HRP-591 - Protocol for Human Subject Research

Protocol Title: STUDY00009606: Standing Cognition and Co-morbidities of POTS Evaluation (SCOPE)

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Version Date: 4/24/19

Clinicaltrials.gov Registration #: in progress

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3. **Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.**
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5. When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the Study Submission Guide available in the Help Center in CATS IRB (http://irb.psu.edu) for using track changes.

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1.0 Objectives

1.1 Study Objectives

The overall goal of this study is to investigate the impact of orthostatic stress on cognitive function in postural tachycardia syndrome (POTS), and to assess the prevalence of Hypermobile Ehlers-Danlos Syndrome (hEDS) and Hypermobility spectrum disorders (HSD) in patients with POTS. **This study will be performed in a large cohort (100 POTS patients) at the Dysautonomia International Conference in Nashville, TN June 22-24, 2018**. Healthy control subjects will be enrolled at Penn State Hershey Medical Center. The central hypothesis is that active standing in POTS worsens cognitive function and related to joint hypermobility. We will test this hypothesis in the following two specific aims:

Aim 1: Determine impact of orthostatic stress on cognition in POTS. Hypothesis 1: Active standing in POTS worsens cognitive function. Cognitive function will be assessed in the supine and standing postures using a short battery of cognitive tests. These tests examine aspects of cognition known to be impaired in POTS patients including executive function (Stroop word color test), attention (CogState Identification test), and working memory (CogState two-back test). Aim 1 will be performed in POTS patients and in healthy subjects.

Aim 2: Determine the prevalence hEDS and HSD in POTS**.** We will assess patients for hEDS and HSD using a questionnaire and physical exam based on the new guidelines. Aim 2 will only be performed in POTS patients.

1.2 Primary Study Endpoints

Our primary endpoints are the scores on the cognitive tests and the Beighton score.

1.3 Secondary Study Endpoints

Our secondary study endpoints are questionnaire answers and blood pressure and heart rate during standing.

2.0 Background

2.1 Scientific Background and Gaps

2.2 Previous Data

POTS is a form of chronic orthostatic intolerance that produces daily symptoms such as fatigue, lightheadedness, palpitations, dyspnea, and nausea. POTS is defined by the presence of these symptoms along with an increase in heart rate of at least 30 beats/minute in adults within 10 minutes of standing.[1] It is estimated that 1 to 3 million Americans have POTS and it predominantly effects women of childbearing age.

Cognition in POTS

Cognitive impairment or "brain fog" is experienced by almost all POTS patients and affects daily life including school and work performance.[2] While most symptoms of POTS have an onset with orthostasis, it is unclear whether "brain fog" is posturally related. In my previous study, over 95% of POTS patients reported cognitive impairment, with many experiencing symptoms on a daily basis and even while supine.[2] However, there is limited objective data to support this claim, with few studies evaluating cognitive function in POTS. To date, only five studies have objectively measured cognition in POTS.[3-7] Working memory is the only cognitive domain that has been evaluated in the supine posture in POTS, and these studies found no impairments in working memory in POTS patients while supine.[4, 5, 7] Multiple domains of cognitive function have been evaluated in POTS patients while seated and during head-up tilt (HUT). While seated, one study showed that POTS patients have clinically meaningful impairment in selective attention, cognitive processing speed, and executive function with no differences in psychomotor speed, memory function, or verbal fluency compared to age-matched healthy participants.[3] During graded HUT, studies have demonstrated impaired attention, processing, and working memory in POTS patients compared to healthy participants.[4-7] Therefore, evidence suggests that POTS patients

have impaired cognition even while seated, when tachycardia and orthostatic symptoms are minimized, perhaps indicating that this phenomenon is not solely related to posture. However, no studies have evaluated cognitive function in POTS during active standing. There are marked physiological differences between active standing and passive HUT. For example, during active standing the body engages the skeletal muscle pump to improve venous return to the heart. Furthermore, passive HUT can elicit exaggerated hemodynamic responses and vasovagal episodes even in health participants with no prior experience of clinical faints (false positives). Since active standing is more physiologically relevant in terms of daily life, it is critical to better understand how standing impacts cognitive function in POTS.

