

VHA COOPERATIVE STUDIES PROGRAM

- 1. REASON FOR ISSUE:** This Veterans Health Administration (VHA) Directive provides policy for the VHA Cooperative Studies Program (CSP).
- 2. SUMMARY OF CHANGES:** This Directive was revised to update program elements including the renaming of CSP epidemiology centers and the Network of Dedicated Enrollment Sites (NODES), and discussions related to their activities.
- 3. RELATED ISSUES:** VHA Directive 1200 and VHA Handbook 1205.01.
- 4. RESPONSIBLE OFFICE:** The Office of Research and Development's Cooperative Studies Program (10P9CS) is responsible for the contents of this Directive. Questions may be addressed to 202-443-5600.
- 5. RESCISSION:** VHA Directive 1205, dated November 4, 2008, is rescinded.
- 6. RECERTIFICATION:** This VHA Directive is scheduled for recertification on or before the last working day of April, 2019.

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1. PURPOSE: This Veterans Health Administration (VHA) Directive provides policy for Cooperative Studies Program (CSP) activities and serves as a guide to additional resources for program-specific information and procedures. This Directive describes the most important tasks and responsibilities in developing and conducting a VA cooperative study. A successful cooperative study requires communication, cooperation, and a willingness to pursue a common goal. CSP emphasizes a quality approach through program standards and operational documentation that provide specific guidance and consider the various scenarios that may occur in the conduct of such cooperative efforts. **AUTHORITY:** Title 38 United States Code (U.S.C.) 7301(b) and 7303, and 38 Code of Federal Regulations (CFR) 16.114.

2. BACKGROUND:

a. The CSP, a division of the Department of Veterans Affairs (VA) Office of Research and Development's (ORD) Clinical Science Research and Development Service (CSR&D), was established as a clinical research infrastructure to provide coordination for and enable cooperation on multi-center clinical trials and epidemiological studies that fall within the purview of VA. 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 planning, evaluation, human subjects protection, study execution, interim monitoring, final analysis, interpretation of results, and dissemination of findings.

c. Cooperative studies are particularly advantageous in 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. 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 multi-center approach that facilitates the accumulation of participant samples that are:

- (1) Sufficiently large in number to provide a definitive answer to the research questions.
- (2) Sufficiently diverse in demographic factors to permit broad generalization of results.

d. The large number of VA facilities presents an ideal environment for conducting multi-center cooperative studies. VA has a large and relatively stable population which is especially appropriate for research and that addresses medical problems and diseases prevalent among Veterans. These characteristics facilitate the conduct of multi-center 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. VA's administrative structure contributes to this kind of 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, a biorepository, and a pharmacogenomics analysis laboratory. Expertise at these centers includes a range of personnel that cover 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. In addition, CSP collaborates with experts in health economics; health care service delivery and administration; implementation research; and rehabilitation. CSP studies are carried out at VA facilities and collaborating sites with appropriate Federal Wide Assurances for conducting clinical research.

(1) CSPCO is under the leadership of the Director, CSR&D, with direct support from the Deputy Director, CSP. It has overall responsibility for all CSP activities and reports to the VA Chief Research and Development Officer. CSPCO leads strategic planning for the national program and manages scientific review; funding authorizations; fiscal management; program operations and policies; center coordination; and collaborative efforts with VA and non-VA entities.

(2) 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. These activities encompass all phases of the research project, including: proposal development; study implementation; central coordination of study conduct; data management; interim statistical analyses and study progress monitoring; and final analyses for study publications; as well as archiving of study documents and data at study completion. These centers also conduct methodological research to improve the design, conduct, and analysis of clinical trials. **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.*

(3) The CSP Clinical Research Pharmacy Coordinating Center (CRPCC) provides pharmaceutical project management and additional resources for CSP studies that involve drugs or devices and participant safety issues. Personnel from this center collaborate in the planning and development of the study; participate in monitoring the study; serve as liaisons between the CSP, the pharmaceutical and device industries, and the Food and Drug Administration (FDA); provide guidance and information on FDA regulations; review and distribute reports of serious adverse events; review adverse events collected during the course of the study; centrally control and distribute study drugs and devices; and assist in program quality efforts. The CSP CRPCC provides clinical trials monitoring; auditing; Good Clinical Practices (GCP) training; and quality assurance. **NOTE:** *At the time of publication, the CSP CRPCC is affiliated with the VA medical facility in Albuquerque, NM.*

(4) CSPECs provide epidemiological and statistical expertise and coordinate large-scale epidemiological studies. CSPECs have particular expertise in population-based and genomic/genetic research. These centers conduct VA sponsored epidemiological research on key disease areas impacting Veterans and also provide information on the prevalence, incidence, and associated risk factors to guide VA in ways that help improve and augment patient care.

