement indicating that the procedure(s) to be evaluated have had sufficient preliminary trials to be considered refined enough for a cooperative study evaluation should be included. The letter should also contain a statement of the Principal Proponent's eligibility to receive Medical Research Service funds and estimates of the number of medical centers required, the duration of the study in years, and the annual and total budget. A tentative protocol and other relevant background materials, including reprints, references and summaries of the Principal Proponent's experience, may be appended to this request. Appendix G provides a checklist of items that should be included in this request.

At various times during the year (usually three times; see Appendix B), requests for planning funds are first reviewed by VA program specialists who provide a written critique of the proposal and then evaluated by a "triage review committee" constituted by the VACO Medical Research Service (see Appendix C), which may either reject them, assign a priority rating, or ask for additional information. The requests assigned a priority are put on a waiting list and those with the highest priority are chosen for planning. The actual number of studies released for active planning will depend primarily on the travel funds available and the current work load capacities of the CSPCCs.

All VA cooperative studies (regardless of the source of funding) must have the approval of the Director, Medical Research Service (and the Director, HSR&DS or RER&DS as appropriate). All protocols, whether funded by the VA or by outside sources such as the Public Health Service, will have to be evaluated by the Cooperative Studies Evaluation Committee (CSEC) before VA approval will be granted. Each protocol will be submitted for evaluation through the assigned CSPCC and the Chief, CSP, VACO. All rules and regulations that govern cooperative studies in the VA must be adhered to in both the development of the protocol and in the conduct of the study when approved. In general, submissions of protocols to outside agencies for funding should occur after evaluation by CSEC and approval of the Director, Medical Research Service (and the Director, HSR&DS or RER&DS as appropriate). These protocols must identify all participating medical centers and be approved by all local R&D and Human Studies Committees and the respective medical center directors prior to submission to outside agencies. When necessary or highly desirable, an exception to this may be sought by petitioning the Director, Medical Research Service (and the Director, HSR&DS or RER&DS as appropriate), through the Chief, CSPCC and the Chief, CSP.

B. Planning of Study

When funds for planning a study have been authorized, the Chief, CSP will assign the study to one of the four CSPCCs. The Chief of the assigned CSPCC will notify the Principal Proponent, with a copy of this letter to the local ACOS for Research and Development (and the Chief, CSPCRPCC if the study involves study articles), that the study has been approved for planning. The Chief will then assign the project to a biostatistician who will collaborate with the Principal Proponent in setting up the planning meetings.

1. **Planning Committee.** Once funds for planning have been authorized, a Planning Committee must be established. This committee should include the Principal Proponent, the CSPCC Biostatistician, at least two potential Participating Investigators who are eligible for VA research funding and any additional relevant consultants. If several disciplines are involved (such as medical and surgical), the composition of the Planning Committee should reflect this and may require a consultant for each discipline. The total planning group should usually consist of four to eight persons. Supporting resource personnel from VACO (including the Chief, CSP, or representatives from Nursing Service, Pathology Service, etc.) and the Chief, CSPCC are not usually included in this count. When a study involves drugs or other study articles, the Chief, CSPCRPCC will assign a Clinical Research Pharmacist to the project to collaborate with the committee. This pharmacist or the Chief, CSPCRPCC will ordinarily attend the first planning meeting and any additional planning meetings as determined to be appropriate by the Chief, CSPCRPCC and the Chief, CSPCC. In such studies, a discussion with the Chief, CSPCRPCC concerning attendance at the planning meetings will occur prior to the meetings.

2. **Meetings.** Planning will ordinarily require two major meetings lasting two or three days each. Under special circumstances, additional minor planning activities may be funded. The Principal Proponent should submit a list of proposed attendees through the appropriate CSPCC to the VACO, CSP office at least five weeks prior to a meeting. It is strongly encouraged, when travel costs allow, that planning meetings be held in the vicinity of the participating CSPCC to permit attendance of other relevant CSPCC staff. This is obligatory for the final planning meeting to facilitate the Human Rights Committee review of the proposal during a portion of that meeting. Meeting dates will be at the joint convenience of the CSPCC Biostatistician and the other attendees, and meetings will not be funded by VACO, CSP unless the biostatistician is able to attend.

Under ordinary circumstances, if the first planning meeting is not held within three months of notification that funding for planning is authorized, or if subsequent planning meetings and activities do not occur within six months of the prior 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 Chief, CSPCC to notify VACO, CSP at the appropriate time to discontinue support for planning or, if the Chief, CSPCC concurs that the circumstances in a given situation are unusual and justify a deviation from this practice, to petition the Chief, CSP for an extension.

3. **Duties.** The Planning Committee is responsible for the preparation of a final protocol for ethical review by the CSPCC Human Rights Committee and ethical, professional, and scientific merit review by the Cooperative Studies Evaluation Committee (CSEC). This protocol should reflect a close, collaborative, in-depth effort in its planning and essential agreement on major issues of goals, experimental design, sample size, variables to be measured, methods of monitoring the study, data analysis, etc. The CSPCC Biostatistician has primary responsibility for the general scientific methodology and validity of the experimental design, sample size estimates, plans for monitoring data summaries, final data analysis, and biostatistical interpretation of the results. In studies involving drugs or other study articles, the CSPCRPCC Clinical Research Pharmacist has primary responsibility for assisting the Principal Proponent in designing treatment regimens, obtaining study articles and assuring their quality, assuring compliance with drug accountability and other legal requirements by designing study article handling protocols, adverse drug reaction reporting procedures, and preparing and coordinating the IND and IDE submissions to the FDA when applicable.

Before the first planning meeting, the Principal Proponent should distribute to the committee members any material bearing on the subject of the study, such as pertinent journal articles, the request for planning funds, and a rough draft of the proposed protocol or a detailed outline for a draft protocol. This material will allow the committee members to acquaint themselves beforehand with the proposed study. At this first meeting, the committee should define the primary question(s) to be answered by the study, the patient population to be studied, the therapeutic regimens (if any), the response to be measured, the

optimal method of comparisons, what types of outcome will be of interest, the number of patients needed and how they will be assigned to regimen groups (if any), other specifics of the experimental design, the method of analysis to be employed, and any secondary questions that seem important. After these issues have been considered, the Planning Committee must decide the feasibility of doing the study and the probability of its providing valid information.

If the Planning Committee decides that the study is not feasible, the Chief, CSP should be notified in writing by the Principal Proponent through the appropriate CSPCC Chief giving reasons so that further planning support can be canceled. If it is decided that the study should be conducted, as is usually the case, the committee must make plans for writing a final protocol. This generally means that, on the basis of the discussions at the meeting, the best qualified committee members write the individual sections of the protocol. These sections are then sent to the Principal Proponent who is responsible for integrating them into a well-organized draft protocol.

The final planning meeting should be spent in refinement of the protocol, final formulation of the budget and other details of the final proposal, and a review by the Human Rights Committee. To ensure that these activities can be completed and particularly that there is a valid human rights review, an essentially complete protocol must be mailed to each member of the Planning Committee prior to the meeting. If the protocol is not received at the CSPCC three weeks before the meeting or if the protocol is substantially incomplete, as determined by the Chief, CSPCC, the final planning meeting will need to be rescheduled. This period of time will also allow other relevant personnel at the CSPCC to review the protocol so that their comments can be considered at this final meeting.

Ideally, the CSPCC should be able to prepare the final protocol for submission to CSEC immediately after the final planning meeting. However, there will usually need to be some additional work by the committee before the CSPCC can begin production of the final protocol. This additional work should be completed as quickly as possible.

4. **Pilot Studies or Feasibility Trials.** It is sometimes necessary to explore the feasibility of a cooperative study. In such cases, a pilot study or feasibility trial will be conducted in two or three medical centers to determine whether the protocol for a study is workable or to answer some preliminary question required by the main protocol. Pilot studies require the approval of the Director, Medical Research Service (and the Director, HSR&DS or RER&DS as appropriate). They are generally developed by the usual planning process and presented to CSEC for evaluation since they are typically small-scale trials of a completely developed protocol.

C. CSPCC Human Rights Committee

In studies that involve risks (physical, psychological, sociological, or other) for the participants, the most important single consideration is always the protection of the individual. To assure that the rights of patients are protected in a cooperative study, a Human Rights Committee has been established at each of the four CSPCCs.

1. **Composition.** Currently the Human Rights Committee should consist of a minimum of seven persons. A person should represent fulfilling only one requirement, even though qualifications indicate the ability to represent two or three categories. This committee should include a lawyer (not selected for expertise in forensic medicine), a person concerned with human ethics (such as a member of the clergy, a sociologist, philosopher, humanist, etc.), a veteran who has been hospitalized (or an outpatient) in a VA medical center (not officially representing a veterans' organization), and a member of a recognized minority group. None of these members should be a full- or part-time VA employee when appointed. The fifth member, who will chair the committee, will be a VA employee, but will not be a physician or directly involved in research. In addition to the CSP requirements for Human Rights Committee membership, it is necessary to be in full compliance with current agency requirements for Human Rights Committee membership (at present covered in Interim Issue 10-81-44, October 8, 1981).

2. **Responsibilities.** The responsibility of this committee is to assess the cooperative study at the proposal stage with respect to the patient's rights and welfare. This is generally done at the final planning meeting but always prior to submission for CSEC review. The committee must ensure that each patient (or a guardian if the patient is judged incompetent) is made fully aware of exactly what participation in the study involves and what risks it entails. This review should include an in-depth consideration of the protocol and the informed consent procedures and form(s).

The Human Rights Committee may, on considerations of human rights issues only, accept the study as proposed, accept it with conditions, or reject it outright. If the study is rejected, the Planning Committee must make the necessary changes and resubmit the study to the Human Rights Committee. A recommendation by a Human Rights Committee may not be reversed except by its own action. Therefore, no study will be submitted to CSEC for evaluation unless the Human Rights Committee has approved it. If the study is accepted with conditions, it does not necessarily have to be resubmitted to the Human Rights Committee, but the CSPCC Biostatistician is responsible for ensuring that the conditions are met before it is submitted for CSEC evaluation. *A letter to this effect, co-signed by the Chief, CSPCC and the Chairman, Human Rights Committee, is required.* It should be stressed that the CSPCC Human Rights Committee provides a global assessment of the human rights aspects of the proposal. Neither this review nor the CSEC review, which is a global assessment of the scientific merit, relevance, and professional ethics, is conducted as a substitute for the review by the local participating facility's R&D and Human Studies Committees.

3. **CSPCRPCC Drug Information Report.** When a study involves drugs, the Clinical Research Pharmacist, through the Chief, CSPCRPCC and the Chief, CSPCC will provide the Chairperson of the CSPCC Human Rights Committee with a comprehensive drug information report (prior to the second planning meeting). The report will include known side effects, adverse effects, contraindications, and precautions of the drugs to be used in the study. This information is to be used by the CSPCC to brief their Human Rights Committee on the unwanted effects peculiar to the study drugs. A copy of the report will also be sent to the Principal Proponent and the Study Biostatistician.

D. **The Proposal**

Although not all proposals can have exactly the same format, they all must contain certain elements. The following is a list of these common elements. In general, every proposal requires some introductory material, the formal protocol, a complete budget, and a complete set of data forms. Technical details, such as procedures for biostatistical and research data processing, should be described in appendices. (Each proposal must include the following material. The order given below is the suggested sequence.)

