CDMRP
Department of Defense

Congressional Directed Medical Research Programs

Fiscal Year 2020 Scleroderma Research Program Stakeholders Meeting Summary April 29, 2020

U.S. Army Medical Research and Development Command

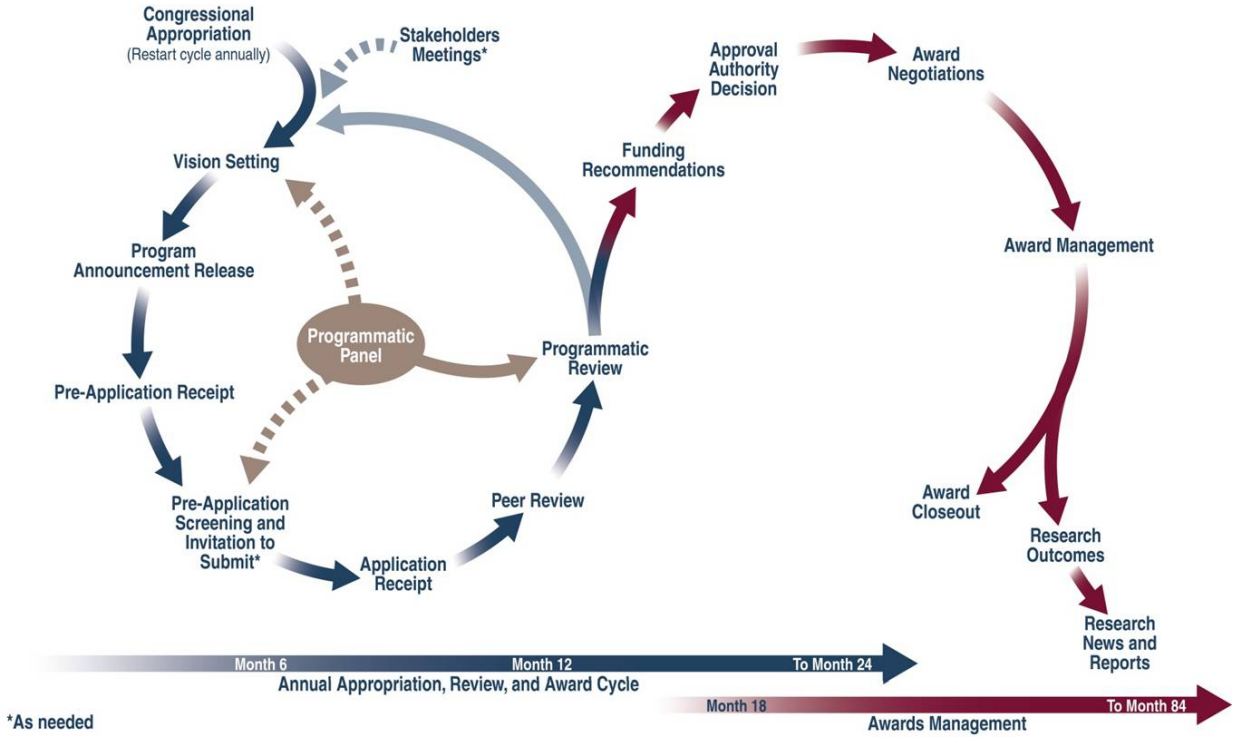
Overview: CDMRP History

The Defense Health Agency J9, Research and Development Directorate manages the Defense Health Program Research, Development, Test, and Evaluation appropriations, including funds assigned to the United States Army Medical Research and Development Command Congressionally Directed Medical Research Programs (CDMRP) for management. Since its first appropriation of congressional funding in fiscal year 1992 (FY92), CDMRP has been responsible for managing more than $14.4 billion in appropriations.

The origins of the CDMRP reach back to 1992 when Congress first appropriated funds targeted specifically for women's health research. In 1993, funds were appropriated for the establishment of the Breast Cancer Research Program. Since that time, additional research programs and topics have been added to the Department of Defense (DoD) appropriation by Congress, and the CDMRP has evolved into a global funding organization that fosters novel approaches to biomedical research in response to the expressed needs of its stakeholders. The CDMRP implements the investment of congressionally directed dollars provided to fund groundbreaking, high-impact, meritorious research that targets critical gaps. In addition, the CDMRP provides support for the management of core dollars (Presidential budget) directed at both intramural and extramural military medical research portfolio areas.

