VETERANS HEALTH ADMINISTRATION
COOPERATIVE STUDIES PROGRAM

1. REASON FOR ISSUE. This Veterans Health Administration (VHA) Directive defines the Cooperative Studies Program (CSP) policy.

2. SUMMARY OF MAJOR CHANGES. This VHA Directive describes CSP and its main components, and delineates roles and responsibilities.

3. RELATED DOCUMENTS. VHA Handbook 1205.01, and VHA Directive 1200.

4. RESPONSIBLE OFFICE. The Office of Research and Development's Cooperative Studies Program (125) is responsible for the contents of this Directive. Questions may be addressed to 202-461-1676.

5. RESCISSION. VHA Manual M-3, Part II, Chapter 9 dated October 30, 1989, is rescinded.

6. RECERTIFICATION. This VHA Directive is scheduled for recertification on or before the last working day of November 2013.

Michael J. Kussman, MD, MS, MACP
Under Secretary for Health

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1. PURPOSE: This Veterans Health Administration (VHA) Directive provides policy and guidance for Cooperative Studies Program (CSP) activities and serves as a guide to additional resources for program-specific information and procedures.

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 collaboration 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, academic medical centers, private industry, and international agencies.

b. A cooperative study is a research activity in which two or more investigators from two or more different medical centers agree to carry out a common research protocol in an identical manner. In a cooperative study, there must be adequate mechanisms for planning, evaluation, execution, interim monitoring, final analysis, and interpretation.

c. Cooperative studies are particularly advantageous in the later stages of evaluating safety, efficacy, and cost effectiveness of health care interventions that have already had the necessary preliminary trials in humans. For more common medical conditions, they can more rapidly pool observations made across several facilities. For rare medical diseases or disorders, they 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 patient 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 medical centers (VAMCs) presents an ideal environment for conducting multi-center cooperative studies. VA has a large and relatively stable patient base; this patient base is especially appropriate for research that addresses medical problems and diseases prevalent in the veteran population. 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 patient follow-up is completed.

e. Successful cooperative studies require central administration to ensure uniformity of research methodology, 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 (CSPCCs), a Clinical Research Pharmacy Coordinating Center, epidemiological research centers, and a Health Economics Resource Center (HERC). CSP also has genomic medicine research facilities, a Deoxyribonucleic acid (DNA) Bank, and a biorepository. Expertise at these centers includes: biostatistics; epidemiology; clinical research methodology; informatics; research programming; database management; study project administration and management; drug and device procurement or manufacturing, distribution, management and accountability; patient safety and regulatory affairs; health economics; biological sample collection and storage; and genetics.

(1) CSPCO is based in ORD, VHA Central Office. It is headed by the Director, CSR&D, who 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 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 at study completion. These centers also conduct methodological research to improve the design, conduct, and analysis of clinical trials. ***NOTE:*** *At the time of this Directive, five CSPCCs are located at the VAMCs in Boston, MA, Hines, IL, Palo Alto, CA, Perry Point, MD, and West Haven, CT.*

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

(4) CSP epidemiological research centers provide epidemiological and statistical expertise and coordinate large-scale epidemiological studies. 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 this Directive, three Epidemiologic Research and Information Centers (ERICs) are located at VAMCs in Boston, MA, Durham, NC, and*

Seattle, WA, and a Clinical Epidemiology Research Center (CERC) is located at the West Haven VAMC.

(5) CSP and the ORD Health Services Research and Development Service provide joint support for the Health Economics Resource Center (HERC) at the Palo Alto VAMC. HERC provides design and analytical expertise in the conduct of CSP studies in instances where there are important cost effectiveness questions or other economic components.

(6) A CSP DNA Bank and Biorepository storage facility located at the Palo Alto and Boston VAMCs, respectively, assist VA cooperative studies in the process of collection and storage of blood, tissue, and other biological specimens.

(7) A Pharmacogenomics Analysis Laboratory (PAL) helps CSP investigators develop and design studies aimed at evaluating the clinical utility of genomic data and provides genotyping for such data collected in CSP studies. ***NOTE:*** *At the time of this Directive, the PAL is located at the Little Rock VAMC.*

g. This Directive describes the most important tasks and responsibilities in developing and conducting a cooperative study. A successful cooperative study requires communication, cooperation, and a willingness to pursue a common goal. CSP maintains program standards and operational documents that provide specific guidance and that consider the various scenarios that may occur in the conduct of such cooperative efforts.

3. POLICY: It is VHA policy that CSP's mission is to advance the health and care of veterans through collaborative research studies that produce innovative and effective solutions to national health care problems. This mission is carried out through the support of scientifically meritorious and VA-relevant research activities that are directly supported and managed by the CSPCO and its centers.