1. **Introductory Material.**

a. *Cover Letter.* This letter, preceding everything else in a submission, is a simple statement that the Principal Proponent, the Study Biostatistician, and the Chief, CSPCC agree that the proposal is ready to be submitted for evaluation. In cases where there is disagreement, this letter would point out where the disagreement lies. It may also relay other relevant information, for instance, in the case of resubmission, it may indicate where the recommended changes have been made. Resubmissions must also include, after the cover letter, the summaries of the previous review (letter from the Director, Medical Research Service and the Director, HSR&DS or RER&DS as appropriate, reports of CSEC and the Budget Review Group).

b. *Letter of Justification.* In a separate letter, the Principal Proponent must summarize other relevant work in the field and state why the proposed study is unique. If the study is not unique, the reasons for its being replicated must be given. Whenever possible, this letter should include an estimate of the potential impact of the study on improved patient care and/or reduced medical center costs.

c. *Study Article Letter.* This letter is required whenever a study involves drugs or other study articles. The Clinical Research Pharmacist and the Chief, CSPCRPCC will provide a Letter of Certification identifying (1) any drug-related problems that may possibly exist in the study, (2) whether or not an IND or IDE is required, and (3) if an IND or IDE is required, that the appropriate forms (completed by the CSPCRPCC and Principal Proponent) have been reviewed by the CSPCRPCC and in its opinion, are ready for submission to the FDA. The IND or IDE submission will follow CSEC's approval of the proposed study.

d. *Table of Contents.*

2. **The Study Protocol.** The protocol should reflect a cooperative effort of all members of the Planning Committee. Since different types of studies will require different formats, the following is provided as a guide and should not be construed as an all-inclusive list of what should be contained in the main protocol.

Each protocol should have background information and references indicating previous and current related research and a statement why the authors feel that the study should be done, specifically, why it should be done as a VA cooperative study. If the study involves the use of drugs, all pertinent pharmacological and toxicological data should be included with appropriate documentation.

The purposes of the study, both primary and secondary, should be clearly stated. The protocol should also contain the experimental design of the study, patient selection criteria, methods of treatment, schedule of observations and laboratory tests, measures of success, and appropriate consideration of sample size. Within this framework, details such as double-blindness, controls, methods of follow-up, training procedures, specialized rating scales, central readings, central laboratories, assignment of patients to therapy groups, and methods of assuring uniformity of care and follow-up should be discussed along with certain administrative aspects such as the use of a pilot trial, duration of the study, number of medical centers, and data flow.

A section devoted to moral and ethical considerations should include a description of the safeguards to protect the patients, assurance that they may withdraw from the study at any time without prejudicing their medical care or VA benefits and the informed consent procedures and form(s) to be used. It is with these considerations that the Human Rights Committee will be most concerned so they should be clearly spelled out. This section should also give consideration to the duties of the witness of the informed consent. Should the witness merely witness the signature or should the witness be an auditor witness who witnesses the entire informed consent procedure? Although the Planning Committee will initially decide the type of witness to be used, the Human Rights Committee has the option of requiring the study to use an auditor witness if, in its opinion, the risks of participation in the study are of such a magnitude or if the patients will be in such a confused state that the committee feels that someone other than the Study Investigator should be present to determine that the patient is really given a fully informed consent. If the Human Rights Committee does require an auditor witness, this decision will be binding on the study and all medical centers in the study.

It is suggested that the individuals who participate in a cooperative study be referred to as "patients," "participants," or "volunteers" rather than as "subjects." Also, because of recent legislation, Social Security numbers and VA Claim numbers should not be used to identify patients if at all possible. If they are considered necessary for the conduct of the study, as they might be in studies that require a long follow-up period, the patient must consent to the use of these numbers. This is most easily achieved by including this request in the informed consent the patient signs when agreeing to participate in the study.

If nonveterans must be used in the study because not enough veteran patients are available, it is important that they provide a clear consent, that they do not encumber the medical center's operating

budget, and that they are admitted to the study for the sole purpose of participating in the project and not for obtaining treatment from the Veterans Administration. All costs for caring for the nonveterans should be charged against the study's research appropriation. The VA physician should not assume a doctor-patient relationship outside the scope of the study with nonveterans unless it is through the VA medical center's medical school affiliation. All of this must be clearly stated in the protocol and must have the approval of CSEC and the Director, Medical Research Service (and the Director, HSR&DS or RER&DS as appropriate). If a decision to use nonveteran patients is made during the study, the proposal must be formally resubmitted to CSEC as a protocol modification, and if approved, resubmitted for R&D Committee approval at the participating medical centers (see General Counsel's Opinion VA-Op, GC. 28-58, June 25, 1958).

3. Appendices. In addition to the appendices required of every protocol, it may be appropriate to include other supporting material relevant to the study as appendices rather than in the body of the text, e.g., summaries of reliability or validity studies of proposed research data forms or a report of pilot studies.

a. *Human Rights Committee Report and Informed Consent Forms.* The report of the Human Rights Committee, signed by the chairperson, showing that the committee has approved the study, must be included in the proposal. In case of resubmissions, all reports must be included in chronological sequence.

The informed consent forms to be used for the study must be included with the final proposal. VA Form 10-1086, "Agreement to Participate in Research By or Under the Direction of the Veterans Administration," must always be completed. This form requires the signatures of the patient, a witness, and the Participating Investigator or designated professional equivalent. VA Circular 10-81-20 (dated 2/2/81, Subj: Revised Instructions for VA Form 10-1086, Obtaining Informed Consent From Investigational Subjects) further directs that a separate document be used in conjunction with the VA Form 10-1086. This document should describe the study in language that will be easily understood by the patient or his/her representative so that a reasonable decision concerning participation can be made. Each sheet of the document must be headed with "Information About the VA Cooperative Study on. . ." followed by the title of the study. It must include the following:

1. A statement that the patient is being invited to participate in a clinical research project, the purpose of the investigation and an explanation of its nature including how it relates to other knowledge, the use to be made of the results obtained, expected duration of the patient's participation, and identification of any procedures which are to be experimental.

2. The procedures to be used, including invasive techniques, restrictions on normal activities, and the possibility of receiving inactive material in a double-blind trial.

3. Known risks, inconveniences, such as frequent clinic visits, or side effects that can be expected and what measures will be taken to minimize any hazard or discomfort or, where applicable, a statement that the risks cannot be predicted.

4. Any benefits that may accrue to the patient as a result of participation in the trial, including therapeutic benefits, payments, and recognition.

5. Any alternate courses of action open to the patient in lieu of participation in the study.

6. When appropriate, a statement of the result to be anticipated if nothing is done, e.g., when neither an experimental nor a control drug (placebo or standard drug) is taken.

7. A statement that the patient may decline to participate or decide to withdraw from participation at any time without prejudicing his/her medical care or other VA benefits.

8. If patient compensation or the medical treatment available is different than that provided for in VA Form 10-1086, then a statement is required informing the patient of the compensation and medical treatment that is available should he/she sustain physical injury as a result of participation in the study.

The Food and Drug Administration further requires (Volume 46, Federal Register, 8951) for all projects that fall within its purview that the following elements be included in the informed consent:

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

2. 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 by the FDA.

When appropriate, the following elements should also be included.

3. Anticipated circumstances under which the patient's participation may be terminated without regard to the patient's consent.

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

5. The consequences of a patient's decision to withdraw from the study and procedures for orderly termination of participation.

6. A statement that any significant new findings developed during the course of the study which may relate to the patient's willingness to continue participation will be provided to the patient.

7. The approximate number of patients involved in the study.

This information sheet may also be used to ask the patient for permission to use Social Security or VA Claim numbers.

In obtaining informed consent, the investigator must specifically inform the patients of their right to compensation and treatment for physical injury. The required information must be given in conformity with federal laws and the contents of Circular 10-78-300 (dated 12/29/78, Subj: DHEW (DHHS) Required Information About Compensation and Treatment of Injured Clinical Research Participants) and the FDA regulations (Volume 46, Federal Register, 8951). Different information will have to be provided to veterans eligible for medical care on the one hand and to noneligible veterans and nonveterans on the other. Eligible veterans are entitled to medical care and treatment for any injury sustained. Compensation may also be payable under 38 USC 351 or, in some circumstances, under the Federal Tort Claims Act. Noneligible veterans and nonveterans are entitled to medical care and treatment only on a humanitarian emergency basis with the medical care appropriation reimbursed from research funds. Any compensation for them, however, would be limited to situations where negligence occurred and would be controlled by the provisions of the Federal Tort Claims Act.

Each patient must be allowed to read the informed consent form or have it read and understood before discussing consent with the investigator. Each page of the document must be signed by the patient. In discussing the study with the patient, the investigator may have to go somewhat beyond the

statements in the information sheets, but there must be no substantive addition, deletion, or modification of these statements. For cooperative studies, no local changes of the information sheets will be allowed. The information sheets are the tangible evidence of what the investigator tells the patient. A copy shall be given to the individual signing the form. In addition to the aforementioned circulars and regulations, this document and procedure should also be consistent with the HHS guidelines for informed consent. If anesthesia, surgical operations, or other procedures are to be used, consent for these procedures must also be obtained on SF 522.

b. *Research Data Forms.* They must be designed in a format which will permit the investigator to record usable, complete, and accurate data. They should permit assessment of all planned aspects of the study, and represent a data repository for later retrospective probes into questions related to the study. For these reasons, a complete set of prototype forms is required when the proposal is submitted to CSEC for scientific evaluation.

The case report forms should provide a complete patient data record for research purposes. Tailored to the specific aims and objectives of the study, they are not routine hospital or clinic medical records and are not intended to replace them, but to supplement them. They must contain all data and information pertinent to the conduct of the study, be easy to use and understand, in logical sequence for the recorder, meet biostatistical and data processing needs to minimize checking, encoding and automated data processing handling, and be acceptable to the study participants, the Study Biostatistician, the computer specialist, the encoders, and the keypunch operators. If the forms are to be filled out by the patient or used to interview the patient, the privacy act statement must be included on the first page of each form. Whenever possible, the forms should avoid narrative replies, but rather make use of objective questions.

In general, the forms should be time-oriented. The initial forms should provide space for screening information, such as specified elements of the patient's history, physical examinations, routine and special laboratory testing, checklists of eligibility and exclusion criteria, and should include rather complete baseline information, such as identification information, age, race, sex, etc. Follow-up forms should be formatted to accommodate planned follow-up visits, records of interval history, physical examinations and laboratory assessments. Final report forms relating to death, early withdrawal, and successful completion of the planned observation period and final evaluation are also needed.

c. *Budgets.* Every protocol must have a study budget, a CSPCC budget and, when appropriate, a CSPCRPCC budget and a special laboratory budget.

1. *Study Budgets.* To provide CSEC with an overview of the funds required for the conduct of a proposed study, each proposal should contain as complete and detailed an estimate of the costs involved as possible (see Appendix F for format). Although it is sometimes possible to increase the budget later should the need arise, this should not be counted on and all foreseeable expenses should be included. The budget should be computed for the first year and each succeeding year with justification for items such as added personnel and patient travel. The breakdown should show the cost per medical center as well as the total cost of the study. Furthermore, the Study Chairperson's office budget should be separate from that of his/her participating medical center's costs as should expenditures of all special reference laboratories, etc. Any costs incurred by the CSPCC or CSPCRPCC above and beyond the normal or core costs of the center, such as hiring a technician for use only on the study, should also be listed in this budget. The core costs of the CSPCC and CSPCRPCC should not be listed here.

Items to be included in the budget are the salaries of supporting personnel, consultation fees, equipment, supplies, investigational or study articles and other medications and chemicals, nonveteran care, and costs of patient travel if required by the study. The budget should allow for a start-up period so that newly hired personnel can familiarize themselves with the protocol and their

medical center. This start-up period will usually be no more than three months, but it is study-oriented so that studies requiring a longer start-up time should budget for it. Supporting personnel are those hired solely for working on the study and not existing personnel who work on it as part of their regular duties. They might include technicians or other assistants at each medical center, a clinical coordinator for the Study Chairperson's office, or additional secretarial help. The Principal Proponent must prepare a generic position description with tentative grade levels for each of these positions as part of the budget request. Personnel hired for the study are to be used solely for the study and are not to be used for other work unless they have no study functions to perform.