Programmatic Cycle

Figure 1. CDMRP Annual Program Cycle



To ensure that each program's research portfolio reflects not only the most meritorious science, but also the most programmatically relevant research, the CDMRP developed a two-tiered model based upon recommendations from a 1993 Institute of Medicine (IOM) report.[§] The IOM (now the National Academy of Medicine) recommended a two-step review procedure for research applications that was composed of a scientific peer review and a separate programmatic review (Figure 1). The scientific peer review is conducted by an external panel that is recruited specifically for each peer review session. Peer review involves the expertise of scientists, clinicians, military members, and consumers (patient advocates). Each application is judged on its own scientific and technical merit with respect to the described criteria in the funding opportunity solicitation. The second tier of review, programmatic review, includes discussions by experts in the field, such as the Programmatic Panel for the SRP. These experts, which include scientists, clinicians, consumers, and members of the military, assess the applications based on the scientific peer review ratings and summaries, a balanced portfolio, programmatic intent, and scientific merit. Scientifically sound applications that best meet the program's interests and goals are recommended for funding by the Programmatic Panel. Once approval is received for the funding list, awards are made in the form of 1- to 4-year grants and assigned to Science Officers for full-cycle support of research and outcomes.

[§] Strategies for Managing the Breast Cancer Program: A Report to the U.S. Army Medical Research and Development Command, 1993.

Introduction to the FY20 Scleroderma Research Program

Scleroderma is a poorly understood heterogeneous disease with poor survival, no validated biomarkers, and no effective disease modifying treatment. Systemic Scleroderma (SSc) presents as a chronic connective tissue multisystem disorder characterized by vasculopathy, autoimmunity, inflammation, and fibrosis. The prevalence of SSc is about 250 per million and the incidence is about 20 per million adults, with approximately 70,000 SSc cases in the United States. SSc has the highest mortality rate of any systemic autoimmune disease with interstitial lung disease as the leading cause of disease-related mortality. Although it strikes patients of all ages, including children, incidence is most likely between the ages of 40-60. There is a higher prevalence in some Native American populations. Congress directed that the Scleroderma Research Program (SRP) be included in the U.S. FY20 DoD appropriation at $5 million (M) and be established as a CDMRP program. With this new program, SRP will invest in research for the benefit of Service members, Veterans, their families, and the American public.

Moment of Silence

Mr. Ed Harris, a scleroderma researcher, patient, and founder of The Scleroderma Education Project, provided the Moment of Silence at the FY20 SRP Stakeholders meeting to reflect on the impact that scleroderma has on patients and to remember those who have passed from the disease. He shared that researchers and clinicians observe the disabling and disfiguring aspects of the disease for which limited treatments are available to alter disease course and alleviate symptoms. He noted, however, that there is an additional view of scleroderma that many do not see, which is revealed in the social media interaction among scleroderma patients. In this setting, scleroderma patients share their daily struggles — how their partners want to leave them, how they look disfigured, incontinence issues, and lack of physical intimacy. Mr. Harris added that the current pandemic has placed many scleroderma patients at a higher risk of complications if they become infected with COVID-19 because of associated cardiac and respiratory issues as well as being immunosuppressed. Mr. Harris shared that because of the pandemic, he is no longer able to receive the therapeutic plasma exchange treatments that keep him in remission. He commented that the lack of improvement in treatment options for scleroderma is what motivates him, at the age of 72, to spend 5-6 hours a day educating patients and writing scleroderma-related articles. He emphasized that priority should be given to research that will benefit patients in the short term. He concluded the Moment of Silence by asking those in attendance to remember those that are living with, have been affected by, or passed from scleroderma.

SRP Stakeholders Meeting Objectives

Purpose

- The Stakeholders meeting is a forum for an open dialogue among experts to (1) identify critical issues facing scleroderma research and patient treatment and (2) acknowledge the underfunded areas of research and patient care in the field of scleroderma.

Participants

- Forty representatives from scleroderma non-profit organizations, academia, and Government institutions were invited to share broad perspectives on which initiatives have the greatest potential to propel the science forward, break down potential barriers in research and patient outcomes, address key knowledge or scientific gaps, and identify potential approaches for the treatment of scleroderma.

Key Meeting Outcomes

- Review scleroderma research landscape (presentations highlighting key areas of research and review of stakeholder survey).
- Define and prioritize research areas to close the research gaps to be used by the SRP Programmatic Panel at Vison Setting.

