



**DEPARTMENT OF VETERANS AFFAIRS
OFFICE OF RESEARCH & DEVELOPMENT
PROGRAM GUIDE: 1205
VHA COOPERATIVE STUDIES PROGRAM**

As of April 5, 2019, the VHA Cooperative Studies Program Directive (VHA Directive 1205) and Cooperative Studies Program (CSP) Study Initiation and Management Processes (VHA Handbook 1205.01) have been replaced with this Program Guide.

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1. PURPOSE

The Veterans Health Administration (VHA) Program Guide provides policy for Cooperative Studies Program (CSP) activities and guidance for the initiation and management of CSP activities.

A successful cooperative study requires communication, cooperation, and a willingness to pursue a common goal. This Guide describes the most important tasks and responsibilities when developing and conducting a VA cooperative study.

2. BACKGROUND

a. CSP is a division of the Department of Veterans Affairs (VA) Office of Research and Development (ORD). It was established as a national clinical research infrastructure that designs, conducts, provides coordination for and enables cooperation on multisite clinical trials and epidemiologic studies that fall within the purview of VA.

CSP emphasizes a quality approach through program standards and operational documentation that 1) provide specific guidance and 2) consider the various scenarios that may occur in the conduct of such cooperative efforts.

Its scope and capabilities also enable innovative methods and practices that help advance the larger VA clinical research enterprise. When appropriate, CSP may work with other divisions of VA or non-VA entities, including the National Institutes of Health, Department of Defense, academic medical centers, private industry, and international research organizations.

b. A cooperative study is a research activity in which investigators from two or more VHA facilities agree to carry out a common research protocol in an identical manner. In a cooperative study, there must be adequate mechanisms for the following:

- Planning
- Evaluation
- Human subjects protection
- Study execution
- Interim monitoring
- Final analysis
- Interpretation of results
- Dissemination of findings

c. Cooperative studies are particularly advantageous at the later stages of evaluating safety, efficacy, and effectiveness of health care interventions that have already had the necessary preliminary trials in humans. For most medical conditions, cooperative studies can more rapidly pool observations made across several facilities. For rare medical diseases or disorders, cooperative studies may be the only feasible approach to adequately address a clinical question.

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In certain instances, cooperative studies may contribute to the early development and refinement of new therapeutic techniques. Cooperative studies that are clinical trials or that focus on epidemiological, health services, or rehabilitation research can benefit from a multisite approach that facilitates the accumulation of participant samples that are sufficiently:

- Large to provide a definitive answer to the research questions
- Diverse in demographic factors to permit broad generalization of results

d. The large number of VA facilities presents an ideal environment for conducting multisite cooperative studies. VA has a sizeable, relatively stable population that is especially appropriate for research, and that addresses medical problems and diseases prevalent among Veterans. These characteristics facilitate the conduct of multisite studies that require strict adherence to a common protocol. In this setting, it is more likely that the essential participant follow-up will be completed.

e. Successful cooperative studies require central administration to ensure uniformity of research methodology and human subjects protections as well as fiscal, administrative, and regulatory controls. VAs administrative structure contributes to this coordination.

f. CSP maintains a network of centers located across the United States. These centers report directly to CSP Central Office (CSPCO) in VHA Central Office and include CSP Coordinating Centers (CSPCC); a CSP Clinical Research Pharmacy Coordinating Center (CRPCC); and CSP Epidemiology Centers (CSPEC). CSP also has genomic medicine research facilities, a deoxyribonucleic acid (DNA) bank, two centralized biorepositories, and a pharmacogenomics analysis laboratory (PAL).

Expertise at these centers includes a range of personnel that covers major responsibilities in the conduct of quality clinical and/or genetic research. CSP also supports a Network of Dedicated Enrollment Sites (NODES) to enhance how clinical research is done at the site level. In addition, CSP collaborates with experts in health economics; health care service delivery and administration; implementation research; and rehabilitation. CSP studies are performed at VA facilities and collaborating sites with appropriate Federal Wide Assurances for conducting clinical research. (Section 11 provides more specific details about the CSP organization.)