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

(5) A CSP DNA Bank and Biorepository located at the Palo Alto and Boston VA medical facilities; respectively, are central repositories for blood, tissue, and other biological specimens from CSP and other VA studies, intended 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.

(6) A Pharmacogenomics Analysis Laboratory (PAL) is a CSPEC that helps CSP investigators develop and design studies aimed at evaluating the clinical utility of genomic data and can genotype samples collected in CSP studies. *NOTE: At the time of publication, the PAL is located at the VA medical facility in Little Rock, AR.*

(7) A Network of Dedicated Enrollment Sites (NODES) focuses on improving CSP study efficiency and quality through enrollment, regulatory compliance, human subjects protection, safety, and operational activities. Each site, or node, also seeks to build a local community of clinical research among clinician-investigators, patients, facility leadership, and other 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 Boston, MA; Dallas, TX; Hines, IL; Houston, TX; Long Beach, CA; Minneapolis, MN; Palo Alto, CA; Portland, OR; Salt Lake City, UT; and San Diego, CA.*

(8) CSP provides joint support for the Health Services Research and Development Service's Health Economics Resource Center (HERC) at the Palo Alto VA medical facility. HERC provides design and analytical expertise in the conduct of CSP studies where there are important cost effectiveness questions or other economic components.

3. POLICY: It is VHA policy to advance the health and care of Veterans through cooperative research studies that produce innovative and effective solutions to Veteran and national health care problems. This policy is carried out through the support of scientifically meritorious and VA-relevant research activities that are directly supported and managed by the CSP.

4. RESPONSIBILITIES:

a. **Chief Research & Development Officer.** The Chief Research & Development Officer's (CRADO) responsibilities for ORD activities are provided in VHA Directive 1200. The CRADO is responsible for setting program priorities for CSP, assuring the integration of CSP activities with VA and VHA program priorities, providing the necessary resources for CSP to conduct world-class epidemiologic research and clinical trials, and assuring that clinical

leadership in VHA is made aware in a timely manner of CSP results that may benefit Veterans' health care. CSP personnel report to the CRADO through the Director, CSR&D.

b. **Director, Clinical Science Research & Development.** The Director, CSR&D, is responsible for the overall policy, planning, coordination, and direction of CSP activities. The Director, CSR&D has overall responsibility for all decisions regarding CSP centers and their personnel, the conduct of CSP cooperative studies, and related activities. This authority includes, but is not limited to: matters related to study management and operations; center and study funding; research and policy compliance; and personnel actions related to CSP activities for all approved CSP studies. These matters are reviewed and approved by the Director, CSR&D or designee.

c. **VA Facilities.** Refer to VHA Handbook 1200.01 for a description of the responsibilities of facility directors, the Research & Development (R&D) Committee, and the Associate Chief of Staff (ACOS) for R&D or Coordinator for R&D, and Administrative Officer (AO) for R&D in relation to the research program at their facilities.

d. **CSP Center Directors.** CSP Center Directors report directly and are responsible to the Director, CSR&D, on all CSP activities assigned to them and their respective center. CSP Center Directors have performance evaluations completed by the Director, CSR&D. CSP Center Directors or their designees are responsible for the: 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; and promoting a collaborative spirit within a study and within the national program.

e. **CSP Study Chairs.** CSP Study Chairs are responsible for clinical leadership and joint scientific leadership with CSP Centers on their respective CSP study. CSP Study Chairs must follow CSP procedures and policies; emphasize compliance with all applicable policies in CSP studies; communicate CSP study activities to the Director, CSR&D through the assigned CSP Center Director; and promote a collaborative spirit within a study.

5. REFERENCES:

a. VHA Directive 1200, Veterans Health Administration Research and Development Program.

b. VHA Handbook 1200.01, Research and Development (R&D) Committee.

c. VHA Handbook 1205.01, Cooperative Studies Program (CSP) Study Initiation and Management Processes.

6. DEFINITIONS:

a. **Cooperative Studies Program Clinical Research Pharmacy Coordinating Center.** The CSP CRPCC participates in CSP studies that involve drugs or medical devices or have participant safety issues. 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; GCP monitors and auditors; and research and financial administrators. Key responsibilities of the CSP CRPCC 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; and working with other groups involved with drugs and devices including VHA Pharmacy Benefits Management, the VA National Center for Patient Safety, and the FDA. The CSP CRPCC provides oversight for the safety of CSP studies in collaboration with the CSP Centers and handles site monitoring and audits to ensure the integrity of a study. The CSP CRPCC Director, or designee, has a primary management and oversight role for drug, device, and safety issues on CSP studies.