FY20 SRP Stakeholders

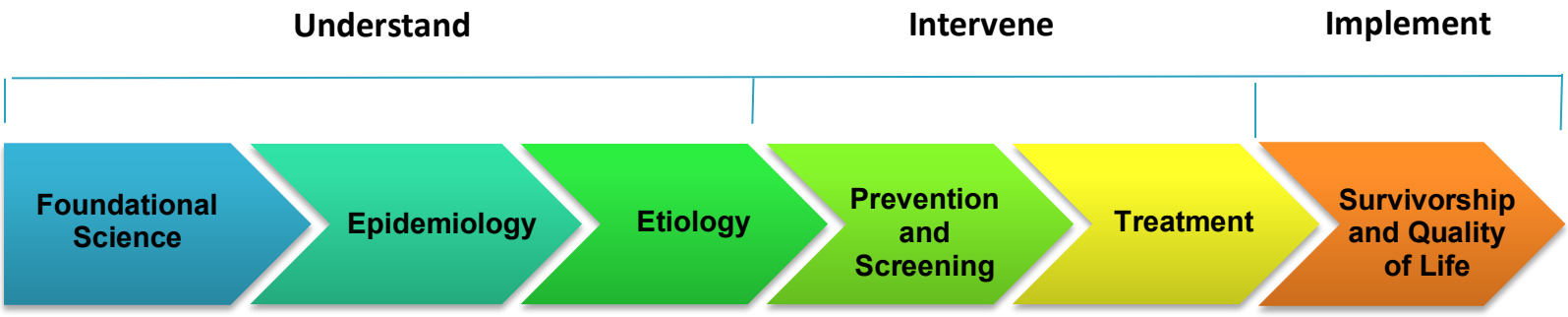
Stakeholder	Affiliation
Dr. Carol Artlett	Drexel University School of Medicine
Dr. Shervin Assassi	University of Texas Health Science Center at Houston
Ms. Kathleen Beauchamp	Consumer
Dr. Howard Chang	Stanford University
Dr. Quinn Dinh	Corbus, Pharmaceuticals, Inc.
Dr. Sharon Dobie	Scleroderma Research Foundation
Dr. Robyn Domsic	University of Pittsburgh School of Medicine
COL Jess Edison	Walter Reed National Military Medical Center
Dr. Luke Evnin	Scleroderma Research Foundation
Dr. Carol Feghali-Bostwick	Medical University of South Carolina
Dr. David Fox	University of Michigan
Dr. Tracy Frech	VA Medical Center, Salt Lake City, Utah
Mr. Ed Harris	Consumer
Dr. Monique Hinchcliff	Yale School of Medicine
Dr. Laura Hummers	Johns Hopkins Scleroderma Center
Dr. Masood Khan	Department of Veterans Affairs
Dr. Benjamin Korman	University of Rochester
Dr. Robert Lafyatis	Boston University
Dr. Brendan Lee	Baylor College of Medicine
Dr. Maureen Mayes	University of Texas Health Science Center at Houston
Dr. Zsuzanna McMahan	Johns Hopkins Scleroderma Center
COL Stephen Olson	Walter Reed National Military Medicine Center
Dr. Heiyoung Park	National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH)
Dr. Harris Perlman	Northwestern University
Dr. Ani Philip	McGill University Health Centre Research Institute
Dr. David Piestsky	VA Medical Center, Durham, North Carolina
Mr. Robert Riggs	Scleroderma Foundation
Dr. Bernie Rubin	GlaxoSmithKline
Dr. Ami Shah	Johns Hopkins Scleroderma Center
Dr. Mehul Shah	Actelion Pharmaceuticals
Mr. Robert Tufel	Scleroderma Research Foundation
Dr. John Varga	Northwestern University
Dr. Michael Whitfield	Geisel School of Medicine at Dartmouth
Ms. Deann Wright	Scleroderma Research Foundation

The SRP acts in partnership with scleroderma non-profit organizations, academia, and Government institutions to benefit of Service members, Veterans, their families, and the American public

Scleroderma Research Continuum

The Scleroderma Research Continuum represents a research framework within which studies can be organized along a progression that includes six topic areas: foundational science, epidemiology, etiology, prevention and screening, treatment, survivorship and quality of life. This also facilitates analysis of gaps and identification of future areas of focus.

