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14. ABSTRACT The goal of this 24-month proposal is to establish the critical infrastructure for the initiation of a five year prospective follow-up study to identify those at risk for developing PD or a related Lewy body disorder in three study populations. The ultimate goal of this work is to develop low-cost non-invasive screening methods to detect pre-motor Parkinson's disease (PD) that can be implemented population-wide. Our hypothesis is that cardiac autonomic dysfunction assessed as heart rate variability (HRV) using a standard EKG, in combination with hyposmia and other simple screening tests, will be highly predictive of abnormalities in DAT imaging and ultimately predict the emergence of full-blown PD or a related Lewy body disorder.					
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INTRODUCTION

This work addresses the next frontier in Parkinson's disease (PD) research: developing new tools to diagnose PD in its earliest stages, well before motor symptoms manifest. Currently, PD is diagnosed only when classic motor features present, when 60-80% of striatal dopamine is already depleted. Clinical trials with neuroprotective agents are much more likely to succeed if carried out before the major portion of the damage has already been incurred. However, these transformative goals will be clinically useful for screening the general population only if non-invasive tools can be easily administered in the primary care physician's office. Our hypothesis is that cardiac autonomic dysfunction assessed as heart rate variability (HRV) using a standard EKG, in combination with hyposmia and other simple screening tests, will be highly predictive of abnormalities in dopamine transporter (DAT) imaging and ultimately predict the emergence of full-blown PD or a related Lewy body disorder. The ability to identify individuals with pre-motor PD could have enormous public health consequences, particularly once an effective disease-modifying therapy is identified. Our goal is to develop a battery of tools to identify pre-motor PD that can be administered with relative ease and low cost, such that it can be incorporated into a routine annual physical examination, beginning when individuals reach an age where they are at increased risk for PD.

BODY

This 24-month proposal will establish the critical infrastructure for the initiation of a five year prospective follow-up study to identify those at risk for developing PD or a related Lewy body disorder in three study populations. The current proposal has four objectives: 1) to develop the required internal and collaborative infrastructure to establish a large cohort with idiopathic REM behavior disorder and test a comprehensive clinical assessment protocol for pre-motor PD, 2) to establish a protocol for collecting digital EKGs from collaborating studies, 3) to initiate data collection in each study population, and 4) to conduct preliminary analyses of EKG data for HRV. On January 28, 2012 we requested a 12-month extension of the Period of Performance to support completion of the above award. We requested this extension in order to complete the statement of work. Regulatory approval of the project has been extremely complicated, requiring review and coordination between the regulatory agency of the Parkinson's Institute and the USAMRMC HRPO. Final regulatory approval was not obtained until June 1, 2012. The approval delays prevented initiation of the actual human contact work and receipt of data from collaborating institutions for a prolonged time. After HRPO approval was received, enrollment and data acquisition have proceeded as anticipated. The extension was approved on January 31, 2013 (revised period of performance is April 30, 2014 (research ending March 31, 2014). With approval of the extension, we expect to accomplish the funded work as originally described. There have been no modifications to the statement of work as originally awarded.

As of 31 March, 2013, we have established collaborative relationships with San Francisco Bay Area sleep medicine clinics and neurologists in order to recruit study subjects. After pre-IRB review by the Regulatory Compliance Specialist, all study documents were approved by our local IRB, and forwarded to USAMRMC ORP HRPO for final review. We received approval from USAMRMC ORB HRPO on June 1, 2012. Databases and operations procedures have been developed, and receipt of data from collaborating institutions has commenced.

KEY RESEARCH ACCOMPLISHMENTS AS OF 31 MARCH, 2013

1. Assemble an iRBD Cohort: Identify eligible iRBD patients and controls; establish collaborative relationships with all San Francisco Bay Area sleep medicine clinics; develop physician outreach methods and materials; develop community outreach methods and materials; develop RBD screening methods to identify likely cases.
 - *Cohort recruitment is ongoing*
 - *We have, and continue to actively establish collaborative relationships with San Francisco Bay Area sleep medicine clinics*
 - *Physician outreach materials have been developed. Materials continue to be distributed to sleep clinics and neurologists in the region*
 - *Subject recruitment materials have been developed and IRB approved, and continue to be distributed*
 - *Direct outreach recruitment methods are being implemented*
2. Standardize application of diagnostic criteria for iRBD. Develop methods for rescoring polysomnographic (PSG) data and applying diagnostic criteria (funding months 12-18)
 - *Methods for application of iRBD diagnostic criteria are in development. As specified in the study protocol, some subjects with possible iRBD will undergo de novo PSGs.*
3. Develop a secure database to track subject recruitment and enrollment efforts
 - *A secure relational database has been developed and continues to be populated*
4. Prepare and submit study documents for institutional review board (IRB) approval
 - *Preliminary study documents were submitted to Ms. Brigit Ciccarello, Regulatory Compliance Specialist, on August 4, 2011 for IRB pre-review feedback. Ms. Ciccarello provided detailed comments by email on August 22, 2011. Documents were revised in response to her recommendations, and were sent for her review November 21, 2011. After several iterations, Ms. Ciccarello notified us December 7, 2011 that we could move forward with submission to our local IRB. The study protocol and flowchart, consent forms, recruitment materials, screening and diagnostic questionnaires, data collection forms, and clinical and risk factor questionnaires were submitted to the El Camino Hospital IRB, Mountain View, CA in January, 2012, and*