b. **Cooperative Studies Program Coordinating Centers.** CSPCCs provide study design, data management, statistical analysis, and study project management and oversight for CSP studies. These centers have key clinical research personnel that may include: biostatisticians; epidemiologists; statistical and database programmers; informatics specialists; research administrators; data managers; study project managers; and quality managers. CSPCC Directors, or designees, have a primary management and oversight role for studies assigned to their respective centers.

c. **Cooperative Studies Program DNA Bank and Biorepository.** The CSP DNA Bank and Biorepository provides administrative, technical, and scientific coordination and a central repository to enable CSP to collect and store blood, tissue, and other biological specimens from CSP and other VA studies for use in biomedical and genetic research. They maintain and analyze data associated with these efforts.

d. **Cooperative Studies Program Epidemiology Centers.** CSPECs have expertise in VA-based population research and facilitate the conduct of epidemiological research aimed at improving the health of Veterans and helping VHA providers improve patient care. Center personnel may include: epidemiologists; biostatisticians; statistical and database programmers; informatics specialists; research administrators; study project managers; and quality managers. 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.

e. **Cooperative Studies Program Study Chair.** A CSP Study Chair is the individual who puts forth 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 with CSP Centers, as a team, 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. They 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, Deputy Director, CSP, and Director, CSR&D are ex officio members of this committee. The CSP Executive Committee is responsible for scientific management of the study and reports to the Director, CSR&D 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; the importance of sub-studies; publications of study results; and data sharing and access.

g. **Cooperative Studies Scientific Evaluation Committee.** The CSSEC is a chartered federal advisory committee that provides expert advice on VA cooperative studies, multi-center clinical research projects, and policies related to conducting and managing these efforts within CSP to ensure that new and ongoing activities are: based on scientific merit; efficiently, safely, and economically conducted; and mission relevant. To accomplish these objectives, the Committee reviews proposed activities and specifically makes recommendations to the Director, CSR&D on their scientific merit. The CSSEC is comprised of a diverse group of experts in clinical research and includes representatives from multiple medical specialties, including biostatistics and epidemiology. Ad hoc members may be included if additional subject matter expertise is needed.

h. **Data Monitoring Committees.** Each CSP clinical trial has a data monitoring committee (DMC) that consists of medical experts in the field of study and experts in biostatistics or epidemiology. DMCs provide a continuing critical and unbiased evaluation of the study's progress and formulate recommendations to facilitate activities that are consistent with best practices in current biomedical research. CSP epidemiological studies may also convene a DMC with input from CSP Central Office. This committee is responsible for monitoring the study for participant accrual; overall study performance; treatment efficacy; adverse events and patient safety; fertility; relevant external information; and adequate monitoring to ensure participant safety and data integrity. The DMC assesses the performance of each participating site and makes recommendations regarding continuation, probationary status, or termination, in addition to reviewing and providing recommendations regarding protocol changes, interim analyses, sample size re-estimation, and sub-protocols or sub-studies. DMC summary reports may be provided to other oversight groups including Institutional Review Boards (IRB) and the Human Rights Committee (HRC). DMCs are responsible to the Director, CSR&D through the respective CSP Center Director or designee.

i. **Health Economics Resource Center.** The HERC is often involved in CSP trials to perform health economic sub-studies. The HERC is a national center comprised of health economists, programmers, and other staff that collaborate with VA researchers in assessing the cost-effectiveness of medical care, evaluating the efficiency of VA programs and providers, and conducting high-quality health economics research.

j. **Human Rights Committee.** The HRC is a group based at a CSP Center that independently provides guidance on human rights, ethical considerations, and advocacy on participant considerations in the design, planning, and conduct of CSP studies. HRCs are comprised of individuals from the community and VHA, including some members with medical and scientific expertise. This group may seek input on regulatory compliance and ethics as needed. CSP may have multiple HRCs. HRCs focus on human rights; study feasibility; participant experience; and ethical issues in the study proposal. HRCs also conduct site visits

and interviews with study participants to carry out their duties. HRCs inform the Director, CSR&D through the CSP Center Director of any issues that may arise over the course of a study.

k. **Network of Dedicated Enrollment Sites.** NODES are teams comprised of groups of clinical investigators, managers, and administrative personnel experienced in the conduct of clinical research based at designated VA medical facilities. NODES help provide efficiencies and economies of scale at local facilities for CSP studies and contribute to the overall quality of CSP research. NODES personnel interact with CSP Centers and CSPCO to provide local insight and expertise for addressing key barriers and developing innovative approaches to conducting clinical research. Primary objectives for the NODES are to improve study enrollment; regulatory compliance and safety; and operational aspects for CSP studies at a given location.

l. **Pharmacogenomics Analysis Laboratory.** The PAL is a certified laboratory with the capacity to genotype genetic samples collected in CSP studies. It can be considered as a CSP Center for operational and management purposes.