Scleroderma Research Continuum



Foundational Science	Epidemiology	Etiology	Prevention and Screening	Treatment	Survivorship and Quality of Life
Basic discovery science	Population-level (to include at-risk) descriptive and characterization in nature; the study of the distribution of associations between health related states	Neurobiological mechanisms of the disease to include possible causes of disorder	Population, indicated prevention/ intervention at different stages of illness; screening measures; assessment tools and measurement; training	Aimed at symptom amelioration (includes psychotherapies and drugs) at different stages of illness including refractory, chronic, relapse, relapse prevention; address comorbidities; follow-up	Encompasses length and durability of treatment, and long-term consequences of treatment rehabilitation

Summary of Scleroderma Research Landscape

Scleroderma Foundation Overview – Mr. Robert Riggs

Mr. Riggs offered an overview of the Scleroderma Foundation. He described the various research grants offered by the Scleroderma Foundation (Established Investigator Grants, New Investigator Grants, and Collaborative Research Grants), which support the generation of pilot data, collaboration, and training of the next generation of scleroderma researchers. He indicated that the foundation has funded 286 grants at 77 research institutions totaling $28.56M in research dollars, all of which is provided by individuals and families living with scleroderma. He highlighted the Scleroderma Foundation Early Career Investigators Workshop, a biennial event in which early career investigators present research to established researchers in a mentoring environment. Mr. Riggs stated that the Scleroderma Foundation was instrumental in advocating for scleroderma-specific research appropriations from Congress. The foundation endeavors to help advocates find their "voice" and legislative advocacy does that.

Scleroderma Research Foundation Overview – Dr. Luke Evnin

Dr. Evnin gave an overview of the Scleroderma Research Foundation. He reviewed the membership of the Scleroderma Research Foundation Board of Directors and Scientific Advisory Board. He noted that the foundation invests more than $1.5M in direct grants for research programs in addition to funding other priorities. He described the major elements of the Scleroderma Research Foundation research program, which includes the unraveling the pathobiology of scleroderma, enabling precision medicine, and developing essential community scientific platforms. He also highlighted the Foundation's establishment and its contribution of over $1M to the development of the Collaborative National Quality and Efficacy Registry (CONQUER) for Scleroderma, which consists of 13 different research sites that have already enrolled over 370 patients. And also noted the Foundation's role in establishing the Genome Research in African American Scleroderma Patients (GRASP) effort. The Foundation partners with a number of other entities in the scleroderma research continuum such as the Scleroderma Clinical Trials Consortium (SCTC), the Johns Hopkins University Scleroderma Center of Excellence, and a biotech firm Blade Therapeutics. He concluded his presentation by describing pressing open research questions for the scleroderma community, including (1) who are the "bad cells" in scleroderma? (2) why (mechanistically) does the disease persist and progress? (3) can this disease be reset and how do we do that? (4) how does fibrosis propagate in scleroderma? and (5) highlighting pathways to decrease reliance on animal models noting the opportunity to focus on 3D human organoid models.

NIAMS Overview – Dr. Hieyoung Park

Dr. Park provided an overview of the NIAMS investment in scleroderma research. She explained that the NIH is comprised of 27 different institutes and centers and that roughly 85% of research funds are distributed to extramural grants, contracts, and cooperative agreements, while 10% fund intramural research. She reviewed the roles of the NIH extramural research team and the overall life cycle of an NIH grant application. She stressed that funding decisions are made by the Directors of NIH institutes after the peer review, but recommendations from council members and program directors are considered. She continued by providing details related to the various types of NIH funding opportunities announcements. She then reviewed the NIH scleroderma research portfolios, which showed that about 58% of all scleroderma projects are funded through the NIAMS as research grants (e.g. R01 and R21 grants). She concluded her presentation by asking the attendees overarching questions related to scleroderma research including (1) what are the gaps or obstacles to advance the research on scleroderma? (2) are researchers using valid metrics? (3) what can the NIH/NIAMS and the broader scientific community do to accomplish research goals?