The services of consultants and special research laboratories inside or outside the VA will be funded, if needed by the study, for providing such services as expert advice, central readings and assessments, and quality control. Equipment and supplies include any material that is to be used solely for the study, such as testing materials, laboratory equipment, and office supplies. Patient travel should only be included if the patient is required to travel for the sole purpose of being in the study. If the patient's presence is required for reasons other than those of participation in the study, then travel funds should come from the usual medical center sources. Any other costs that the study requires should also be included. There are procedures for requesting an increase to the budget after a study has been funded, but approval will only be given in exceptional circumstances. Requests for such increases with complete justification should be sent by the Participating Investigator through the Study Chairperson and Chief, CSPCC for concurrence to the Chief, CSP. For costs greater than $5,000, action will not be taken until the concurrence of the study Operations Committee and the Chief, CSPCC has been forwarded to the Chief, CSP.

Funds for units and functions in general use by most cooperative studies, such as the CSPCCs and the CSPCRPCC, will be provided and directed by the VACO, CSP. A proportionate share of their costs will be assigned by the respective Chief to each study using those facilities. Funding for extra travel and attendance at various nonroutine meetings before and during the study should be budgeted as a separate item but, if approved, will be provided from centrally directed funds. The proposal budget should only include extra travel needs such as training meetings and site visits, and should not include the routine meetings of the Study Group, Executive Committee or Operations Committee; estimates of the latter will be provided by the CSPCC.

Funds provided for a cooperative study will be limited to the needs of the study and must not be used to supplement other clinical or research activities. Unused cooperative study funds are not available locally for other research activities. Furthermore, funds for a cooperative study at a given VA medical center are considered "line item" type allocations, especially in regards to personnel, but also for unusually costly equipment or other operating costs (i.e., greater than $500 annually). Funds may not be arbitrarily transferred from one category (e.g., personnel) to another (e.g., equipment or other operating costs) within a given cooperative study at a VA medical center without submission of written justification by the Participating Investigator through the Study Chairperson and the Chief of the appropriate CSPCC for endorsement to VACO, CSP for approval. Any unused funds will ordinarily be returned to VACO, CSP on at least a quarterly basis, unless a specific exception is granted.

2. *Cooperative Studies Program Coordinating Center Budget.* This budget contains a cost estimate of the biostatistical and data processing support for the study. It will ordinarily include estimates of personnel and other costs for handling the study at the CSPCC or if the CSPCC performs only a monitoring role, a detailed breakdown of the outside contractor's estimated costs and the CSPCC's costs for monitoring the study. Budget and justification for term appointment staff should be included if the study requires additional manpower support beyond that of the center's core staff.

3. *Cooperative Studies Program Clinical Research Pharmacy Coordinating Center Budget.* As part of the final study proposal, the CSPCRPCC will submit a projected cost estimate of existing

CSPCRPCC core resources necessary to support the proposed study. An additional projected cost estimate and justification for resources beyond core costs will be submitted (when applicable) for additional pharmacy staff term appointments (centrally and at the field station level) for specific large work load projects and for study articles (drugs, medical devices, diagnostic agents, biologicals, electronic devices, etc., for human use) and related supplies. The estimated beyond core resources budget must also be included in the study budget as a separate line item.

4. *Special Laboratory Budget.* If a special laboratory is needed for the study, a detailed cost estimate for the laboratory must be included. This should include such things as personnel costs, materials needed, and shipping and packaging. The total cost of the laboratory should be listed separately on the study budget.

d. *Biostatistical and Research Data Processing Procedure (B.R.D.P.).* The protocol must also contain a set of plans for analysis that is as complete as can be envisioned at the time for both periodic (monitoring summaries) and final analysis. It should include a statement of the variables to be analyzed, the intervals at which summaries and analyses will be done, and the specific methods to be used. Details for these procedures should be furnished in the Biostatistical and Research Data Processing Procedure Appendix (Appendix B.R.D.P.). This appendix should include a detailed description of the planned biostatistical data monitoring and management procedures to be used in the study, as well as the planned biostatistical analyses to be performed at the close of the study. It should include prototype tables, charts, data summaries, summaries of analyses, etc., and an outline of the format of the progress reports to be provided to the Study Chairperson, the Executive Committee, the Study Group, and the Operations Committee. It is expected that at least 80% of the preplanned final data summaries and biostatistical analyses will be defined and described in this appendix.

This appendix should also include the following two items:

1. *Patient Intake Graph.* For each proposal, the biostatistician must prepare a graph of the anticipated patient intake and patient follow-up for the proposed duration of the study, including the start-up period. This will usually be based on the sample size estimated by biostatistical rationale. Expected number of patients should constitute the vertical axis and time the horizontal axis.

2. *Summary of Quality Assurance.* A summary page of planned quality assurance measures to be used to monitor the study and the data must also be a part of the proposal. This is submitted on a standard form completed by the CSPCC Biostatistician.

e. *Drug Handling Protocol (D.H.P.).*

1. *Drug Handling Procedure.* A detailed procedure for handling drugs used in the proposed study must be furnished in the Drug Handling Protocol (Appendix D.H.P.). If investigational or study articles and other medications and/or chemicals are to be used, the CSPCRPCC will secure and distribute them and provide drug accounting to the Study Chairperson and Chief, CSPCC. Each drug study proposal submitted for CSEC review must have an Appendix D.H.P. This appendix is written by the CSPCRPCC and includes detailed instructions for distribution, receipt, disposition of unused portions of drugs, and the recording of these activities. The Appendix D.H.P. will be prepared in accordance with Circular 10-80-253, Investigational Drugs and Research.

2. *Notice of Claimed Investigational Exemption for a New Drug (IND) and Investigational Device Exemption (IDE).* If study articles that are to be used in a study do not have Food and Drug Administration (FDA) approval, and in certain other situations also, an IND or IDE must be filed with the FDA before the study can begin. In the case of studies involving study articles, the CSPCRPCC will provide the necessary guidance as to whether the study will require FDA approval.

Ordinarily, one member of the Study Planning Committee (usually the Principal Proponent) will be designated as the sponsor of the study. He/she is required to complete a "Notice of Claimed Investigational Exemption" (FD Form 1571), and a "Statement of Investigator" (FD Form 1573) known as an IND. The CSPCRPCC will assist the sponsor in completing these forms (see Guidelines for an IND Submission to the FDA in the VA Cooperative Studies Program). The completed forms (IND or IDE) must be sent to the CSPCRPCC by the sponsor 15 days prior to the CSPCC deadline. The CSPCRPCC will send copies of the entire submission to the CSPCC, the Principal Proponent, and the Chief, CSP, VACO. Immediately after the study is approved by CSEC, these forms must be sent in triplicate to the FDA by the sponsor along with three copies of the study protocol.

By law, the FDA must either give or refuse approval within 30 days. If word has not been received within 30 days, the investigator is allowed to proceed with the study. Thus, it is advisable to send this material to the FDA by certified mail so that there is a record of when it was received.

Every investigator who will be participating in the study must complete a "Statement of Investigator" (FD Form 1573). The investigator must submit this completed form to the CSPCRPCC. Copies of these forms must be sent to the FDA by CSPCRPCC through the sponsor (chairperson), with reference made to the FDA assigned IND number as soon as they are all received. It is not required that the FD Form 1573 be filed concurrently with the initial submission of the Study Chairperson's FD Forms 1571 and 1573 to the FDA. Completed copies of all FD Form 1573's must be on file in the CSPCRPCC and CSPCC before drugs can be distributed to the participating medical centers.

When the pharmaceutical company is acting as the sponsor of the study, they accept the responsibility of filing a "Notice of Claimed Investigational Exemption for a New Drug" (FD Form 1571) with the FDA. The "Statement of Investigator" (FD Form 1573) of the Study Chairperson and the "Statement of Investigator" (FD Form 1573) from the Participating Investigators are to be sent to the sponsor by the CSPCRPCC through the Study Chairperson. A letter from the pharmaceutical company, identifying their FDA assigned IND number will be accepted as a substitute for FD Form 1571 as described above. Copies of all completed FD Form 1573's must be forwarded to the CSPCC and the Study Chairperson by the CSPCRPCC as previously described.

In the event that clinical pharmacology investigations are to be conducted in the study, FD Form 1572 (Statement of Investigator-Clinical Pharmacology) is to be substituted for the aforementioned FD Form 1573, for those investigators who are responsible for conducting and evaluating this aspect of the study.

f. *Special Laboratories.* If provision has been made for central laboratory determinations, urine testing, centralized readings of EEG's and ECG's, etc., there should be a fairly detailed protocol included as an appendix which describes the procedure for obtaining specimens, evaluating results, and transmittal of data.

g. *Curriculum Vitae.* At a minimum, the curriculum vita of the Principal Proponent and the Study Biostatistician must be included. If consultants or Co-Principal Proponents are to appear before CSEC, their curricula vitae should also be included. In order to limit the length of the curriculum vitae to four pages, the list of publications should, if necessary, be restricted to those relevant to the study.

E. Evaluation

1. **Submission and Deadlines.** As detailed in the preceding section, a proposal that is to be submitted to CSEC for scientific evaluation should be as complete, precise, and scientifically excellent as possible. The Principal Proponent must submit the proposal for evaluation to CSEC through the CSPCC. It is the responsibility of the CSPCC Biostatistician to review the final proposal to assure its completeness and

accuracy. Only after the Principal Proponent, the CSPCC Biostatistician, and the Chief, CSPCC agree that the proposal is ready should it be submitted to CSEC for evaluation. (Appendix B).

In the event that the Principal Proponent believes strongly that the proposal should be submitted for evaluation and the biostatistician believes just as strongly that it should not, an outside consultant (biostatistician) will be engaged on contract to review the proposal and arbitrate the matter. The consultant will be selected by the Chief, CSP, and will provide recommendations to the Chief, CSP. On occasion, this outside consultant may be a senior biostatistician at one of the other CSPCCs. Such a disagreement should be rare since the Principal Proponent should be working closely with the CSPCC Biostatistician in developing the proposal.

The CSEC meets each year in February, June, and October. The three associated deadlines for submission of completed proposals to the VACO, CSP office for CSEC review are December 1, April 1 and August 1. There will be no extensions of these deadlines. If a proposal is received after these dates, it will not be reviewed at the upcoming CSEC meeting, but will be deferred to the next meeting.

Because every proposal must be submitted through and reviewed by a CSPCC Biostatistician, the Principal Proponent must send a complete final draft to the CSPCC at least six weeks before the deadline, i.e., a complete final draft will be due at the CSPCC before October 15 for a December 1 submission, before February 15 for an April 1 submission, and before June 15 for an August 1 submission. There will be no extensions of these deadlines; protocols that are late will automatically be deferred until the next submission. If they are received in time, they will be promptly reviewed by the Chief, CSPCC for completeness and accuracy. If the protocol is complete and accurate, the CSPCC will assume responsibility for the final typing to assure uniformity of the proposal and for making the 25 copies that are necessary for submission of new proposals or the 20 copies necessary for three-year reviews, study extensions or special reviews. However, if the protocol is deficient in any important respect, the deficiencies will be identified and the Principal Proponent will be instructed to resubmit by the next deadline.

2. **Outside Review.** The CSP office reviews the proposal and makes sure that all required information is attached to each copy. It then distributes copies to selected outside reviewers, the Cooperative Studies Evaluation Committee, and to the Budget Review Group. There are generally two or three outside reviewers selected by the Chief, CSP. One of these reviewers will be a biostatistician, while the other(s) will be expert(s) in the subject matter field. They will be asked to submit written critiques of the proposal which will be made available to the CSEC and BRG members before the CSEC meeting. When practicable and as a courtesy, copies will also be made available to both the Principal Proponent and the Study Biostatistician. These reviewers are permitted to request anonymity for their comments if they wish to do so.

The subject matter reviewers will be 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 on any other relevant features of the proposal. The biostatistical reviewer will be asked to comment on the clarity of the proposal and apparent achievability of its objectives; the adequacy and correctness of the plan of investigation and the technical details such as character and adequacy of response variables, definition, measurement, data recording, frequency of observations, adequate patient eligibility and exclusion criteria, sample size, and plans for data handling and analysis; adequacy of safeguards for the welfare of patients; and on any other features considered relevant.