4. RESPONSIBILITIES

a. **Director, CSR&D, VHA Central Office.** The Director, CSR&D, VHA Central Office 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, which are reviewed and approved by the Director, CSR&D, or designee. These decisions include, but are not limited to: matters related to study management and operations, center and study funding, and personnel actions related to CSP activities for all approved CSP studies.

b. **VAMCs.** Refer to VHA Handbook 1200.1 for a description of the responsibilities of facility directors, the R&D Committee, and the Associate Chief of Staff (ACOS) for R&D or Coordinator for R&D (C for R&D), and Administrative Officer (AO) for R&D in relation to the research program at their facilities.

c. **CSP Center Directors.** CSP Center Directors report directly to and are responsible to the Director, CSR&D, on all CSP activities assigned to them and/or their respective center. CSPCC

Directors and other CSP Center Directors supported by CSP funding have performance and evaluations completed by the Director, CSR&D. CSP Center Directors, or their designees, are responsible for: the design, conduct, management, and analysis of assigned CSP studies; the management and oversight of their center personnel and activities; the performance of participating sites in these studies; responding to or attending CSPCO-directed activities; and promoting a collaborative spirit within a study and the national program.

d. **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 CSP Center Director; and promote a collaborative spirit within a study.

5. REFERENCES

a. VA Directive 6500.

b. VHA Directive 1200.

c. VHA Handbook 1200.5.

d. VHA Handbook 1605.1.

e. VHA Handbook 1605.2.

f. VHA Handbook 1205.01

6. DEFINITIONS

a. **Clinical Epidemiological Research Center (CERC).** The CERC develops research methods for conducting studies involving topics in patient-oriented research using observational methods and conducts epidemiological research to help enhance VHA health care delivery. Center personnel may include: epidemiologists, biostatisticians, statistical and database programmers, informatics specialists, research administrators, and study project managers. The CERC Director, or designee, has the primary management and oversight role for studies assigned to the center.

b. **Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC).** The CSPCRPCC participates in CSP studies that involve drugs or medical devices or have patient 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, GCP monitors and auditors, and research and financial administrators. Key responsibilities of the CSPCRPCC 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 or devices; and working with other groups involved with drugs and devices including VHA Pharmacy Benefits

Management, the VA National Center for Patient Safety, and the Food and Drug Administration. The CSPCRPCC 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 CSPCRPCC Director, or designee, has a primary management and oversight role for drug, device, and safety issues on CSP studies.

c. **CSP DNA Bank and Biorepository.** The CSP DNA Bank and Biorepository provide 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 Coordinating Centers (CSPCCs).** 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, and study project managers. CSPCC Directors, or designees, have a primary management and oversight role for studies assigned to their respective centers.

e. **CSP Executive Committee.** A CSP Executive Committee is chaired by the respective CSP Study Chair and consists of approximately six to ten members from the study, including the CSP Study Chair, biostatistician or epidemiologist, and clinical research pharmacist. They may have other key study leaders including the CSP project manager, national study coordinator, key site investigators, and health economist (if any). The CSP Center Director is an ex officio member 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, use of data, feasibility, the importance of sub-studies, and the publications of study results.

f. **CSP Study Chair.** The CSP Study Chair is the individual who puts forth a written idea for a VA cooperative study and is known as the Principal Proponent of the CSP study prior to approval of funding. This individual 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.

g. **Cooperative Studies Scientific Evaluation Committee (CSSEC).** This chartered Federal Advisory Committee 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.

h. **Data Monitoring Committees (DMCs).** Each CSP clinical trial has a DMC that consists of medical experts in the field of study and biostatistics. This committee is responsible for considering whether the study should continue based on patient accrual, overall study progress, treatment efficacy, adverse events and patient safety, futility, and proper monitoring and reporting by the CSPCC or other support units in the study. The DMC assesses the performance of each participating center and makes recommendations regarding continuation, probationary status, or termination, in addition to reviewing and providing recommendations regarding protocol changes and sub-protocols or sub-studies. DMC summary reports may be provided to other oversight groups including Institutional Review Boards (IRBs) and the Human Rights Committee. DMCs are responsible to the Director, CSR&D through the respective CSP Center Director, or designee.

i. **Epidemiologic Research and Information Centers (ERICs).** ERICs 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, and study project managers. These centers have a primary management and oversight role for studies assigned to them. ERIC Directors, or their designees, have a primary management and oversight role for studies assigned to their respective center.

j. **Health Economics Resource Center (HERC).** The HERC is often involved in CSP trials to perform health economic sub-studies. The HERC is a national center comprised of health economists 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.

k. **Human Rights Committee (HRC).** The HRC is a group based at a CSP Center that promotes the protection of patients' rights and welfare in CSP studies. HRCs are comprised of individuals from the community and VHA and include 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 help identify ethical considerations in CSP studies, conduct site visits, and may conduct 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.

l. **Pharmacogenomics Analysis Laboratory (PAL).** 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.