Joint Hypermobility in POTS

The high prevalence of hEDS in POTS was first recognized by Dr. Peter Rowe, et al. in 1999.[8] He found that about 60% of patients with chronic fatigue syndrome and orthostatic intolerance had joint hypermobility but this study was only conducted in 12 subjects. One small study found that 29% of pediatric POTS patients have joint hypermobility.[9] Larger, questionnaire based studies have estimated that 30-40% of POTS patients have been diagnosed with EDS.[10] But because there are very few geneticists that specialize in EDS and most physicians who evaluate POTS patients do not evaluate for EDS. The true prevalence of hEDS in POTS has not been evaluated. Furthermore, HSD is a new diagnosis defined in 2017, and no study to date has attempted to determine the rate of HSD in POTS.

2.3 Study Rationale

POTS patients have impaired cognitive function that impacts their daily life including school and work performance. [2] hEDS and HSD contribute to functional disability and pain in POTS but are often undiagnosed because the prevalence is unknown and most POTS patients are not evaluated. The current study will determine the impact of standing on cognitive function in POTS and investigate the prevalence of hEDS and HSD in POTS. The findings from this study will provide the foundation to explore mechanisms of cognitive function in POTS and improve physician awareness of the importance of evaluating EDS in POTS patients. We will perform this study at the 2018 Dysautonomia Patient Conference in Nashville, TN June 22-24, 2018. Performing this study at the conference will provide a convenience sample in which we can examine cognitive function and hEDS and HSD prevalence in a larger and more diverse cohort of POTS participants than could be accomplished at our institution. The mechanisms underlying cognitive dysfunction in POTS will be investigated more thoroughly at our institution under a separate IRB protocol (study STUDY00009333: Cognition in Postural Tachycardia Syndrome-submission in progress).

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

- Postural Tachycardia Syndrome or healthy control
    - Previously diagnosed with POTS
- Age between 13-60 years
- Participants may be any race, ethnicity, sex, or gender
- Able and willing to provide informed consent

3.2 Exclusion Criteria

- Inability to give, or withdrawal of, informed consent
- Age ≤ 13 or ≥ 61 years
- Prisoners
- Unable to stand
- Healthy controls must be free of chronic and systemic illness and not have a history of recurrent syncope

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

The subject may withdraw from the study at any time for any reason.

3.3.2 Follow-up for withdrawn subjects

No follow-up is required.

4.0 Recruitment Methods

We will conduct this study at the 2018 Dysautonomia International Patient conference if our proposal is selected for the conference by Dysautonomia International's Board of Directors. Healthy control subjects will be recruited using Penn State study finder and a paper flyer.

4.1 Identification of subjects

- POTS patients will be recruited from attendees at the 2018 Dysautonomia International Patient Conference in Nashville, TN June 22-24, 2018. Announcements calling for participation will be made during the conference.
- Healthy control subjects will be recruited using Penn State Study Finder and a paper flyer.

4.2 Recruitment process

We will perform this study at the 2018 Dysautonomia Patient Conference in Nashville, TN. Interested participants will report to the study room. Study personal will obtain informed consent in all subjects. We will contact eligible healthy subjects through email when they respond to STUDYfinder or the paper flyer.

4.3 Recruitment materials

Paper flyer

4.4 Eligibility/screening of subjects

The study team will go over the inclusion and exclusion criteria with subjects prior to consent.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Interested participants will report to the study room at the conference or at Penn State Hershey Medical Center CRC. They will be asked the screening questions. If eligible, study personal will obtain informed consent in all subjects. All subjects will be given sufficient time to read the consent, all procedures will be explain in layman's terms and they will be given a copy of the signed consent form.

5.1.1.2 Coercion or Undue Influence during Consent

The subject will be provided with ample opportunity to have questions answered before participating in the study. All procedures will be explained to them in layman's terms and they will be given a copy of their signed consent form. Subjects will have the right to withdraw for the study at any time.

5.1.2 Waiver or alteration of the informed consent requirement

Not applicable

5.2 Consent Documentation

5.2.1 Written Documentation of Consent
Subjects will sign the IRB-approved consent form.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)
Not applicable

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects
Not applicable

5.3.2 Cognitively Impaired Adults
Not applicable

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission
Parents will sign the IRB-approved consent form.