3. **CSEC and BRG Evaluation.** It is the responsibility of the Cooperative Studies Evaluation Committee to review new study proposals for cooperative studies, to recommend approval for funding or define reasons for disapproval, and to review the progress of each cooperative study every three years or more frequently upon request. For new studies, CSEC advises the Director, Medical Research Service (and

the Director, HSR&DS or RER&DS as appropriate), and the Chief, CSP regarding the scientific merit and VA funding priorities of the studies. Approval by this committee constitutes a recommendation and is not tantamount to funding.

The committee is composed of seven to nine regular members including the chairperson. Two to four of the members are biostatisticians, one is an expert on drugs and drug usage (clinical pharmacology) while the other members come from various fields of medicine, usually psychiatry, surgery, and internal medicine. All of these members should have had some experience in clinical research and in the conduct of cooperative studies. The committee will usually be augmented by an ad hoc member knowledgeable in the particular subject matter of the protocol being reviewed. The Chief, CSP and his staff assistant serve as coordinators for the meetings, but have no voting rights. (Appendix D).

The Principal Proponent and the Study Biostatistician (as well as the monitoring CSPCC Biostatistician if the Study Biostatistician is from outside the Coordinating Center) appear before the committee to discuss and clarify all matters relevant to the proposal. If a discipline other than that of the Principal Proponent or the Study Biostatistician is significantly involved in the study, the Principal Proponent may request that a member of the Planning Committee, knowledgeable in that discipline, be present at the evaluation meeting. Such a request will usually be granted, but should be asked for when the Principal Proponent submits the proposal to the CSPCC.

The CSEC will meet with the Principal Proponent and Study Biostatistician for about one and a half to two hours. The ad hoc committee member opens the discussion by presenting the essentials of the written critiques by the outside reviewers and his/her own opinion. Next, one of the regular committee members (not a biostatistician) discusses additional relevant medical questions and comments. A committee biostatistician then provides an in-depth review of the biostatistical elements.

The Budget Review Group (BRG) attends the CSEC meeting and holds its review of the study budget immediately afterwards. This group, composed of three members experienced in assessing research budgets, reviews the proposed budget to see that it is reasonable. It may accept the budget as is or make recommendations for an increase or decrease if the members feel that the Principal Proponent has underestimated or overestimated certain items. These deliberations will generally take 15 to 30 minutes.

After the Study Investigators have met with the CSEC and BRG, CSEC goes into executive session to formulate its recommendations concerning the study. The CSEC will generally make one of four recommendations to the Director, Medical Research Service (and the Director, HSR&DS or RER&DS as appropriate) through the Chief, CSP:

a. *Completely reject the study.* In this case, the proposed study in its present form is finished. If the investigators wish to resubmit it in a changed form, they must start from the beginning by submitting a new request for planning to the Chief, CSP, proceed through the Medical Research Service triage review, and go onto the waiting list if the new version is accepted.

b. *Reject the study with recommendation for resubmission.* Here, the committee provides specific recommendations for reworking the study which, if followed, will increase the probability of favorable consideration upon resubmission. In such cases, at least one more planning meeting is normally authorized, and the investigators can resubmit the proposal for CSEC evaluation as soon as they and the CSPCC believe they have met the committee's recommendations. The proposal must be resubmitted within one year or the study activity will no longer be supported. An extension may be granted by the Chief, CSP for extenuating circumstances, but such requests should first have the approval of the Chief, CSPCC.

c. *Conditional approval.* In this event, the committee gives its approval under the condition that certain changes or additions be made that will improve the professional, scientific, ethical, and/or

operational quality of the study. Before the study is approved for funding, these changes have to be made to the satisfaction of the Chief, CSP, the Chief, CSPCC, the Study Biostatistician, and the Study Proponent(s).

d. *Unconditional approval.*

For those studies that are approved, CSEC gives two priority ratings; the first is a rating on the basis of scientific merit, while the second expresses the opinion of CSEC on the priority of the study for VA funding. CSEC's approval constitutes only a recommendation to the Director, Medical Research Service (and the Director, HSR&DS or RER&DS as appropriate) and is not tantamount to funding. Funding is based upon fiscal budgetary considerations and, in lean times, only those proposals deemed of highest priority can be immediately funded. Approved proposals must sometimes await reconsideration for funding at a later date. When funds are readily available, all approved proposals are usually funded. Written notification by the Director, Medical Research Service (and the Director, HSR&DS or RER&DS as appropriate), will constitute the only official statement on the status of the proposed study.

III. INITIATING A COOPERATIVE STUDY

In the period between approval of the study for funding and the time the first patient is entered into the study, several considerations must be taken into account.

A. Study Chairperson

The chairperson of a cooperative study (usually the Principal Proponent), is responsible to the Chief, CSP through the Chief, CSPCC, for the general supervision of the professional and scientific conduct and administration of the study. The Chairperson should preferably be a member of the same discipline that is represented by the majority of the Participating Investigators. When two disciplines are involved in a major way, it may be appropriate to consider appointing a co-chairperson for each of these major disciplines. The Study Chairperson should not be a member of the VA Central Office staff or function as the Study Biostatistician. Furthermore, he/she should not be chairperson of more than one cooperative study simultaneously (regardless of sources of funding), nor ordinarily be a participant in another ongoing cooperative study. The chairperson must be a VA employee (at least 5/8 time), except in unusual circumstances when an exception may be made by the Director, Medical Research Service (and the Director, HSR&DS or RER&DS as appropriate). In such a case, a VA employee (at least 5/8 time) is appointed as co-chairperson of the study. In general, the Study Chairperson should not be a Participating Investigator at his/her local facility.

B. Selection of Participating VA Medical Centers

At the initiation of funding for planning, an R&D letter is circulated to all VA medical centers inviting them to express their interest in participation to the Principal Proponent of the study. When a study is approved for funding, another R&D letter will inform the directors of all VA medical centers, domiciliaries, outpatient clinics, and regional offices with outpatient clinics that the study has been approved and that any facility interested in participating in the study should notify the Principal Proponent.

It is the responsibility of the Study Chairperson and the Study Biostatistician to review the eligibility of the medical centers and the Participating Investigators making application to join the study. They will first consider whether a facility has the necessary resources, staff (physicians, nursing staff, psychologists, biochemists, social workers, pharmacists, or others), and a high level of interest, including an eligible staff member willing to accept the duties of the Participating Investigator. The potential Participating

Investigator should be advised and be willing to accept CSP publication policies as stated in the protocol and in Section V.C. of these Guidelines. Ordinarily, one person should not be a Participating Investigator in more than one ongoing cooperative study. Past experiences with the facilities in other studies is also useful in determining a facility's capabilities. Another important consideration is whether the facility can enter enough patients to achieve the required sample size. Other things being essentially equal, facilities that can produce more of the needed type of patient should be chosen. For this purpose, each facility should be asked to screen its records for the last year to see how many of its patients would have qualified for the study. Finally, it is, in general, not appropriate that a facility participate in more than one cooperative study involving identical or very similar patients or whose participation in one cooperative study would interfere with its participation in another.

After the medical centers that are believed to best serve the needs of the study have been selected, the Study Chairperson invites them to participate in the study and sends the list of nominations to the Chief, CSPCC with a copy to the Chief, CSP. Participation in any cooperative study is voluntary. The Participating Investigator at each invited facility must submit the proposal to the local R&D Committee for approval, which should include the approval of the Committee on Human Studies. The local R&D Committee has the following options:

1. Reject the proposal and elect not to participate.

2. Elect not to participate unless certain clearly specified alterations are made in the proposal (i.e., for the entire cooperative study).

3. Approve the proposal in its current form and elect to participate.

For option 2, only major, relevant defects should be identified and not trivial and relatively unimportant ones. If major defects are found, they should be reported to the Study Chairperson through the prospective Participating Investigator, with a statement that the medical center will participate in the project only if the defects are corrected. The chairperson (often with the help of the Study Biostatistician and the CSPCC Human Rights Committee) must then decide if the defect is important enough to require amendment of the study proposal. If the Study Chairperson decides that the defect is too minor to require a change, he/she may so inform the facility and seek a substitute facility. However, if the defect is indeed major, the proposal must be amended and resubmitted to the CSPCC Human Rights Committee for their approval, and to each of the participating centers for another review by their R&D Committees. Since such a procedure is costly in effort and time and will usually delay the start of the study, it should only be used when absolutely necessary.

If a center selects option 3, it agrees to conform to all of the protocol requirements including the informed consent procedures and form(s). This approval by the center also implies that the facility is committing adequate support and resources to the study such as administrative support in the office of the ACOS for Research, pharmacy service, personnel, supply and fiscal support, space, etc. Neither the Participating Investigator nor the medical center has the autonomy to alter the protocol or informed consent unilaterally, as uniformity at all participating centers is required. Local alteration of a protocol or informed consent procedures constitutes a breach of the protocol and is grounds for discontinuing support of that facility for further participation in the study.

A copy of the minutes of the R&D Committee's meetings on the proposal, including the human studies review, must be submitted to the CSPCC within six weeks, or continued funding will be in jeopardy. In the case of a study involving study agents, a copy of these minutes must be sent to the Chief, CSPCRPCC by the CSPCC before any study agents can be distributed to the participating medical center. The local R&D Committees should also review the course of the local participation in the cooperative study annually and send a copy of the minutes of this review to the Chief, CSPCC.

Upon receipt of local approval, the Participating Investigator, with the assistance of the local research office, prepares for the signature of the Medical Center Director a formal request for funds which is sent through local channels to their Regional Director (/151-I). This request should agree with the budgetary estimates submitted to and approved by CSEC and BRG. Any substantial deviation from the approved amount should be sent to the Study Chairperson and the Chief, CSPCC for their endorsement and then to the Chief, CSP. If the deviations are large, it may require resubmission to CSEC. For the hiring of Title 38 personnel, the local personnel office should prepare a simultaneous (but separate) request for an exception and forward it in the usual way. If at any time during the conduct of the study a deviation from the approved budget is needed by a local medical center, the request for the additional funding must be initiated by the Participating Investigator at that 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 CSPCC through the Study Chairperson. The endorsements for this request by both the Study Chairperson and the Chief, CSPCC, as well as a copy of the Participating Investigator's request, should then be forwarded to VACO, CSP. If the request is approved, the Participating Investigator's research office will be contacted and told that they should now request the additional funds. The Chief, CSPCC will also be notified of the approval. If the request is disapproved, the denial will be communicated back to the Participating Investigator through the CSPCC and the Study Chairperson. If the total cost of the request is more than $5,000, the documented approval by the Study Operations Committee as well as the concurrence of the Chief, CSPCC will be required to secure approval.

Once again, it should be stressed that funds provided for a cooperative study will be limited to the needs of the study and will not be used to supplement other clinical or research activities. Unused funds will be returned to VACO, CSP on a quarterly basis.

C. Form Approval and Printing

In the two months between the submission of the final protocol and its evaluation by CSEC, the study forms (including CSPCRPCC forms) should be prepared for OMB approval. Upon notification of approval of the proposal, the Study Biostatistician is responsible for initiating SF 83, as soon as possible, but no later than 30 days after notification. Although they do not always require OMB approval, all forms for all cooperative studies should be sent to VACO through the CSPCC as if OMB approval were necessary. VACO approval and VA form numbers are always required for study forms.

Besides SF 83, a Supporting Statement must accompany the forms when they are submitted for OMB approval. This Supporting Statement must provide detailed information on the following topics: 1) justification and purpose of the form; 2) description of the survey plan; 3) tabulation and publication plans; 4) time schedule for data collection and publication; 5) consultations outside the agency; 6) estimation of respondent reporting burden; 7) sensitive questions; and 8) estimate of cost to Federal Government. A detailed discussion of the Supporting Statement and SF 83 can be found in SF 83A, OMB entitled, "Instructions for Requesting OMB Approval Under the Federal Reports Act."

