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14. ABSTRACT

In this Annual Report, we report the successes with and ongoing challenges to initiation of the SEPVADIS Study. In the report period, we finalized our manual of procedures and case report forms. We have created and tested a relational database in the RedCap system. We conducted a mock patient run-through of the study procedures and protocols. We have established our Data Safety and Monitoring Board. We have confirmed production of study drug and placebo with the Johns Hopkins Investigational Drug Service. We have established and finalized all subcontracts. Most importantly, we have received approval from our Institutional Review Board and the Human Research Protections Office for initiation of the study. With these approvals, we have begun active screening for eligible participants through our recruitment pools at the Johns Hopkins Pulmonary Hypertension Program and the Johns Hopkins Scleroderma Center. We have identified candidates and have approached our first potential subject. We hope to enroll our first subject before the end of the calendar year.

15. SUBJECT TERMS
Scleroderma, Pulmonary vascular disease, clinical trial, sildenafil

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1. INTRODUCTION

In this Annual Report, we provide updates on the SEPVADIS Study (Sildenafil for Early Pulmonary Vascular Disease in Scleroderma). This study is supported by a Peer Reviewed Medical Research Program Clinical Trial Award (PR191839) which was awarded in September 2020. The SEPVADIS study is a multi-center, 16-week randomized clinical trial to determine the effect of sildenafil, a phosphodiesterase type 5 inhibitor, on functional capacity in patients with scleroderma, a rare autoimmune disease with high morbidity and mortality, and early pulmonary vascular disease. Thirty subjects who have scleroderma and early pulmonary vascular disease, defined as a mean pulmonary artery pressure between 21-24 mmHg as ascertained by invasive hemodynamic measurement, will be randomized to receive sildenafil 20 mg three times daily or to matching placebo. The primary endpoint of the study is change in six-minute walk test, an assessment of functional capacity and a validated outcome measure to assess response to therapy in patients with a more severe form of pulmonary vascular disease known as pulmonary arterial hypertension. Additional assessments will include health-related quality of life, right ventricular morphology and function by cardiac magnetic resonance imaging and echocardiography, and serum biomarkers of pulmonary vascular disease. These assessments will be repeated at week 16 and will include invasive assessment of pulmonary hemodynamics with right heart catheterization. Subjects will be followed for 1 year from randomization and undergo repeat 6MWT, echocardiography, health-related quality of life assessment, and serum biomarker collection.

2. KEYWORDS

Scleroderma

Randomized clinical trial

Pulmonary vascular disease

Pulmonary hypertension

Pulmonary arterial hypertension

Sildenafil

Six-minute walk test

Right heart catheterization

Cardiac magnetic resonance imaging

Echocardiography

Serum biomarkers

N-terminal pro-natriuretic brain peptide

Right ventricular function

3. ACCOMPLISHMENTS

a) Major Goals

Initiation of a randomized, clinical trial focused on treatment of patients with a rare disease with cardiopulmonary manifestations has been challenging during the current pandemic. Several of these challenges are discussed in more detail in Section 5. However, despite these challenges, we have achieved several milestones:

1) Successful enrollment and completion of all study procedures up to month 12 of the protocol for 2 subjects and up to 9 months for 1 subject at Johns Hopkins University
2) Successful enrollment and completion of all study procedures up to month 9 of 1 subject at Louisiana State University Health Sciences Center
3) Screening and identification of 16 potential subjects at Johns Hopkins
4) Screening and identification of 6 potential subjects at Louisiana State University Health Sciences Center
5) Continuing weekly SEPVADIS study meetings with Johns Hopkins University School of Medicine and Louisiana State University Health Sciences Center faculty and staff to facilitate coordination and initiation of study
6) Formal study protocol review sessions on-going with faculty and staff at the Johns Hopkins Pulmonary Hypertension Program and Johns Hopkins Scleroderma Center to facilitate recruitment
7) Identification of potentially eligible patients from the Johns Hopkins Pulmonary Hypertension Program Registry and from the Johns Hopkins Scleroderma Center Registry to allow for focused recruitment
8) Transition of Principal Investigator at the Louisiana State University Health Sciences Center from Dr. Matthew Lammi to Dr. Amita Krishnan
9) Updating all necessary sub-contracts
10) We have submitted a methods manuscript to *BMC Pulmonary* describing the study rationale and design. This manuscript has been revised and is currently under second review at the journal.

There are no significant training or professional development accomplishments to report.

There are no results to disseminate to communities of interest.

During the next reporting period, we will continue patient recruitment and enrollment.

4. IMPACT

The impact of our accomplishments to date demonstrate the feasibility of our protocol, acceptability of the protocol to subjects in the study, and highlight our collaborative efforts with the LSUHSC site.

We have enrolled 4 patients and have 1 pending enrollment, so we cannot comment on the impact of our study on patients with scleroderma and early pulmonary vascular disease. However, to date, there remain no planned or on-going studies of therapies for treatment of scleroderma patients with early pulmonary vascular disease listed on https://clinicaltrials.gov . Thus, the SEPVADIS study remains highly relevant by focusing on a high-risk condition that currently does not have any approved treatment options.