approved on February 1, 2012. The approved documents were submitted to Ms. Ciccarello on February 16, 2012. Ms. Ciccarello submitted the approved documents to the USAMRMC ORP HRPO on March 5, 2012. We received approval from USAMRMC ORP HRPO on June 1, 2012. Continuing reviewing documents were submitted to the El Camino Hospital IRB in December 2012. These were reviewed and approved by the El Camino Hospital IRB at their meeting on December 21, 2012 and we received the new approval letter from the El Camino Hospital IRB on January 14, 2013. The study expiration date is December 21, 2013. The continuing renewal report as well as the approval from the El Camino Hospital IRB were sent to Ms. Monique Hawkins at USAMRMC ORP HRPO on February 11, 2013. On March 22, 2013 we were made aware there documents had not been received by USAMRMC ORB HRPO. On March 25, 2013 we sent the continuing review report, new approval letter from the El Camino IRB, current protocol and current consent forms to Ms. Kirdnual at USAMRMC ORP HRPO. There were no modifications to the protocol or consent forms since these documents were last submitted to HRPO.

5. Develop the clinical assessment protocol: Develop standardized clinical data collection protocols; create scannable data collection forms for all clinical instruments; develop blood processing and storage protocols; pilot test clinical data-collection methods

Protocol revisions suggested by Ms. Ciccarello were implemented, reviewed and approved by El Camino Hospital IRB, and resubmitted to Ms. Ciccarello for forwarding to USAMRMC ORP HRPO. All protocol revisions were approved by USAMRMC ORP HRPO on June 1, 2012.

- *Standardized clinical data collection protocols have been developed*
- *Scannable data collection forms have been created*
- *Blood processing and storage protocols have been developed*
- *Piloting of clinical-data collection methods has been conducted*

6. Establish digital EKG collection in the APDC cohort: work with APDC staff to establish a protocol for collection of digital EKG and transfer of data to the Parkinson's Institute

APDC has acquired EKG recording equipment through an independent funding source and has implemented EKG recordings as part of their comprehensive annual clinical assessment under the APDC study protocol.

- *APDC research staff have been trained to collect data using the standardized EKG data collection protocol developed for this project.*
- *A subcontract agreement and statement of work has been executed between Mayo Clinic Arizona and the Parkinson's Institute*
- *A subcontract agreement and statement of work between Banner Health and Parkinson's Institute has been executed.*

7. Establish a study steering committee: Study steering committee members have been identified. The steering committee meeting is being planned.

8. Implement data collection in each study population: Begin enrolling and characterizing iRBD subjects; PARS and APDC baseline digital EKG data will be collected at regular follow-up assessments and transferred to the Parkinson's Institute at regular intervals using secure protocols
USAMRC ORP HRPO approval has been received to establish an iRBD cohort, and to receive de-identified data from PARS and APDC.
- *iRBD cohort enrollment has commenced. Clinical evaluations and DaTSCAN imaging are ongoing*
 - *EKG data transfers from PARS have commenced*
 - *EKG data transfers from APDC have commenced*
 - *Quality control measures to ensure consistently high quality data are ongoing*
9. Data analysis: Analysis of digital EKG data for 15 HRV parameters; descriptive analyses for each cohort, and preliminary explorations of associations between HRV, hypsomia and other putative pre-motor features
- *HRV analyses of EKGs obtained from PARS are ongoing*
 - *HRV analyses of EKGs obtained from APDC are ongoing*
 - *HRV analyses of EKGs obtained from the iRBD cohort are ongoing*

REPORTABLE OUTCOMES

None at this time.

CONCLUSIONS

Substantial progress has been made. Important next steps for the project include the following:

- *continue to ascertain, enroll and clinically evaluate iRBD cohort members*
- *ongoing receipt and analysis of de-identified data from PARS*
- *ongoing receipt and analysis of de-identified data from APDC*
- *convene a study steering committee meeting*
- *ongoing data entry and quality assurance processes*
- *develop and implement an analytic plan*

REFERENCES

None

APPENDICES

None