In the case of cooperative studies where the forms are all related to one research project, only one SF 83 and one Supporting Statement are needed but these must include all required information for each form. The Study Biostatistician then sends to Management Support Division, VACO, four copies each of the proposed data forms, the latest protocol, the Supporting Statement, and the Clearance Request (SF 83). Because the forms require fairly high level approval along the way, the approval process can be and usually is time-consuming and should, therefore, be started as early as possible.

After securing OMB clearance, or an exemption from doing so, the forms must be printed, which may also take considerable time. The most practical solution is to have the CSPCC arrange for local printing of the forms. The request for assignment of form numbers and OMB clearance should also state a preference for where the forms should be printed. Whether the printing is to be done centrally or locally, the

documentation of approval of the forms requires the signature of at least the Study Biostatistician, the Study Chairperson, the Chief of Data Processing, and the Computer Programmer.

D. Operations Manual

After the approval of the study and prior to its funding, the Study Chairperson, the Study Biostatistician, the Clinical Research Pharmacist, and any other study members that the chairperson considers appropriate should prepare an Operations Manual. This manual should include details of data collection, data flow, data recording, encoding, reporting of adverse reactions (when appropriate), the Participating Investigators' responsibilities to the Pharmacy Service concerning prescription writing or drug ordering requirements, Pharmacy Service's responsibility to the Participating Investigator, etc. If appropriate, this manual should include instructions for administering the investigational or study articles. It is to be used by the data collectors at each participating medical center and should cover all problems that they are likely to encounter so that they do not have to frequently call the Study Chairperson. This manual is intended to ensure that the study procedures are followed as uniformly as possible at all participating centers. It will usually be typed and assembled by the CSPCC.

E. Hiring and Training

If the study requires additional personnel at the Study Chairperson's office or at the participating centers, they should be hired as soon after funding as possible. The centers should use the local procedures for hiring, but it is the responsibility of each Participating Investigator to ensure that the persons hired are capable of performing the tasks required by the study protocol. Positions for cooperative studies at participating medical centers and the chairperson's office are generally term appointments. Funding for each fiscal year is subject to the availability of funds and cannot be continued beyond the authorized duration of the study.

Newly hired personnel should be given at least a month to study the protocol and to become familiar with the ways of the medical center. When all personnel have been hired and have had sufficient time to familiarize themselves with the situation, the Study Chairperson, when appropriate, should arrange a training session so that they will know exactly what is expected of them and so that any questions they may have about the study can be answered. Training in new techniques to be used, e.g., surgical techniques, should be completed before any patients enter the study. Arrangements for travel to these training sessions will be similar to those for all other travel as discussed in Section IV.B.

Although every attempt is made to provide only those personnel that are essential for the conduct of the study, peaks and valleys in work load sometimes do occur. In those situations where personnel hired for a cooperative study discharge all of their duties for the study and still have free time, it is presumed that the R&D office will see that these personnel are productively assigned to other duties during this free time. Priority of assignments should be given in the following order: unmet needs of other cooperative studies at the medical center or of a CSPCC or the CSPCRPCC if located there; other approved local research of the Participating Investigator; and, finally, other approved local research of other investigators. If it is possible to convert a full-time position to a part-time one, it is the responsibility of the Participating Investigator and the ACOS for Research and Development to notify the appropriate Chief, CSPCC, through the Study Chairperson, of this situation so that the appropriate actions can be taken.

F. Acquisition of Additional or Replacement Equipment

Should requests for equipment for individual medical centers exceed a total of $5,000 or cost $2,000 or more for a single item, a request for equipment as described in VA Circular 10-79-48 must be made. This request should include a detailed description of the instruments, the approximate hours per week the equipment will be used, a list of all presently available equipment at the facility which can perform the same function, and the reasons that the equipment is needed.

IV. CONDUCTING A COOPERATIVE STUDY

It should be recognized at the outset that, in the absence of objectively demonstrated satisfactory performance (i.e., number of patients enrolled, quality of data acquisition, etc.), funding beyond six to 12 months for an approved study cannot generally be continued solely on the basis of faith, stature and competence of the investigators and/or importance of the subject matter. Studies acquiring less than 60 percent of their projected intake will ordinarily be considered as performing unsatisfactorily, while those entering 60 to 80 percent of their projected intake will be considered as performing marginally at best. The studies with patient acquisition rates greater than 80 percent are those that might reasonably be expected to finish in their originally planned time frame or to need only relatively minimal extensions of their patient intake periods. It is the responsibility of the Chief, CSPCC and the Operations Committee to objectively assess each study's performance in the early stages and to make the appropriate recommendations that will either improve the performance of the investigators or will result in early termination of the study if the problems seem to be unresolvable.

A. Management

Primarily four groups share responsibilities for the proper conduct of a cooperative study: The Study Group, the Executive Committee, the Operations Committee, and the Human Rights Committee. All but the last one – which has already assessed the protocol before CSEC approval was sought – should meet before patient intake begins to review operational and other details. Once patient intake has begun, they should again meet at regular intervals. It is the responsibility of the Study Chairperson and the Study Biostatistician to provide these committees with appropriate reports three weeks before their meetings so that they can perform their functions. The Study Biostatistician and Study Chairperson must also provide relevant written updates to the four groups between meetings (usually every four and a half months). The composition, meeting schedules, and responsibilities of the four groups are as follows:

1. **Study Group.** The Study Group is composed of all Participating Investigators and permanent consultants for the study. The Study Chairperson heads this group, which meets at nine month intervals unless travel funding allocations are not adequate to support this frequency. At each meeting, the group will discuss the progress of the study, any problems that the investigators have encountered, and suggestions for improving the study. The Study Chairperson may also use these meetings to get reactions of the investigators to contemplated changes in the protocol. Results of any blinded part of the study will not be presented to this group. Meetings of this group scheduled for the last six months of patient follow-up serve little purpose and will not ordinarily be funded. Instead, this final meeting will be postponed until after the results of the study are known. It is the Study Chairperson's responsibility to write and distribute a report on each Study Group meeting within two to three weeks of the meeting.

2. **Executive Committee.** The Executive Committee of a cooperative study usually consists of four to eight members and includes the Study Chairperson, the Study Biostatistician, the head(s) of any special central support unit(s) related to the study, two or three Participating Investigators, and selected consultants when necessary. All Participating Investigators may be members of the Executive Committee if there are no more than five participating medical centers. Usually these individuals will have been involved in the planning stage. The Study Chairperson, who is automatically the Chairperson of the Executive Committee, should inform the Chief, CSPCC with a copy to the Chief, CSP (who is an ex officio member), who the members are. This committee will meet at nine-month intervals and acts, in general, as the management group and major decision-making body for the operational aspects of the study. It decides on all changes in the study and on any subprotocols or other use of the study data, on publications of study results, and takes actions on medical centers whose performance is unsatisfactory. As with the Study Group, the results of blinded portions of the study will not be presented to this group. All major alterations in protocol design or operation of the study recommended by the Executive Committee must be endorsed

in writing by the Operations Committee and communicated to the Chief, CSP prior to being instituted. The ACOS for Research and Development at each participating medical center must also be informed because major changes in the protocol may require resubmission to the local R&D Committee. The Study Chairperson is responsible for writing a report on each meeting of the Executive Committee and distributing it to the members within two to three weeks of the meeting.

When a cooperative study involves study articles, the CSPCRPCC Clinical Research Pharmacist is routinely a consultant ad hoc member of the Executive Committee. This means he/she will only attend an Executive Committee meeting when a problem regarding medical center pharmacies or CSPCRPCC support cannot be resolved by telephone, letter, or other means. At the meetings attended, the Study Pharmacist will vote only on those issues related to pharmacy support. If during the course of the study a problem concerning pharmacy support should arise, the Chief, CSPCRPCC should be contacted. If the problem cannot be satisfactorily resolved within a reasonable period, it should be referred to a member of the CSPCRPCC Evaluation Committee listed in Appendix E.

3. **Operations Committee.** The Operations Committee is usually made up of three or four members and is comprised of experts in the subject matter of the study, an independent biostatistician, and other appropriate technical or scientific specialists. The members must not have been participants or consultants in the planning or executive phases of the study. The Study Chairperson and the Study Biostatistician are the study representatives (nonvoting) to the Operations Committee and the Chief, CSP and the Chief, CSPCC are ex officio (nonvoting) members. It is the responsibility of the Study Chairperson to nominate the members of this committee, including the Committee Chairperson, through the Chief, CSPCC and the Chief, CSP for approval by the Director, Medical Research Service (and the Director, HSR&DS or RER&DS as appropriate). The Study Biostatistician and/or the CSPCC Chief will usually suggest the Operations Committee statistician to the Study Chairperson. Each nomination must be accompanied by the curriculum vitae of the proposed member. Alternate nominations for any of the members may be suggested by the VACO CSP office. As soon as the nominations are approved, a complete copy of the study protocol and a copy of these guidelines should be provided to the Operations Committee members by the Chief, CSPCC.

This committee will usually meet at nine-month intervals for the entire length of the study unless there is less than six months left of patient follow-up. The committee may also be convened at any time of special need or "crisis" during the course of the study.

The Operations Committee provides a continuing critical and unbiased evaluation of the study's progress and formulates operational policy consistent with the best current biomedical research practice. At its first meeting, the committee reviews the plans presented for interval monitoring by the CSPCC and, when they are judged adequate and are approved by the committee, the study is ready to proceed. It should be stressed that the Operations Committee has primarily a monitoring and evaluation function. It does not initially evaluate the scientific merit of the study or subsequently participate in the conduct of the study. These duties have been assigned to other committees.

The prime responsibility of the Operations Committee at each of its review meetings is to decide whether or not the study should be continued and to so inform the Chief, CSP through the Chief, CSPCC, who also informs the Study Chairperson. To help it make this decision, the Study Biostatistician and the Study Chairperson must provide the committee with the required monitoring data summaries, or raw data if requested, three weeks before the meeting. Ordinarily, the Operations Committee is the only group privy to the interval summaries of decoded (unblinded) information during the course of the study. Reasons for recommending discontinuation of the study include inadequate quality of performance or lack of progress made by the participants, ethical problems such as poor results in one treatment group or unacceptable side effects, and monitoring functions so poor that it is impossible to assess the current status of the study (and no realistic chance of remedying these within a reasonable time).

The Operations Committee is also responsible for assessing the performance of each of the participating medical centers. When patient intake is low or performance inadequate at a center, they can recommend that the center be put on probation or even terminated from the study. In cases where performance is marginal but the center's presence in the study is considered essential, the committee should recommend reductions in personnel, supplies or other operating costs so that the costs of the center are more in line with the actual work load rather than the projected work load. In those situations where a reduction in funding at a center seems reasonable, a strong statement of justification for not recommending the reduction will be necessary by the committee or the reduction will probably be made administratively by the VACO CSP.

The Operations Committee must be kept informed by the Study Chairperson or the Study Biostatistician of all proposed changes in the protocol, data collection forms, or in plans for analyses since it must review and make a decision on all major changes. Documentation of this approval should be forwarded by the Operations Committee Chairperson through the Chief, CSPCC to the Chief, CSP (Coordinator of CSEC), as well as to the Study Chairperson and the CSPCC Biostatistician.

The Operations Committee should clearly differentiate between its suggestions and its recommendations. Suggestions should be made with the understanding that they will be given serious consideration by the Executive Committee, but are not binding. Response to suggestions should be documented in the Executive Committee reports. Recommendations are expected to be accepted and followed by the Executive Committee and it is the joint responsibility of the Executive Committee and the CSPCC to see that they are. If a dispute between the Executive and Operations Committees about a recommendation cannot be resolved, arbitration will be provided by a group nominated by the Chief, CSP and the Chief, CSPCC and appointed by the Director, Medical Research Service (and the Director, HSR&DS or RER&DS as appropriate). Decisions of this group (usually CSEC) will be binding on both committees.