3. DEFINITIONS

a. **Letter of Intent.** A Letter of Intent (LOI) in CSP is submitted to the Director, CSP, and outlines the proposed research. Final decisions on the LOI are made by the Chief Research and Development Officer. An LOI must include the following:

(1) Objectives of the proposed research

(2) Importance of the study to VA, including any background data from relevant research and its feasibility within VA

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- (3) A brief description of the study design, including patient population
- (4) Treatments, interventions, exposures, or outcomes to be compared
- (5) Randomization or observational approach, type of data collection (retrospective or prospective), and study endpoints
- (6) Number of participants and medical facilities required to meet study endpoints
- (7) Duration of the study in years
- (8) Potential strategies for implementing results
- (9) Curriculum vitae of Principal Proponent(s)

b. **Proposal.** After approval of the LOI by the Chief Research and Development Officer, a CSP Proposal is developed. A CSP Proposal is a description of the rationale, objectives, and methods for a clinical research study aimed at answering an important clinical question. This is submitted to a scientific review committee and to CSPCO for review, approval, and a decision on funding support. It is the result of planning activities involving a Principal Proponent and CSP personnel.

c. **Protocol.** A CSP Protocol is an organized description of the research that is managed by CSP and submitted for review to the Institutional Review Board (IRB) of record and contains at least the following elements:

- (1) Background and significance of proposed research, including VA relevance
- (2) Study hypotheses and objectives
- (3) Study population, including sample size, recruitment strategies, and inclusion or exclusion criteria
- (4) Study design and methodological considerations, including screening, randomization processes, sampling or bias, as applicable
- (5) Study interventions or treatments
- (6) Study endpoints, including safety endpoints
- (7) Study data collection, management, security, analyses, informed consent and privacy procedures, human subjects protection plan(s), and participant follow up
- (8) Safety monitoring plan, including the reporting of serious adverse events (SAEs) and adverse events (AEs), interim data analyses, study monitoring, and reports to oversight bodies
- (9) Publication and data access/sharing plans

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(10) Any additional requirements specified by CSPCO

4. SCOPE

This Program Guide provides requirements, key procedures, and all major aspects of developing and conducting research and related activities under the purview of CSP. These items apply to researchers, review/oversight committees, and others involved in these activities as indicated in the following (see Sections 6-11) or other CSP documents maintained for these purposes.

5. PROGRAM MANAGEMENT

a. **Chief Research & Development Officer.** The Chief Research & Development Officer (CRADO) sets program priorities for CSP and serves as the laboratory director, assuring the integration of CSP activities with VA and VHA program priorities, providing the necessary resources for CSP to conduct world-class clinical trials and epidemiologic research, and assuring that VHA clinical leadership receives timely information about CSP results that may benefit Veteran health care. CSP personnel report to the CRADO through the Director, CSP.

b. **Director, CSP.** The Director, CSP oversees the overall policy, planning, coordination, and direction of CSP activities. The Director, CSP oversees decisions involving CSP centers, the conduct of CSP cooperative studies, and related resources and activities. This authority includes, but is not limited to:

- Study management and operations
- Center and study funding
- Research and policy compliance
- Personnel actions related to CSP activities for all approved studies

These matters are reviewed and approved by the Director, CSP or designee.

c. **CSP Center Directors.** CSP Center Directors report directly and are responsible to the Director, CSP on all CSP activities assigned to them and their respective centers. CSP Center Directors have performance evaluations completed by the Director, CSP. CSP Center Directors or their designees oversee:

- Design, conduct, management, safety, and analysis of assigned CSP studies
- Management and oversight of their center personnel and activities
- Performance of participating sites in these studies
- Responding to or attending CSPCO-directed activities
- Maintaining CSP quality standards
- Promoting a collaborative spirit within a study and within the national program

CSP Center Directors meet other responsibilities that are described, in part, in SOPs and other operational documents maintained by the program.

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d. **CSP Study Chairs.** CSP Study Chairs are responsible to CSP for clinical leadership and joint scientific leadership with CSP Centers on their respective CSP study. CSP Study Chairs must do the following:

- Adhere to CSP procedures and policies
- Emphasize compliance by study personnel with all applicable policies in CSP studies
- Communicate CSP study activities to the assigned CSP Center Director
- Promote quality and a collaborative spirit within a study

6. LETTERS OF INTENT AND PLANNING PROCESS

a. CSP studies are initiated when an eligible VA researcher—or Principal Proponent—submits an LOI (see ORD Program Guide 1200.15). A study also may initiate as a service-directed project by the Director, CSP.

b. LOIs are submitted to the Director, CSP through the Associate Chief of Staff (ACOS) for Research and Development (R&D) and the Director at the Principal Proponent's VA facility.

c. Following administrative and scientific review of an LOI, the Director, CSP may assign meritorious proposals to one or more CSP Centers for planning. The CSP Center(s) (CSPCO and/or CSPEC and CSP CRPCC) and the Principal Proponent(s) work collaboratively to determine steps and complete responsibilities for developing a full study protocol.

d. One important step is to identify a planning committee with appropriate expertise for designing the protocol. The primary objectives of planning are to identify the key clinical question(s) to be answered, determine the feasibility of a study, and develop a full protocol for scientific review by the Cooperative Studies Scientific Evaluation Committee (CSSEC).

e. In some instances, pre-planning meetings may be organized to evaluate merits of a potential study and/or to determine critical elements for facilitating a full planning process.