5.3.3.2 Assent of subjects who are not yet adults
All subjects age 13-17 will sign the IRB-approved assent form.

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☐ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI
Not Applicable

6.3 Waiver or alteration of authorization statements of agreement
Not Applicable

7.0 Study Design and Procedures

7.1 Study Design

For Aim 1, this study will utilize a repeated measures design in which test scores and physiological parameters will be measured at 2 different postures (supine, standing). For Aim 2, questionnaire and exam data will be reported as percentages.

7.2 Study Procedures

Step 1- Questionnaires (15 mins)

Subjects will answer questions about their POTS diagnosis, co-morbid conditions (including hEDS), and current medications, and family history. Participants will also complete standardized questionnaires including the Orthostatic grading scale, Compass 31, RAND-36, and Fatigue-VAS. All questions will be answered on tablets and data will be entered directly into REDCap. Participants will have the option to complete the questionnaires during the study visit on a tablet or after their study visit by providing their email address. A link to the questionnaires in REDCap will be emailed to participants to complete after the study visit.

Step 3- Orthostatic Cognitive Testing (30 minutes)

Subjects will lie down on a bed for 5 minutes. Their blood pressure will be taken in triplicate while supine. Half the subjects will perform cognitive tests (stroop word color test and identification test) before standing up. The testing will take 6 minutes (3 minutes each) and the order of the tests will be randomized. Subjects will then stand up. Blood pressure and heart rate will be taken using a brachial artery oscillometric cuff every 2 minutes. While standing, the blood pressure cuff will inflate at minutes 1, 3, 5, 7, and 9 since it takes approximately 1 minute to get the recording. After 4 minutes standing, subjects will perform cognitive tests again while standing. Subjects will remain standing for up to 10 minutes. Subjects may choose to sit down and stand again to complete testing or choose to end testing at anytime. Subjects will then lie supine for 5 minutes to recover. Half of the subjects will perform cognitive testing following recovery.

The Stroop word color test is a paper-based test and correct answers recorded by a member of the research team. This test takes approximately 3 minutes to complete. The Stroop word color test evaluates executive function. Participants will be asked to name the color of ink a word is printed in, when the word itself is a different color name.[11] For example, subjects will be shown card with a word like "yellow" but will need to say "green" not "yellow" to answer correctly. This is difficult since we read faster than we can recognize color. This is primarily an assessment of concentration ability, but also involves executive function. In a previous study by Arnold, et al. the stroop word color test was most impaired in POTS while seated (cite the prior study). However, cognitive dysfunction in POTS linked to posture is poorly understood. It is important to assess cognitive function supine and during active standing in a large sample of POTS patients. The Identification test evaluates attention based on reaction time to correct responses to "yes or no" questions. In this study, participants will be asked "is this card red?" and then will be shown a random playing card on the tablet and press the "yes" or "no" button as quickly as possible. This test will be performed using Cogstate software on a tablet and takes approximately 3 minutes to complete.

Step 4- EDS evaluation (20 mins)

Subjects will be evaluated for hypermobile EDS (hEDS) and hypermobility spectrum disorders (HSD) by Dr. Clair Francomano or a colleague trained to diagnose EDS using a standardized form.

7.3 Duration of Participation

Study participation will take approximately 1 hour per subject. Subjects may opt to complete questionnaires up to 1 month after their study visit. Only POTS patients will complete questionnaires.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

We will enroll up to 100 participants with Postural Tachycardia Syndrome and 50 healthy controls for this study. Subjects will participate in both aims.

8.2 Sample size determination

We propose to enroll up to 100 POTS patients and 50 healthy controls. We expect that this convenience sample, based on meeting attendance and recruitment feasibility, will allow for sufficient data on the prevalence of hEDS and HSD in POTS and whether cognition is affected by orthostasis in this patient population.

8.3 Statistical methods

We will compare cognitive testing results by position using Wilcoxon signed-rank tests. Results will be compared between groups (POTS, controls) using Mann-Whitney U test.

9.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form.