At their first meeting, the members of the Operations Committee should elect a Committee Chairperson if the Study Chairperson has not nominated one. It is the Committee Chairperson's responsibility to prepare and send a report of each meeting within three weeks to the Chief, CSPCC. This report should delineate between suggestions and recommendations. The CSPCC Biostatistician should then review this report and prepare a cover report listing those suggestions and recommendations with which he/she agrees and those with which he/she disagrees. In the latter case, a brief statement explaining the reasons for disagreement should be made along with substitute suggestions or recommendations. Both the cover report and the Operations Committee report should be submitted to the Chief, CSPCC, who must review both within six weeks of the Operations Committee meeting and indicate concurrence or disagreement for each suggestion or recommendation. Where there is disagreement with both the Operations Committee and the Study Biostatistician, substitute suggestions or recommendations should be formulated. If a recommendation results in a major change of study procedures or direction, the Chief, CSPCC should raise the issue in this cover report to alert the Chief, CSP of the consequences of the recommendation. The Chief, CSP would then decide if the CSEC should review the proposed change. The Chief, CSPCC should then distribute these two cover reports with the original report appended to the Chief, CSP, the Study Chairperson, and the Operations Committee.

The question of liability has been raised and the decision of General Counsel in a memorandum dated July 7, 1975 was that Operations Committee 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. The liability of non-VA members of the Executive Committee, the Human Rights Committee, and the Study Group is also covered.

4. Human Rights Committee. At alternate meetings of the Operations Committee, the Human Rights Committee will participate in that part of the meeting that deals with the patients' rights and safety.

Besides reviewing the protocol for human rights issues prior to submission to CSEC, this committee is responsible for ensuring that the patients' rights and safety are protected during the course of the study. It is the responsibility of the Study Biostatistician and the Study Chairperson to provide the committee with the information that they request, including some or all of the data provided to the Operations Committee and a summary of the progress of the study written in layman's language as well as all or samples of signed patient consent forms from each participating facility. The Human Rights Committee Chairperson is responsible for writing a report of the meeting within two to three weeks of the meeting. This report should be distributed to the Human Rights and Operations Committee members, the Study Chairperson, the Chief, CSPCC, the Chief, CSP and, when appropriate, the Chief, CSPCRPCC. After those meetings of the Operations Committee that the Human Rights Committee does not attend, the Study Biostatistician and the Chief, CSPCC (and the Study Chairperson when appropriate) will meet with the Human Rights Committee within two weeks of the meeting and update them on the progress of the study.

Each year, members of the Human Rights Committee at each CSPCC, accompanied by a member of that CSPCC, make site visits to three medical centers that are participating in cooperative studies assigned to the CSPCC. The purpose of these visits is to ensure that the human rights aspects of the studies are being observed. 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 return from the site visit, the member will write a report about the visit as discussed later in Section IV.E. Since each CSPCC will usually have more than three ongoing studies during each year, each study will not have one of its facilities visited every year. However, if possible, at least one human rights site visit will be performed during the course of every study.

B. Arranging Meetings and Travel

If possible, the Study Group and the Executive Committee should meet on the day(s) just before or after an Operations Committee meeting in order to save travel costs for those members who must attend all three meetings. If this is not possible, the meetings should be held within one month of each other. It is preferable that the Operations Committee meet after the Executive Committee to allow it to review any changes proposed by the Executive Committee. At least every 18 months, the Operations Committee must meet in the vicinity of the CSPCC, in order to facilitate the Human Rights Committee review. If the Executive Committee and/or the Study Group meetings also convene there on contiguous days, CSPCC personnel other than the Study Biostatistician will also be able to attend those meetings.

To initiate one of the regularly scheduled group meetings, the Study Chairperson, before notifying VACO, CSP, should contact the Study Biostatistician at least two months before the proposed meeting date so that arrangements can be made. Except for the meeting in the vicinity of the CSPCC, the Study Chairperson, the Study Biostatistician and the CSPCC Administrative Assistant must choose a location with reasonable accommodations that minimizes the cost of travel and per diem but is still convenient for travelers. The CSPCC Administrative Assistant will select three sites that fulfill these conditions and calculate travel costs for each of them. If the cost projections for the three sites are within $100 of each other, the Study Chairperson may then choose one of these. However, if the differences are greater than $100, the site with the lowest cost will be selected. If the chairperson wants to schedule a meeting in a place that requires more funds than the minimum cost meeting site, the attendees (excluding those from the CSPCC) must obtain the additional funds from sources other than locally or centrally directed VA medical research travel funds. Exceptions to these rules for selecting meeting sites will only be granted if there are rather unique and valid reasons to do so, such as special laboratory facilities for training purposes. Allowing committee members to attend a national meeting is not considered a unique or valid reason for changing the meeting site.

After the Study Biostatistician has concurred and the Chief, CSPCC has given approval for a meeting, the Study Chairperson must inform the Chief, CSPCC by letter 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. A copy of this letter should be sent to the Study Biostatistician and the Chief, CSP. This letter must arrive at VACO at least six weeks prior to the scheduled meeting date or it will not be honored and the meeting will have to be rescheduled. Nonroutine (extra) meetings of any of the groups necessitated by problems arising during the study may be arranged on shorter notice by contact with the Chief, CSPCC or his/her designate, but these requests must be limited to emergency situations and are dependent on funds available. All nonroutine (extra) meetings require prior VACO, CSP approval.

Funding for travel to meetings of the Study Group, Executive Committee, Operations Committee, and other authorized cooperative study activities will be provided from VACO, CSP centrally directed travel funds. When the meeting has been approved, the Study Chairperson will so notify all expected attendees and give them the necessary details. Each VA participant should then submit a travel request through the local facility with the director's concurrence to the Regional Director (/151-I). These individual requests must be received in VACO, CSP office at least three weeks prior to the date of the meeting. Under no circumstances will requests for travel to routine meetings be honored if they are not received in the CSP office at least three weeks in advance of the meeting. When the date and place of a meeting are such that the meetings precede or follow a professional or scientific meeting, the extra support to permit attendance at the professional meeting (per diem, fees, etc.) will not be provided from VACO, CSP centrally directed travel funds, but must be sought elsewhere. The agenda and any materials to be reviewed at the meetings should be in the hands of the participants at least three weeks prior to the scheduled meeting date, with copies sent to the Chief, CSP.

The appropriate chairperson or authorized designee should prepare summary minutes of the meetings, including any actions taken, within three weeks of the meeting and send them to all participants and the Chief, VACO, CSP. It should be emphasized that all participants, including the Operations Committee and CSPCC personnel, are dealing with privileged information from a VA cooperative study that is not available for general dissemination.

C. Data Collection and Editing

In general, data reported on the study forms should be approved by the Participating Investigator at each medical center before being sent to the Study Chairperson for medical (subject matter discipline) review and assessment. If judged satisfactory, the data forms should then be forwarded to the responsible CSPCC for biostatistical and data processing review and assessment. Only when the Participating Investigator, the Study Chairperson, and the CSPCC Biostatistician or their local designees have all approved the data should they be entered into the permanent study data file for interval and final summary and analysis. This is to ensure that the data are legible, accurate, and complete as well as sensible and appropriate. In certain special instances, valid medical (subject matter discipline), scientific, methodologic, or administrative reasons may call for exceptions to this general operational policy and such exceptions will be granted if agreed upon by the Study Chairperson and the Chief of the CSPCC, and approved by the Chief, CSP and/or CSEC.

Certain data may need review by an additional person or group other than the Participating Investigator, the Study Chairperson, and the Study Biostatistician, e.g., central readings of EEGs, ECGs, coronary arteriograms, etc. The Cooperative Studies Program allows for such instances, but they must be planned and provided for in detail in the protocol of the study.

All data from all studies, regardless of funding, must be sent to the appointed CSPCC, whether the CSPCC has primary responsibility for the biostatistical and data processing aspects of the study (where data flow is regular) or is only monitoring. In the latter case, the data may not have to be sent to the CSPCC until after the study is completed. During the study, a copy of each patient's signed informed consent form must also be sent to the responsible CSPCC. This allows the Study Biostatistician and the Human Rights

Committee to check that every patient has given consent and that all facilities are using the same consent form(s). It is an absolute requirement in a VA cooperative study that all facilities use the same consent form(s) and procedures. The original consent forms should be retained in the patient's hospital record (not research data records) at the medical center.

D. Newsletter

The Study Biostatistician and the Study Chairperson or the Executive Committee should issue a study newsletter regularly. This newsletter may sometimes be only a brief communication of one paragraph or a more extensive report as called for by the development of the study. It should focus on items of general interest to the participants, such as progress, performance, and problems, but must not contain unblinded data or study results. It should be issued at least twice a year during active patient intake and at least annually throughout follow-up. The newsletter should be sent to all Participating Investigators, the Executive Committee, the Operations Committee, the Human Rights Committee, the Chief, CSP, and the Chief of each CSPCC and of the CSPCRPCC.

E. Site Visits

Site visits by the Study Chairperson, the CSPCC Biostatistician, the CSPCRPCC Pharmacist, or other technical experts are not routinely a part of cooperative studies, but may be required in certain cases. When site visits are an essential part of the study plan, they should be included as a special line item in the study budget. If an unforeseen problem arises that can only be resolved by visiting the medical center, a site visit may be funded if endorsed by the Study Chairperson, the Chief, CSPCC, the Chief, CSPCRPCC (where applicable), and the Chief, CSP, and if travel funds are available. These "emergency" visits are not encouraged, and will only be considered when deemed truly necessary and essential.

For all site visits connected with a cooperative study by persons other than the Study Chairperson, a report of the visit should be sent to the Study Chairperson within ten days. The Study Chairperson should forward these reports (or his/her own) through the Chief, CSPCC, to the Chief, CSP within 21 days. A copy of this report should also be sent to the Participating Investigator through the appropriate regular channels and, for information purposes, to the Chairpersons of the Operations Committee and the Human Rights Committee and, when appropriate, to the Chief, CSPCRPCC. The Study Chairperson may simply endorse the report, add his/her own recommendations or conclusions, or, if necessary, attach a summary of the actions of the Executive Committee or Operations Committee, or both, together with his/her own recommendations and conclusions. This report should include what specific actions must be taken to correct any deficiencies. The Study (or Monitoring) Biostatistician must ensure that these actions are taken. When appropriate, the local Participating Investigator will receive feedback through regular local channels.

F. 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 before completion. This early termination is usually based on recommendations from the Operations Committee and may be due to poor performance or lack of patient intake at the centers. Once the decision has been made to terminate a center, the Study Chairperson must promptly notify the Participating Investigator that the medical center has been dropped from the study. Copies of this letter must be sent to the local ACOS for Research and Development through the director of the local center and to the Chief, CSPCC, who will be responsible for notifying the Chief, CSP and, when appropriate, the Chief, CSPCRPCC. Funding up to 90 days after notification will be made available for the placement of personnel who are being phased out in this unplanned fashion. Funding will only be continued during the 90-day period until all personnel have been placed in other jobs.

If special equipment (other than the usual office equipment and furniture) was purchased for the study, the Study Chairperson and the Study Biostatistician must determine if such equipment is needed at another medical center, either known or to be selected. If it is needed at a known facility, the Chief, CSPCC will notify the ACOS for Research and Development at the terminated center that the equipment is to be transferred and, if funds are not available for shipment, a request should be made to the Regional Director (/151-I) for such funds. In the event that a new center is not yet identified, the Study Chairperson might want to have this equipment transferred to his/her center; the same type of letter would need to be prepared by the Chief, CSPCC to the local ACOS for Research and Development. In the event that the equipment is not needed by the study, its deployment will be the same as that given in Section V.A.