7. REVIEW OF PROPOSALS

a. The scientific review of CSP Proposals is conducted by the Cooperative Studies Scientific Evaluation Committee (CSSEC). The peer review process involves an in-person meeting among CSSEC members, any ad hoc reviewers, and the study proponents to discuss the proposal. Activation of studies reviewed by CSSEC requires the recommendation of CSSEC and the approval of the CRADO.

b. Ad hoc reviews may be obtained by the Director, CSP, or designee, if a full committee meeting is not warranted given the scope or size of the project.

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8. STUDY INITIATION

a. Upon funding approval, the Principal Proponent(s) becomes the Study Chair(s), and the study is administered by the CSP Center(s) designated by the Director, CSP. Conduct of the study is a cooperative effort of the Study Chair(s), assigned CSP Centers, and their respective staff. CSP CRPCC is responsible for AE collection and reporting for all CSP interventional trials, procurement and distribution of drugs and devices, and any related regulatory requirements. Other components of CSP—including NODES—may be allocated as needed.

b. The CSP Center(s) and Study Chair(s) initiate the study. This process may include revising the protocol based on scientific review or Human Rights Committee (HRC) recommendations (see Paragraph 11 (i), as well as the following:

- Developing data collection tools
- Identifying participating study sites
- Establishing a study Executive Committee (see Paragraph 11(f))
- Hiring study personnel
- Drafting and producing study management and procedural documents

c. A study Executive Committee is required for all CSP studies and is responsible to the Director, CSP through the assigned CSP Center Director(s) for study activities.

d. An independent Data Monitoring Committee (DMC) is required for each CSP clinical trial to monitor and review study progress and safety (see Paragraph 11 (h)) A CSP HRC also provides independent ethical review and advocacy of participant considerations for studies. Each CSP study must undergo IRB review and approval, and obtain any other local approvals for conducting research.

e. CSP Center Directors or their designees will communicate relevant VA and CSP policies and procedures to appropriate groups to inform them on how the study will be conducted.

f. Any agreements with collaborators are established through CSPCO and can be developed with assistance from the CSP Center responsible for the study, if needed.

g. Any sites engaged in a CSP study must comply with requirements in the Common Rule (38 CFR Part 16), all other applicable federal regulations, and VA and VHA policies (see VHA Directive 1200.05). In addition, the site must hold a Federal Wide Assurance (see VHA Handbook 1058.03) and have an IRB of record registered with the Department of Health and Human Services, Office for Human Research Protections.

9. STUDY MANAGEMENT

CSP study management is the responsibility of the CSP Study Chair(s), assigned CSP Center Director(s), and respective CSP center staff. These activities are guided by

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program policy and operational documents maintained by CSP. CSP Center Director(s) is responsible for fully informing the Director, CSP/CSPCO of all major study activities and for forwarding any actions or recommendations requiring Director, CSP approval.

- a. CSP may perform visits or audits of participating sites without prior notice to the study personnel or VA facility.
- b. CSP Center Director(s) or the Director, CSP may terminate a site's participation based on performance, safety, or ethical concerns.
- c. The CSP Center Director(s) or the Director, CSP may direct for-cause audits at study sites or suspend study activities for potential performance, safety, or ethical concerns.
- d. The Director, CSP may require midterm scientific or progress reviews of ongoing studies.
- e. A cooperative study will be terminated when the objective has been met or when it is not feasible or ethical to continue.

10. STUDY PUBLICATIONS

CSP study publications require review and approval from the study's Executive Committee and the respective CSP Center Director(s), in addition to complying with VHA Directive 1200.19.