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

Safety is constantly monitored during a study because our studies involve continuous monitoring of physiological variables. The PI immediately reviews any concerns. Adverse events are not anticipated, but any occurring will be documented and reported according to HSPO policies and procedures. The PI will be solely responsible for data collection and verification, and review of cumulative adverse events.

10.2 Data that are reviewed

Physiological variables will be reviewed continuously during the study for safety purposes. Any concerns will immediately be brought to the attention of the PI.

10.3 Method of collection of safety information

Physiologic variables and general well being of the subject will be monitored continuously during study visits and reported on paper worksheets.

10.4 Frequency of data collection

Data collection will start on the first study visit and continue until the subject leaves the study. Safety will be continuously monitored.

10.5 Individuals reviewing the data

The PI and research team will review data in real-time throughout the study. A data safety monitor will also provide an objective review of treatment results as they relate to subject safety and data quality. The data safety monitor for this study will be Dr. Urs Leuenberger. Dr. Leuenberger has over 30 years of clinical research experience in various patient populations and the methods in this protocol, and does not have any significant conflict of interest with the PI or the study.

10.6 Frequency of review of cumulative data

Safety is constantly monitored during the studies and any concerns are brought to the attention of the PI immediately. The PI will analyze subject data within one week of the experimental visit. Adverse events will be documented and reported appropriately according to HSPO policies and procedures.

The data safety monitor will meet every 6 months with the PI, or more often if needed. In preparation for these meetings, the PI will provide information by email regarding enrollment, protocol adherence, and data quality. The data safety monitor will also assess safety data including common and serious adverse events. In the case of an unanticipated or serious adverse event, the data safety monitor will be notified within 24 hours of the PI's notification of the event. The PI will provide the data safety monitor with a list of non-serious adverse events during regularly scheduled meetings.

10.7 Statistical tests

Any occurrences will be evaluated immediately on a case-by-case basis.

10.8 Suspension of research

If a serious adverse event occurred, we would assess the need to suspend the research with the data safety monitor.

11.0 Risks

Confidentiality: There is a risk of loss of confidentiality if medical information or identity are obtained by someone other than the investigators, but precautions will be taken to prevent this from happening.

Blood Pressure and Heart Rate Measurement: Frequent blood pressure measurements with the cuff around the arm may be inconvenient and may produce some discomfort and occasional bruising of the upper arm.

Questionnaires: No risk

Physical Exam: No risk

Cognitive Tests: No risk

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

There will be no direct benefit to subjects in this study.

12.2 Potential Benefits to Others

This study may provide new insight for research scientists on cognitive function and the prevalence of hEDS and HSD in POTS.

13.0 Sharing Results with Subjects

Subjects with POTS will receive a copy of their hEDS evaluation form to discuss with their physician.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Subjects will receive a $20 giftcard for participation in the study.

15.0 Economic Burden to Subjects

15.1 Costs

There is no cost to the subject for taking part in this study.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

Studies will be conducted at the 2018 Dysautonomia International Patient Conference. Subjects will be recruited from participants at the 2018 Dysautonomia International Patient Conference. Studies at Penn State Hershey Medical Center will occur in the General Clinical Research Center.

16.2 Feasibility of recruiting the required number of subjects

The Dysautonomia International Patient conference has 500 attendees which are mostly POTS patients and caregivers. In past years, over 100 participants have volunteered for the research study conducted at the conference. We expect to recruit and approximately 100 POTS patients at the conference. We expect to recruit 5-10 healthy subjects per month.

16.3 PI Time devoted to conducting the research

The PI will devote 10% effort to this project.

16.4 Availability of medical or psychological resources

Physicians will be present during the study if any concerns arise.

16.5 Process for informing Study Team

All members of the study team have access to approved documentation for this study. The PI will review the protocol with all members of the study team and will communicate with them regularly in person and through email. The PI is responsible for direct communication related to any changes in the protocol and the individual duties of each study member.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Not applicable

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☒ Clinical Research Center (CRC) Advisory Committee – All campuses – Research involves the use of CRC services in any way.

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☐ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

17.0 Multi-Site Research

Not applicable.

19.0 Adverse Event Reporting

19.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

21.0 Future Undetermined Research: Data and Specimen Banking

Not Applicable

22.0 References

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