G. **Replacement of a Participating Investigator or Study Chairperson During the Course of a Study.**

Cooperative studies frequently take several years to complete. During that time, a Participating Investigator or a Study Chairperson may find it impossible to continue with the study. Should this occur, it is important that suitable replacements be found as quickly as possible so as not to interrupt the progress of the study any more than is absolutely necessary. It is essential that the local medical center and its R&D Committee, the Study Chairperson and the Executive Committee, the CSPCC and the Chief, CSP all accept the replacement Participating Investigator or Study Chairperson as being suitable and qualified.

If a Participating Investigator finds that it is not possible to stay with the study until its completion, he/she should, if possible, give at least three months advance notice prior to leaving. If the medical center is to continue in the study, a new Participating Investigator must be selected promptly and have the written endorsement of the center's R&D Committee. The local ACOS for R&D (or counterpart) should initiate a letter, attaching a copy of the R&D Committee's endorsement, through the Study Chairperson and the Chief of the appropriate CSPCC to the Chief, CSP requesting the replacement of the original Participating Investigator with the newly nominated one. Upon receipt of this letter, the Study Chairperson should contact the Study Executive Committee and obtain their endorsement of the nominated replacement Participating Investigator. If the Committee is in agreement, the Study Chairperson should write an endorsement (indicating agreement of the Executive Committee) and send it to the Chief of the appropriate CSPCC. If the Chief, CSPCC finds everything in order, the request should be endorsed and the entire packet sent to the Chief, CSP. This process should be completed as quickly as possible in order to avoid complications in continued funding for the medical center. In cases of "emergency," with little or no advance notice, temporary assignment of an investigator by the local center is permissable until the accomplishment of the formal replacement process. If no suitable or available replacement for the departing Participating Investigator exists, the center's participation in the study will be terminated.

In the case of the Study Chairperson, it is requested that, except for an unanticipated "emergency," at least six months advance notice be given prior to leaving so that a suitable replacement can be found. Upon notification of the Chairperson leaving the study, the Executive Committee should nominate a new Chairperson. This nominee does not necessarily have to be from the same center as the original Chairperson. If the nominee accepts the nomination, then his/her medical center should be contacted to obtain the approval and support of the center and its R&D Committee. The local ACOS should then initiate a letter endorsing the nominee as described previously for the replacement of the Participating Investigator. In cases of an "emergency," where there is little or no advance notice of the Chairperson's leaving, the Executive Committee may temporarily appoint one of its own members Chairperson until the formal process is accomplished. However, if no suitable or available replacement Chairperson exists, the study may be terminated prematurely.

H. **Subsequent CSEC Review**

All cooperative studies will have an in-depth review by CSEC at three-year intervals. The first review will be scheduled for the CSEC meeting nearest to the three-year anniversary of the first station funding

unless there has been an intervening special CSEC review dealing with major changes in the original proposal. In the latter case, CSEC will determine the interval until the next review. Ordinarily, a three-year review will not be scheduled if there is less than 12 months until the close of patient follow-up. The CSPCC Biostatistician and the Study Chairperson are responsible for scheduling these reviews through the VACO, CSP office. The deadlines for submitting these reviews to VACO, CSP are the same as for reviews of new proposals (see Appendix B).

It is also the Study Biostatistician's and the Study Chairperson's joint responsibility to prepare a written progress report that is clear, complete, concise, and highlights all important and relevant aspects and problems of the study at that time. This report should include: 1) the latest version of the protocol and data forms; 2) summaries of what changes in the original protocol and data forms were adopted and when; 3) number of patients entered into the study by semiannual periods and medical center, and comparison with the projected number; 4) losses to the study such as dropouts and changes of therapy due to failure or toxicity, when they occurred and why; 5) preliminary findings, including unblinded data summaries, indicating efficacy and safety status, comparison with study objectives, and estimates of the prospects of success; 6) current cost – overall for each study unit; and 7) cumulative cost since the beginning of the study. In addition, detailed projected plans for the future of the study should be presented for review and endorsement, as well as copies of the Operations Committee's reports. Although this report should fully cover the study up to this stage, the relevant features and special problems will be highlighted in a verbal presentation to the committee.

Besides the above information provided by the Study Chairperson and the Study Biostatistician, the Chief, CSPCC will prepare a report which should appear at the front of the submission package. This report will be a complete, accurate but brief review of the study from onset to time of submission for review.

I. Breaking the Double-Blind Code of Study Medications

The majority of cooperative studies involving drugs are double-blind studies, where neither the patient nor the Participating Investigator knows which drug the patient is receiving. Blinded medication code envelopes for breaking study medication codes are generated by the CSPCC with the assistance of the CSPCRPCC Clinical Research Pharmacist. These envelopes are sent to the CSPCRPCC and are shipped with the study medications to the study participants. The code envelopes are placed in the custody of the participating Pharmacy Services along with the study medications. When it is absolutely necessary that a study medication code must be revealed, the Pharmacy Service may open the envelope and reveal the medication code for a given patient to the Participating Investigator. However, protocol procedures for breaking the blind must be complied with. The participating Pharmacy Service must then return the opened code envelope to the CSPCRPCC within 72 hours after it has been opened. The CSPCRPCC will immediately inform the Study Biostatistician at the CSPCC via telephone and send him a hard copy of the opened code envelope. When a study has been completed or terminated early at a medical center, the unopened blinded medication code envelopes must be returned to the CSPCRPCC. The CSPCRPCC will verify that the envelopes were or were not intact and promptly notify the biostatistician of their condition. The blinded medication code envelopes should not be confused with the randomization code envelopes used in some studies to assign patients to a given treatment regimen.

J. CSPCC Files

Together with the data forms and copies of the signed informed consents (study consent forms and VA Form 10-1086), the CSPCC will maintain a file for the study that contains:

1. Record of CSEC review(s) and CSPCC Human Rights Committee review(s) prior to beginning the study.

2. Record of final protocol and informed consent procedures and forms. Copies of these will also be maintained at the CSPCRPCC for studies involving study articles.

3. Record of each participating facility's R&D Committee review(s) and approval(s) of the protocol prior to its entry into the study. The minutes of the meeting of the Committee on Human Studies should also be included. Copies of these will also be maintained at the CSPCRPCC for studies involving study articles.

4. Record of annual review by the R&D Committee and the Committee on Human Studies, where applicable, from each participating center during the active life of the study.

5. Reports and/or minutes of every meeting of the Operations Committee, the Executive Committee, and the Study Group during the active life of the study. Copies of these will also be maintained at the CSPCRPCC for studies involving study articles.

6. Appended to the appropriate Operations Committee Report, the record of each Human Studies Committee review during the active life of the study.

7. A record of all CSEC reevaluations after the study is initiated.

8. Copies of INDs and IDEs, statements of investigators, and other documents sent to FDA. Copies of these will also be maintained at the CSPCRPCC for studies involving study articles.

K. Reports

1. **Research and Development Information System (RDIS).** The Medical Research Service requires annually certain information from every VA medical center that conducts medical research. This information is utilized for effective planning and program analysis. VA Form 10-5386, Research and Development Information System Report, is to be completed by each Participating Investigator in an ongoing cooperative study and forwarded through the local research office. This form asks for the "Cooperative Study Number," which is assigned by the VACO, CSP office of the Medical Research Service. The Reports Control Symbol for this report is RCS 15-5.

2. **Annual Report to Congress of Medical Research in the Veterans Administration.** The CSPCC will annually obtain from the Study Chairperson a narrative summary of the study's highlights and progress during the preceding fiscal year and prepare a complete list of individuals who have participated in or otherwise contributed to the cooperative study during that period. This report is prepared with the intention that it will be sent to Congress.

3. **Smithsonian Science Information Exchange (SSIE).** The SSIE provides accurate, up-to-date information on all VA medical research projects. VA Form 10-1436, "Medical Research Information Project Data Sheet," is to be completed for each research project by the responsible investigator. After review by the local R&D Committee, the project data sheets should be submitted, in triplicate, to the Scientific Communication Unit, VACO. Cooperative studies are to be reported only by the Study Chairperson. The above mentioned Reports Control Symbol 15-5 has been assigned to this report.

An initial SSIE Report should be submitted 15 working days after work on the research project has begun. The abstract should include the purpose or significance of the project, the design, and the methodology. An annual progress report should be submitted in the anniversary month of the initiation of the project, indicating the current status and progress made during the year. A final report should be submitted 15 working days after a manuscript has been accepted for publication or if for any reason the project is terminated before completion. The abstract should include the results and the conclusions reached. Only one final report should be submitted for a project.

V. CONCLUDING A COOPERATIVE STUDY

A. Closing Down

Once follow-up has been completed on all patients enrolled in the study, there is ordinarily no need for further assessment by the Operations Committee or Human Rights Committee. The Chief, CSPCC will inform the Chief, CSP when these committees' services are no longer necessary. The CSPCC now has the responsibility for final data summaries and analyses of the study, which it must accomplish in a reasonable time after receipt of the last piece of data. The Executive Committee is responsible for the publication of all data and results from the study. Material for publication should ordinarily be submitted within one year of receipt of all data at the CSPCC or the outside-contract biostatistical coordinating center. Normally, the Executive Committee will be funded for one meeting during this year to prepare the manuscript for final publication.

At the close of the study all data must be sent to the assigned CSPCC. This is true whether the CSPCC had the primary biostatistical-data processing responsibility or was only monitoring the study. The CSPCC will maintain readily accessible (i.e., within the CSPCC's medical center) files on the study for five years after its completion, at which time the data will be placed into dead storage and reevaluated at five-year intervals regarding continued storage.

When appropriate, the CSPCRPCC, in cooperation with the Study Chairperson, the Study Biostatistician, and the participating VA medical centers, will direct the return and provide a final accounting of surplus investigational or study articles or chemicals/reagents that were centrally distributed. The CSPCRPCC will also provide an accounting of the drugs utilized by participants. The surplus drugs will be disposed of by the CSPCRPCC at a time and date agreed upon by the Study Chairperson and in a manner, determined by the CSPCRPCC, that is in compliance with the Environmental Protection Agency (EPA) guidelines and found to be acceptable to the involved pharmaceutical companies (when applicable).

At the completion of the study, any special equipment (other than the usual office equipment and furniture) that was purchased specifically for the study will be disposed of in the following manner: 1) the first choice is give it to another cooperative study at the medical center; 2) the second choice is give it to other research activities at the medical center; and 3) if neither of the needs stated above exist, then the equipment should be excessed to the Central Research Instrumentation Program at the VA Medical Center, Little Rock, AR.

B. Final Study Group Meeting

The Study Group will have a final "feedback" meeting as soon as the major analyses and results of the study are available for distribution and discussion. This meeting should ordinarily take place from three to 12 months after the last patient follow-up and can be prior to, after, or in conjunction with the manuscript writing meeting of the Executive Committee or its designated Writing Subcommittee(s). At this meeting, the Study Chairperson and the Executive Committee should present the major study results and their interpretation of those results to all of the Participating Investigators. General discussion of the results by the Study Group might provide the manuscript writers with other interpretations of the results which they might find useful as well as allowing each investigator to have a chance to discuss the study, its results, and its ramifications with colleagues.

It should be noted that any Study Group having a meeting during the final six months of patient follow-up will ordinarily not be funded for the final "feedback" meeting. Therefore, Study Group meetings scheduled for the final six months of patient intake should be postponed until after the data has been analyzed and the results are ready for distribution.

C. Publications

The presentation or publication of any or all data collected by Participating Investigators on patients entered into a VA cooperative study is under the direct control of the study's Executive Committee. This is true whether the publication or presentation is concerned with the results of the principal undertaking or is associated with the study in some other way. No individual Participating Investigator has any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any or all of the data other than under the auspices and approval of the Executive Committee.

The Executive Committee has the authority to establish one or more publication committees, usually made up of subgroups of Participating Investigators and some members of the Executive Committee, for the purpose of producing manuscripts for presentation and publication. Any presentation or publication, when formulated by the Executive Committee or its authorized representatives, should be circulated to all Participating Investigators for their review, comments, and suggestions at least four weeks prior to submission of the manuscript to the presenting or publication body.