CDMRP Scleroderma Portfolio Overview – Mr. Jonathan Ryder, CDMRP Science Officer

Mr. Ryder provided an overview of the CDMRP scleroderma portfolio. He introduced the DoD Peer Reviewed Medical Research Program (PRMRP) and explained that PRMRP is a large program that funds research in a number of specific disease topic areas, as directed by Congress. The PRMRP funds research projects in seven different research portfolios, including the immunology/auto-immune portfolio, which includes scleroderma research and other immunological and auto-immune research. Mr. Ryder stated that scleroderma was first offered as a PRMRP Topic Area in FY08 and then again in FY10-FY13 and FY15-FY19 and that during its time as a PRMRP Topic Area, 26 scleroderma awards have been funded totaling $23.21M. He explained that for FY19, the scleroderma Topic Area had five Areas of Encouragement that identified some of the most critical needs in scleroderma research. He expanded upon the CDMRP scleroderma portfolio, which showed that 77% of the 26 funded scleroderma awards are invested in Investigator-Initiated Research Awards to understand the cell biology, pathobiology, and detection and diagnosis of scleroderma. He concluded his presentation by highlighting Dr. Chandra Mohan's FY15 Discovery Award focusing on optical electrography of systemic sclerosis skin.

Pharmacotherapeutics for Scleroderma-What's on the Horizon? – Dr. Quinn Dinh

Dr. Dinh provided an overview of pharmacotherapeutics for scleroderma. He reviewed the current treatments for the various disease manifestations of systemic sclerosis with an emphasis on the need for additional therapies and research to advance the treatment process. He explained that compared to other immunological disorders, general and emotional health is

worse in scleroderma patients despite an overall decrease in mortality. He described a recent study from a group in Greece where eight centers were evaluated over a 2-year period to determine treatment patterns among scleroderma patients. He related these findings to patients in the United States and explained that the majority of scleroderma patients are on at least one immunosuppression agent, but adherence to therapy is poor because of lack of drug efficacy and/or adverse events associated with immunosuppression therapy. He described potentially new treatments for scleroderma that focus on alterations in clinical trial endpoints, early disease predictors, and drugs that target scleroderma manifestations. He continued by referencing a recent publication that summarized the pipeline for Phase I and Phase II clinical trials investigating early diffuse cutaneous scleroderma and noting that the majority of trials target proinflammatory or profibrotic molecules. He described the results of selected scleroderma pharmacotherapeutics and how none met the primary endpoint and that additional planning is required to successfully execute study endpoints. Current therapies have modest efficacy and many drug targets focus on vasculopathy, inflammation, or fibrosis. Recent trials have not been able to achieve clinical endpoint of mRSS, so we need more endpoints that reflect patient reported health. In summary current therapies have modest efficacy and that additional study endpoints that reflect patient-reported health are required.

Johns Hopkins Scleroderma Center Overview – Dr. Laura Hummers

Dr. Hummers provided an overview of the Johns Hopkins Scleroderma Center. She described the extensive heterogeneity associated with scleroderma that is not captured by the limited and diffuse scleroderma subsets and indicated that patients are better grouped based on presence of scleroderma-specific antibodies. She emphasized that the mission of the Johns Hopkins Scleroderma Center is to provide the highest quality of care to patients, which is accomplished through various collaborations with cardiology, dermatology, rheumatology, and surgical departments to provide comprehensive care. Their research operation is founded in longitudinal care of patients in context of providing clinical care. They collect data on phenotypes, treatments and outcomes as well as biologic samples with the goal to interrogate biological mechanisms in clinically relevant subgroups. She explained the Johns Hopkins Scleroderma Center database and that the antibody profiles and subtypes observed in their database are similar to those observed globally. She indicated that there has been special interest in identifying markers of cancer risk in scleroderma patients. She highlighted the Johns Hopkins University Precision Medicine Initiative and the use of its revolutionary tools, data science, and connectivity to discover clinically relevant and biologically anchored subgroups to impact the value of healthcare. She explained that the Johns Hopkins Scleroderma Center uses precision medicine to neutralize the complexity associated with scleroderma by defining patients into groups that are more homogeneous, allowing for a framework for multiple connections to be made to yield a better predication of a patient's outcome and disease course. She concluded by stating the Johns Hopkins Scleroderma Center vision and goals for precision medicine in scleroderma disease management.

Summary of Breakout Sessions

After reviews of the Scleroderma Research Landscape and the Stakeholders Survey, the stakeholders broke into three assigned groups. Each group was assigned two of the research lines of effort (foundational science, epidemiology, etiology, prevention and screening, treatment, and survivorship/quality of life) and then identified the most important research priorities (areas of emphasis) to address each research gap. Each participant identified their own perspectives and then worked to consider the combined perspectives from all group participants to identify the three most important for each area of the research continuum.