There is nothing to report regarding the impact on development of the principal discipline of the project.

There is nothing to report regarding the impact on other disciplines.

There is nothing to report on the impact on technology transfer.

There is nothing to report on the impact on society beyond science and technology.

5. CHANGES/PROBLEMS

As referenced in Section 2, there have been numerous challenges to initiation of the SEPVADIS study, mostly related to the global COVID pandemic. These have improved to some degree, but there remain ongoing limitations to recruitment and execution of the study protocol.

1) Availability of certain research procedures such as cardiac magnetic resonance imaging and echocardiography remains reduced by 25% due to institution of necessary infection control policies that mandated extensive cleaning of equipment and study space between use. This continues to impact study workflow, increasing the duration of the study visit and potentially requiring additional study visits to complete the necessary testing.
2) About 25% of the patient encounters for the Johns Hopkins Pulmonary Hypertension Program and more than 50% of the patient encounters for the Johns Hopkins Scleroderma Center continue to be conducted via telemedicine visits. Many patients continue to decline in-person visits for concerns of exposure to COVID in the hospital. As such, recruitment for active clinical trials fell by 50% during 2020-2021 and 30% in 2022 at Johns Hopkins University School of Medicine. Updated data for 2023 are not yet available.

3) Dr. Lammi has recently accepted a faculty position at Johns Hopkins University. He will transfer his Co-Principal Investigator position at LSU to Dr. Amita Krishnan. This transfer is in process with expected completion in the upcoming weeks. Dr. Lammi retains an adjunct appointment at LSU and will serve as a co-Investigator to provide oversight during the transition and to serve as a resource for Dr. Krishnan.

Importantly, more than 80% of patient clinical visits are in-person and procedures integral to the successful completion of this study have resumed to 50-75% capacity (accounting for the safety measures referenced above). There have not been any changes with significant impact on expenditures, in use or care of human subjects, vertebrate animals, biohazards, and/or select agents, in use or care of human subjects (except as outlined above), or in use of biohazards and/or select agents.

6. PRODUCTS

There is nothing to report.

7. PARTICIPANTS AND OTHER ORGANIZATIONS

Name:	Stephen C. Mathai
Project Role:	Principal Investigator
Researcher ID:	NA
Nearest person-month worked:	2.5
Contribution to Project:	Dr. Mathai has overseen all aspects of the study to date, including IRB application, CRF development, MOP development, Database creation, finalization of subawards, and budget oversight.
Funding support:	None for this work

Name:	Kyle Carey
Project Role:	Study Manager/Research Coordinator
Researcher ID:	NA
Nearest person-month worked:	12
Contribution to Project:	Mr. Carey has prepared and submitted all necessary regulatory documents, including the IRB application. He has coordinated the research operations with individual service centers (Pulmonary function lab, cardiac MRI, echocardiography lab, etc). He has coordinated the RedCap database maintenance with our statistical core. He has also coordinated with his LSU counterpart, Marie Sands, to ensure uniformity in these

	processes across sites.
Funding support:	None for this work

Name:	Anil Shah
Project Role:	Co-Investigator
Researcher ID:	NA
Nearest person-month worked:	0.6
Contribution to Project:	Dr. Shah has set up the biorepository core and developed processes to collect, process, and store all biosamples obtained as part of the study protocol.
Funding support:	None for this work

Name:	Paul Hassoun
Project Role:	Co-investigator
Researcher ID:	NA
Nearest person-month worked:	0.2
Contribution to Project:	Dr. Hassoun has collaborated with the PIs to develop plans for identification of patients to enhance recruitment. His ongoing research projects outside this award serve as referral bases for this study.
Funding support:	None for this work

Name:	Laura Hummers
Project Role:	Co-Investigator
Researcher ID:	NA
Nearest person-month worked:	0.2
Contribution to Project:	Dr. Hummers has worked with Dr. Shah to coordinate recruitment strategies, to organize collection and storage of biosamples, and to provide logistical support.
Funding support:	None for this work

Name:	Monica Mukherjee
Project Role:	Co-Investigator
Researcher ID:	NA
Nearest person-month worked:	0.3
Contribution to Project:	Dr. Mukherjee has facilitated and organized the workflow for research echocardiography for this study and has developed an image repository for the study.
Funding support:	None for this work

Name:	Stefan Zimmerman
Project Role:	Co-Investigator
Researcher ID:	NA
Nearest person-month worked:	0.3

Contribution to Project:	Dr. Zimmerman has facilitated and organized the workflow for research cardiac MRI and has developed an image repository for the study.
Funding support:	None for this work

Partner Organizations:

Organization Name: Louisiana State University Health Sciences Center

Location of Organization: New Orleans, LA

Partner's Contribution to project: Study Site for clinical trial, scientific collaboration

Name:	Matthew Lammi
Project Role:	Co-Principal Investigator
Researcher ID:	NA
Nearest person-month worked:	2.5
Contribution to Project:	Dr. Lammi has overseen all aspects of the study to date at the Louisiana State University site, including IRB application, finalization of subawards, and identification of local compounding pharmacy. He has recruited and enrolled one subject and has one pending enrollment.
Funding support:	None for this work

Special Reporting Requirements

Appendices