All publications must give proper recognition of the VA Medical Research Service and the Cooperative Studies Program support and HSR&DS or RER&DS support as appropriate, and should list all participants in the study. If an investigator's major salary support and/or commitment is from the VA, it is obligatory for the investigator to list the VA as his/her primary institutional affiliation. Submission of manuscripts must follow the usual VA policy. Ideally, a subtitle is used stating, "A VA Cooperative Study," or, in the case of shared funding, e.g., "A VA-NHLBI Cooperative Study." In a footnote or acknowledgement it should be stated, "Funded by the Veterans Administration Cooperative Studies Program of the Medical Research Service" or "Funded by the Veterans Administration Cooperative Studies Program of the Medical Research Service and the NHLBI by interagency agreement No. ," or "Funded by VA HSR&DS (or RER&DS as appropriate) and supported by the VA Cooperative Studies Program of the Medical Research Service." A copy of the letter to the editor and the manuscript submitted for publication should be sent to the Chief, CSP, VACO and, for information purposes, to the members of the study's Operations Committee.

It is a requirement of the VA Cooperative Studies Program that a copy of every manuscript submitted for publication from a VA cooperative study, accompanied by a copy of the letter of submission to the anticipated journal or publisher, be on file in the CSPCC within one week of its submission for publication. Furthermore, when a major manuscript has been submitted which reports the final results of the study, the Study Chairperson should write a brief statement estimating the impact of these results on the VA patient population. This Impact Statement should be sent by the Study Chairperson through the Chief, CSPCC, the Chief, CSP, and the Director, Medical Research Service and the Director, HSR&DS or RER&DS as appropriate, to the ACMD for Research and Development.

At the time a major manuscript is submitted for publication, the Study Chairperson and the Study Biostatistician should write a "Highlights" of the results. This should be a brief statement, of no longer than two paragraphs, in simple, expressive, and informal language which describes the results of the study and their importance. When the date of publication of the article is known, a copy of the "Highlights" should be sent to the CSP office stating when the article will be published and in which journal. At the time that the article is to be published, the Chief, CSP will then forward these "Highlights" to the Director, Medical Research Service (and the Director, HSR&DS or RER&DS as appropriate) and the ACMD for Research and Development requesting that it be released in the next published "Highlights" format.

In order to give these publications a wider dissemination within the VA, the Study Chairperson, with the approval of the Executive Committee, should send an extra copy of the manuscript to the Chief of the assigned CSPCC who will then forward it within one week of receipt to the Chief, CSPCC, Perry Point, who has undertaken the task of publicizing the results of all cooperative studies. One form of publicity, at the option of the Study Chairperson or the Executive Committee, will be the inclusion of the manuscript in the

"VA Cooperative Studies Reports," a semiannual serial, for distribution within the VA only, of cooperative studies prepublication manuscripts. If the Study Chairperson wants his/her manuscript included in this report, he/she should give authorization in the cover letter accompanying the manuscript to the Chief of the assigned CSPCC. If a revision is required for a submitted manuscript, a copy of the revised manuscript should be sent to both the Chief, CSP and the Chief, CSPCC, Perry Point as should the notice of acceptance of a paper for publication. When the manuscript is published, the Chief, CSPCC, Perry Point should be informed of the journal reference so that arrangements for other publicity, such as a news release, can be made. When reprints are available, the Study Chairperson should send 12 copies to the Chief, CSPCC. Six of these will be forwarded to CSP, VACO and a courtesy copy will be sent to the other CSPCCs and the CSPCRPCC.

VI. RESPONSIBILITIES IN A COOPERATIVE STUDY

To successfully plan, organize, conduct, and bring to conclusion a cooperative study requires the complete and active cooperation of a great many individuals. It is important that everyone involved should have a clear understanding of what their responsibilities are and what commitments they are making when they agree to participate in one way or another. The intent of these guidelines is to contribute to the understanding of the total process. The scientific and administrative problems encountered in cooperative studies are too numerous and complex to rely on simple good faith understandings arrived at by word of mouth.

Participation in a VA cooperative study is voluntary. Any individual or medical center that cannot or will not accept these operational guidelines should not elect to participate. Similarly, it is essential from the scientific and ethical point of view that a specific study will be conducted in the same manner at each participating site and agreement to participate implies a willingness to adhere to the research protocol in all respects.

Involvement in cooperative studies in any role is likely to be demanding in time and effort. A Principal Proponent, a Study Chairperson, or a Participating Investigator should realize that he/she is making a personal commitment to the study and must be willing and able to devote time and energy to its success. In the event that he/she cannot continue in this role until the end of the study, he/she should make this information known to the Study Chairperson, the Chief, CSPCC, or the Chief, CSP, whichever is most appropriate, so that a substitute can be found. When the R&D Committee at the medical center approves participation in a cooperative study, the implication is that the study is feasible at that site, that the essential personnel are willing to be involved and are prepared to accept both the guidelines and the research protocol, and that the center is prepared to supply the necessary support including space for the duration of the study.

It may be necessary in the course of a cooperative study to terminate or replace a participating facility upon the recommendation of the Executive Committee or Operations Committee. Although this action will always be taken in response to what is considered the best interests of the study, it does not necessarily imply poor performance by the Participating Investigator or the facility, e.g., it is not unprecedented for a center to be unable to recruit sufficient patients in spite of their best efforts.

Any member of a cooperative study who does not perform satisfactorily within these guidelines or who does not adhere to the study protocol may be expected to be disengaged from his/her role in that cooperative study and/or have VA cooperative study funding discontinued by the Chief, CSP, upon recommendation of the study's Executive Committee and Operations Committee or by the Operations Committee alone. When such action is taken, that investigator would not ordinarily be considered for future activities of the VA Cooperative Studies Program.

Mechanisms for appeal of any dissatisfied investigator who feels he/she has a justifiable grievance during a cooperative study are: appearance in person before the study's Executive Committee; if not satisfied, appearance before the study's Operations Committee; if not satisfied, appeal to the Assistant Chief Medical Director for Research and Development. Initiation of each step in this appeal process must be preceded by submission of written documentation illustrating the nature of the grievance to be addressed. Information copies should be sent to the Chief, CSPCC, the Chief, CSP and, in the event of appeal to the ACMD for R&D, to the Director, Medical Research Service and the Director, HSR&DS or RER&DS as appropriate, as well.

APPENDIX A

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APPENDIX B

SCHEDULE OF IMPORTANT EVENTS

DEADLINES

Request for Planning (Page 2)
- To Chief, CSP from Principal Proponent through ACOS
  - December 1 for February review
  - April 1 for June review
  - August 1 for October review

Submission of Final Draft of Proposal
- To CSPCC Study Biostatistician from Principal Proponent (Page 13)
  - October 15 for December 1 submission to CSEC
  - February 15 for April 1 submission to CSEC
  - June 15 for August 1 submission to CSEC

Submission of Final Proposals for CSEC Review
- To Chief, CSP from CSPCC (Page 13)
  - December 1 for February review
  - April 1 for June review
  - August 1 for October review

REQUEST FOR TRAVEL APPROVAL

To Chief, CSPCC from Principal Proponent (Chairperson); copy to Chief, CSP
Planning Committee (Page 3)
- At least five weeks prior to meeting

Training Meetings or Organizational Meetings (Page 23)
- At least two months prior to meeting

Study Group, Executive Committee, Operations Committee (Page 23)
- At least two months prior to meeting

Emergency or unplanned meetings (Page 23)
- If at all possible at least three weeks prior to meeting

REPORTS

Study Group (Page 19), Executive Committee (Page 20), Operations Committee (Page 21), Human Rights Committee (Page 22)
From Committee Chairperson to all members and Chief, CSPCC; copy to Chief, CSP
- Within three weeks after meeting

Site Visit Reports, etc. (Page 24)
- To Study Chairperson from Site Visitor
  - Within 10 days after visit
- To Chief, CSPCC from Study Chairperson; copy to Chief, CSP
  - Within 21 days after visit

APPENDIX C

MEDICAL RESEARCH SERVICE "CORE COMMITTEE" FOR TRIAGE REVIEW FOR VETERANS ADMINISTRATION COOPERATIVE STUDIES

COORDINATOR AND NONVOTING CHAIRPERSON:

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NOTE: Ad hoc members may be added to the "Core Committee" as needed.

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*When review of a specific proposal occurs, which is not primarily in the area of Medical Research Service, the AO to the ACMD for Research and Development will attend and serve as Chairperson and an additional ad hoc member from that area (such as HSR&DS or RER&DS) may be added for that specific review.

APPENDIX E

COOPERATIVE STUDIES PROGRAM CLINICAL RESEARCH PHARMACY COORDINATING CENTER EVALUATION COMMITTEE (CSPCRPCCEC)

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APPENDIX F

STUDY BUDGET EXAMPLE

	Special Travel		YEAR 1						YEAR 2					TOTAL					
			Personnel			Other Oper.			Personnel			Other Oper.		Personnel			Other Oper.		
	Site Visits	TNG	FTP*	FTE**	Cost	Costs	Equip.	Total	FTP	FTE	Cost	Costs	Total	FTP	FTE	Cost	Costs	Equip.	Total
Chairperson's Office			2a	1.5b			d												
Medical Center 1						c	e												
.																			
.																			
.																			
.																			
.																			
.																			
10																			
Special Laboratory						f													
CSPCRPCC						g													
TOTAL																			

a. Study Coordinator and Clerk Typist.
b. 1.0 Study Coordinator; 0.5 Clerk Typist.
c. Operating costs include: drug analyses; local consulting; test scoring and supplies.
d. Typewriter, filing cabinets, desk.
e. Equipment for Behavioral Tests and special equipment needed for study.
f. Costs associated with Central Readings, special analysis (blood, urine, tissue), quality control, etc.
g. Cost involving drugs, biological products and devices for the study.

* FTP denotes actual number of people.
** FTE denotes equivalent ceiling count (FTEE).

APPENDIX G

REQUEST FOR PLANNING A VA COOPERATIVE STUDY
PRECIS SUBMISSION CHECKLIST

When a request to plan a cooperative study is submitted to the Chief, Cooperative Studies Program, the precis should include the following information. Although the details included in the precis are not binding, and modifications and changes undoubtedly will be made during the actual planning phase, the initial request should provide sufficient detail to assure that due consideration has been given to all facets of the proposed study. Use the checklist as a guide in preparing the precis.

- ☐ Primary objectives of the proposed study. Be specific regarding the aim of the research, e.g., to test new drug/medical procedure, to identify characteristics or prognostic factors of a disease, etc.
- ☐ Secondary objectives, if any.
- ☐ The importance of the study.
- ☐ Justification for a cooperative study approach.
- ☐ Description of the type of study proposed. Include all items that apply.
  - ☐ Prospective data collection.
  - ☐ Randomized.
  - ☐ Nonrandomized.
  - ☐ Retrospective data collection (chart review or review of patient history).
  - ☐ Comparison of new treatment/medical procedure to control.
  - ☐ No control or comparison to historical control.
  - ☐ Epidemiological or observational.
  - ☐ Other: _____
- ☐ Population from which patients are to be drawn. Include all that apply.
  - ☐ VA inpatients.
  - ☐ VA outpatients.
  - ☐ Non-VA inpatients (e.g., at affiliated university).
  - ☐ Non-VA outpatients.
  - ☐ Males and/or females.
  - ☐ Other: _____
- ☐ Brief description of the study procedures proposed.
- ☐ Provide a preliminary estimate for the following items:
  - ☐ Number of VA medical centers required.
  - ☐ Number of non-VA medical centers required.
  - ☐ Number of laboratories anticipated.
  - ☐ Duration of the study (in years).
  - ☐ Total estimated cost of the study.
- ☐ Summarize background and supply references of work accomplished on which request for the proposed cooperative study is based.
- ☐ Principal Proponents eligibility to receive Medical Research Service funds.