The areas of emphasis will be used by the SRP Programmatic Panel at the FY20 Vison Setting.

Research Continuum	Research Gaps	Research Priorities (Areas of Emphasis)
Foundational Science: **Basic discovery science**	The molecular mechanisms and pathogenesis of scleroderma are poorly understood and there is a need to identify novel and/or innovative therapeutic targets.	• Understand the strong female sex bias in scleroderma and why males have more severe disease. • Understand the different biological/ metabolic pathways that differentiate subsets of patients (genetic, clinical phenotype, race/ethnicity).
Epidemiology: **Population-level (to include at-risk) descriptive and characterization in nature; the study of the distribution of associations between health-related states**	Population-based or cohort studies are needed to understand the prevalence, heterogeneity and course of this disease, its manifestations and its impact on health outcomes and activities for daily living.	• Expansion of early disease registries linked to biological samples and high-quality clinical data and patient reported outcomes. • Direct patient recruitment: Enroll patient partners through Facebook or other platforms to avoid referral bias at tertiary centers. • Investigate fine phenotyping of clinical subsets to address heterogeneity.
Etiology: **Neurobiological mechanisms of the disease** **to include possible causes of disorder.**	Scleroderma has the highest mortality rate of any systemic autoimmune disease and further research is critical to decrease organ involvement, especially in the lungs.	• Understand the functional implications of epigenetic changes in scleroderma and the role of epigenetic changes in disease development. • Define the target cells of the autoimmune response that initiate and/or propagate organ-specific disease activity. • Develop models that are more suitable to study the disease or closely mimic the disease.

Research Continuum	Research Gaps	Research Priorities (Areas of Emphasis)
Prevention and screening: Population, indicated prevention/ intervention at different stages of illness; screening measures; assessment tools and measurement; training	There is a need for validated biomarkers and other approaches for early diagnoses, monitoring disease progression and its associated complications, assessment of treatment response to prevent, arrest, or reverse the symptoms of scleroderma.	• Define biomarkers ('omics, and or molecular markers, cell subsets, imaging, and patient reported outcomes) that help inform choice of therapeutics or predict course of treatment response of lung fibrosis, pulmonary, vascular disease, cardiac, and renal in patients with early disease. • Define biomarkers that help inform choice of therapeutics (immunosuppressive/ anti-fibrotic) or predict course or treatment response of ulcers, gastrointestinal, or severe skin disease (morbidity) • Develop cohorts from diverse populations to validate potential biomarkers.
Treatment: Aimed at symptom amelioration at different stages of illness including refractory, chronic, relapse, relapse prevention; address comorbidities; follow-up	There are very few therapies that are modestly effective for certain manifestations of scleroderma; these have considerable risks and adverse effects that limit their usefulness. There is a critical need for novel and/or innovative therapies and re-purposing of existing therapies.	• Develop and design innovative clinical trials. • Develop and validate organ specific and composite outcomes measures that help identify what treatments are actually working. • Utilize clinical and molecular/laboratory measures to define homogeneous groups or relevant subsets of patient(s) to determine treatment and response - personalize medicine.
Survivorship/quality of life: Focused on system of care improvements and provider and non-healthcare provider.	Research is needed to understand and improve the impact of the disease and its treatment on the patient's experience and quality of life. Research is also needed to develop interventions to improve coping with the disease.	• Identify main concerns of patients to inform development and validation of patient-reported outcomes. • Develop interventions that improve the quality of life. • Understand the link between what we see in terms of molecular, laboratory, and clinical measures and the patient's quality of life.

Appendix 1: Acronyms and Abbreviations

CDMRP	Congressionally Directed Medical Research Programs
CONQUER	Collaborative National Quality and Efficacy Registry
DoD	Department of Defense
FY	Fiscal Year
GRASP	Genome Research in African American Scleroderma Patients
IOM	Institute of Medicine
M	Million
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH	National Institutes of Health
PRMRP	Peer Reviewed Medical Research Program
SBIR	Small Business Innovation Research
SCTC	Scleroderma Clinical Trials Consortium
SRP	Scleroderma Research Program
SSc	Systemic Sclerosis
STRR	Small Business Technology Transfer
U.S.	United States
VA	Department of Veterans Affairs