11. CSP STRUCTURE

CSPCO is under the leadership of the Director, CSP. It has overall responsibility for all CSP activities and reports to the CRADO. CSPCO leads strategic planning for the national program and manages the following:

- Scientific review
- Funding authorizations
- Fiscal management
- Program operations and policies
- Center/program coordination
- Collaborative efforts with VA and non-VA entities

The following Centers are included within CSP/CSCPO and support all activities related to research studies:

a. Cooperative Studies Program Clinical Research Pharmacy Coordinating Center. CSP CRPCC participates in studies that involve drugs or medical devices, or have participant safety issues. In this role, CRPCC also serves as the liaison among relevant regulatory agencies that include the Food and Drug Administration (FDA), and Drug Enforcement Administration (DEA). Additionally, CRPCC oversees the safety of

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CSP studies in collaboration with CSP Centers and handles site monitoring and audits to ensure study integrity. The CRPCC Director, or designee, has a primary management and oversight role for drug, device, and safety issues (i.e., AE monitoring and reporting) on CSP studies.

Center personnel include:

- Clinical research study pharmacists
- Pharmaceutical project managers
- Computer assistants and programmers
- Clinical manufacturing and materials management technicians
- Quality control monitors
- Quality control chemists
- Quality managers
- Research and financial administrators

Key responsibilities for drug and device-related activities include:

- Developing the drug or device handling protocol
- Negotiating with pharmaceutical and medical device companies
- Manufacturing, packaging, distributing, and accounting for drugs and devices
- Contributing to CSP quality efforts
- Working with other groups involved with drugs and devices including VHA Pharmacy Benefits Management, and the VA National Center for Patient Safety
- Provide guidance and information on FDA and DEA regulations

Co-located with CRPCC is the Site Monitoring and Auditing Resource Team (SMART). SMART provides clinical trial monitoring; auditing; Good Clinical Practices (GCP) training; and study protocol quality assurance.

NOTE: *At the time of publication, the CSP CRPCC is affiliated with the VA medical facility in Albuquerque, NM.*

b. Cooperative Studies Program Coordinating Centers. CSPCCs provide expertise in biostatistical and clinical research methods, database management, administration, fiscal and study project management, and quality management, including oversight of study compliance with CSP policies and standards. They are responsible for study design, data management, statistical analysis, and study project management and oversight for CSP studies.

These centers also conduct methodological research to improve the design, conduct, and analysis of clinical trials. CSPCCs have key clinical research personnel that may include:

- Biostatisticians
- Epidemiologists
- Statistical and database programmers

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- Informatics specialists
- Research administrators
- Data managers
- Study project managers
- Quality managers

CSPCC Directors, or designees, have a primary management and oversight role for studies assigned to their respective centers.

NOTE: *At the time of publication, five CSPCCs are located at the VA medical facilities in Boston, MA; Hines, IL; Palo Alto, CA; Perry Point, MD; and West Haven, CT.*

c. **Cooperative Studies Program DNA Bank and Centralized Biorepositories.**

The CSP DNA Bank and Centralized Biorepositories provide administrative, technical, and scientific coordination and central repositories. This enables CSP to collect and store blood, tissue, and other biological specimens from CSP and other VA studies for use in biomedical and genetic research.

CSP maintains capabilities for study design, analysis, data management, and informatics at various CSP centers and within VA where they maintain and analyze data associated with these efforts.

NOTE: *At the time of publication, the CSP DNA Bank is located at the Palo Alto, VA medical facility, and the two centralized CSP Biorepositories are located at the CSP Centers at the Boston and Albuquerque VA medical facilities.*

d. **Cooperative Studies Program Epidemiology Centers.** CSPECs have expertise in VA-based population research and provide statistical expertise and facilitation for the conduct of epidemiological research aimed at improving the health of Veterans and helping VHA providers improve patient care.

CSP-sponsored research focuses on key disease areas that impact Veterans. Research goals are to provide information on the prevalence, incidence, and associated risk factors to guide VA in ways that help improve and augment patient care. CSPECs also conduct methodological research and maintain resources for enhancing how clinical research activities are done.

Center personnel may include:

- Epidemiologists
- Biostatisticians
- Statistical and database programmers
- Informatics specialists
- Research administrators
- Study project managers
- Quality managers

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These centers have a primary management and oversight role for studies assigned to them. CSPEC Directors, or their designees, have a primary management and oversight role for studies assigned to their respective center.

NOTE: *At the time of publication, five CSPECs are located at VA medical facilities in Boston, MA; Durham, NC; Little Rock, AR; Palo Alto, CA; Seattle, WA; and West Haven, CT.*

e. **Cooperative Studies Program Study Chair.** A CSP Study Chair is the individual who submits a written idea for a VA cooperative study and is the Principal Proponent of the CSP study prior to approval of funding. This individual (or individuals) has a lead scientific role in how a study protocol is managed and executed. The CSP Study Chair works collaboratively with CSP Centers to oversee the scientific and operational responsibilities required to successfully conduct the study, including actions involving participating study sites.

f. **Cooperative Studies Program Study Executive Committee.** A CSP Study Executive Committee consists of approximately six to ten study personnel, including the CSP Study Chair (who is also Chair of this committee), biostatistician or epidemiologist, and clinical research pharmacist. It may have other key study leaders, including the CSP Center's project manager, national study coordinator, key site investigators, and health economist (if any).

