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CONTRACTING ORGANIZATION: Johns Hopkins University School of Medicine

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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.					
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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) Submission of Institutional Review Board Application (Johns Hopkins Medicine eIRB study number: IRB00265164)
 - a. Initial review and resubmission of application; approval date: 3/30/21
- 2) Human Research Protections Office approval of study: 9/15/21
- 3) Finalization of manual of procedures and case report forms
- 4) Completion of relational database for multicenter application using the RedCap system
- 5) Confirmation of study drug and placebo production and disbursement by the Johns Hopkins Investigational Drug Service for the Johns Hopkins study site and by the Pennington Research Pharmacy for the Louisiana State University Health Sciences Center study site
- 6) Establishment of the Data Safety and Monitoring Board and membership with experts in clinical trials and management of cardiopulmonary disease in scleroderma.
- 7) Establishment of 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
- 8) Engagement of clinical trials consultant to assist with addressing challenges of initiation and conduct of clinical trials during the COVID pandemic
- 9) 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
- 10) Identification of potentially eligible patients from the Johns Hopkins Pulmonary Hypertension Program Registry to allow for focused recruitment upon anticipated IRB approval

- 11) Mock patient run-through for Johns Hopkins site in August 2021
- 12) Establishment and finalization of all necessary sub-contracts
- 13) Screening of potential candidates and identification of first potential subject.

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 begin enrollment for this study as we have just received approval of the study from HRPO on 9/15/21.

4. IMPACT

The impact of our accomplishments to date will facilitate rapid initiation of the trial upon IRB and HRPO approval. We have completed all tasks necessary to ensure seamless initiation of study procedures, as detailed in Section 3.

As we have not enrolled any subjects to date, 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.

- 1) Non-critical clinical research activities at both Johns Hopkins University and Louisiana State University Health Sciences Center were paused for several months until November 2020.
- 2) The acute need for clinical trials addressing the COVID pandemic required the Johns Hopkins Medicine Institutional Review Board to focus on review of clinical trials in this area. This led to delays in timely review of new applications that were not focused on COVID-related research.
- 3) Requirements at Johns Hopkins University School of Medicine mandated that procedures with a high-risk of aerosolization be restricted. The six-minute walk test was determined to be a high-risk procedure and therefore was restricted. This procedure is the primary outcome measure for the SEPVADIS study.
- 4) As a restricted procedure, performance of the six-minute walk test (6MWT) required a negative COVID test for participants prior to conducting the test. Availability of COVID testing in the fall of 2020 and winter of 2021 was limited and often took several days to result, creating challenges with the proscribed requirements of the Pulmonary Function Laboratory (whose technicians conduct the 6MWT) recommendation for a negative COVID test within 72 hours of the 6MWT. This recommendation has recently been relaxed to requiring a negative COVID result 5 days prior to conduct of the 6MWT.
- 5) Availability of certain research procedures such as cardiac magnetic resonance imaging and echocardiography was reduced by 50% due to institution of necessary infection control policies that mandated extensive cleaning of equipment and study space between use. This impacted the workflow proposed for the study, increasing the duration of the study visit and potentially requiring additional study visits to complete the necessary testing. These restrictions have been relaxed in the past 3 months and capacity has returned to 75% of pre-pandemic levels.
- 6) More than 50% of the patient encounters for the Johns Hopkins Pulmonary Hypertension Program and more than 75% of the patient encounters for the Johns Hopkins Scleroderma Center were conducted via telemedicine visits. Many patients declined in-person visits for concerns of exposure to COVID in the hospital. As such, recruitment for active clinical trials fell by 50% during 2020 at Johns Hopkins University School of Medicine. With reduction in the number of COVID cases locally and high vaccination rates amongst our target population, in-person encounters have returned to 80% of pre-pandemic levels in the past 3 months. We anticipate a return to pre-pandemic levels by the end of the calendar year.
- 7) The Johns Hopkins Investigational Drug Service (JH IDS) policy regarding shipping study medication out-of-state was revised since our initial application for the award. As such, the JH IDS was not permitted to ship study drug and matching placebo to the Louisiana State University Health Sciences Center study site. Dr. Lammi

identified and set up a contract with Pennington Research Pharmacy, a local compounding pharmacy in

Louisiana, who will provide study drug and matching placebo.

Importantly, in the most recent quarter, these issues have largely been resolved as clinical and research practices have resumed, albeit with ongoing surveillance and safety measures to minimize the risk of COVID exposure and spread.

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:	Dezeray Cephas-Dutton
Project Role:	Study Manager/Research Coordinator
Researcher ID:	NA
Nearest person-month worked:	12
Contribution to Project:	Ms. Cephas-Dutton has prepared and submitted all necessary regulatory documents, including the IRB application. She has coordinated the research operations with individual service centers (Pulmonary function lab, cardiac MRI, echocardiography lab, etc). She has developed the CRFs and MOP, and has coordinated the RedCap database development with our statistical core. She has also coordinated with her LSU counterpart, Marie Sands, to ensure uniformity in these processes across sites.
Funding support:	None for this work

Name:	Ami 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.
Funding support:	None for this work

Special Reporting Requirements

Appendices