The CSP Center Director and Director, CSP are ex officio members of this committee. The CSP Executive Committee is responsible for scientific management of the study and reports to the Director, CSP through the CSP Center Director. Decisions made by this group may relate to:

- Proposed changes in the study protocol or operational aspects of the study
- Use of data
- Feasibility issues
- Management of participating sites
- Importance of sub-studies; publications of study results
- Data sharing and access

g. **Cooperative Studies Scientific Evaluation Committee.** CSSEC is a chartered federal advisory committee that provides expert advice on VA cooperative studies, multicenter clinical research projects, and policies related to conducting and managing these efforts within CSP. This ensures that new and ongoing activities are based on scientific merit; efficiently, safely, and economically conducted; and mission relevant.

To accomplish these objectives, CSSEC reviews proposed activities and makes specific recommendations to the Director, CSP on their scientific merit. CSSEC comprises a diverse group of experts in clinical research and includes representatives from multiple medical specialties, such as biostatistics and epidemiology. Ad hoc members may be included if additional subject matter expertise is needed.

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h. **Data Monitoring Committees.** Also referred to as Data and Safety Monitoring Boards, each CSP clinical trial has a DMC that comprises medical experts in the field of study and experts in biostatistics or epidemiology. DMCs provide a continuing critical and unbiased evaluation and oversight of the study's progress and formulate ideas to facilitate activities that are consistent with best practices in current biomedical research. CSP epidemiological studies also may convene a DMC with input from CSPCO. This committee is responsible for the following:

- Monitoring participant accrual
- Overall study performance
- Treatment efficacy
- AEs and patient safety
- Futility
- Relevant external information
- Data integrity

DMC assesses the performance of each participating site and addresses considerations regarding continuation, probationary status, or termination, in addition to reviewing and providing recommendations regarding protocol changes, interim analyses, sample size re-estimation, and subprotocols or substudies. DMC summary reports may be provided to other oversight groups including IRB and the Human Rights Committee (HRC). DMCs are responsible to the Director, CSP through the respective CSP Center Director or designee.

i. **Human Rights Committee.** HRC is a CSP Center-based group that independently provides guidance on human rights, feasibility, ethical considerations, and advocacy on participant considerations in the design, planning, and conduct of CSP studies. CSP may have multiple HRCs. These groups comprise individuals from the community and VHA, including some members with medical and scientific expertise. HRCs conduct site visits and interviews with study participants and may seek input on regulatory compliance and ethics, as needed. HRCs inform the Director, CSP through the CSP Center Director of any issues that may arise over the course of a study.

j. **Network of Dedicated Enrollment Sites.** NODES comprises groups of clinical investigators, managers, and administrative personnel experienced in the conduct of clinical research based at designated VA medical facilities. Primary objectives for NODES are to improve study enrollment; regulatory compliance and safety; and operational efficiencies and overall conduct of CSP studies at sites.

Through economies of scale, NODES provides efficiencies at local facilities for CSP studies and contributes to the overall quality of CSP research through enrollment, regulatory compliance, human subjects protection, safety, and operational activities. NODES personnel also interact with CSP Centers and CSPCO to provide local insight and expertise for addressing key barriers and developing innovative approaches to conducting clinical research. Each NODES site also seeks to build a local community of clinical research among clinician-investigators, patients, facility leadership, and other

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stakeholders. NODES efforts collectively help to establish CSP best practices and innovative approaches to conducting clinical research.

NOTE: *At the time of publication, NODES locations are at the VA medical facilities in Dallas, TX; Hines, IL; Houston, TX; Long Beach, CA; Minneapolis, MN; Palo Alto, CA; Portland, OR; Salt Lake City, UT; and San Diego, CA.*

k. **Pharmacogenomics Analysis Laboratory.** PAL is a CSPEC and certified laboratory with the capacity to genotype genetic samples collected in CSP studies. Its role is to help CSP investigators develop and design studies aimed at evaluating the clinical utility of genomic data and it can genotype samples collected in CSP studies. PAL can be considered a CSP Center for operational and management purposes.

NOTE: *At the time of publication, PAL is located at the VA medical facility in Little Rock, AR.*

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