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TITLE: Validating Diagnostic and Screening Procedures for Pre-Motor Parkinson's Disease

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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. As of 31 March, 2012, 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 have been approved by our local IRB, and forwarded to USAMRMC ORP HRPO for final review. These include the study protocol and flowchart, consent forms, recruitment materials, screening and diagnostic questionnaires, data collection forms, and clinical and risk factor questionnaires. Databases and operations procedures are in development, and receipt of data from collaborating institutions will commence upon receipt of HRPO approval.

15. SUBJECT TERMS
Pre-motor; Parkinson's Disease; Lewy Body Disease; REM Behavior Disorder (RBD); Cardiac dysautonomia; Electrocardiogram; Heart Rate Variability (HRV); Diagnostic Screening

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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. As of 31 March, 2012, 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 have been approved by our local IRB, and forwarded to USAMRMC ORP HRPO for final review. These include the study protocol and flowchart, consent forms, recruitment materials, screening and diagnostic questionnaires, data collection forms, and clinical and risk factor questionnaires. Databases and operations procedures are in development, and receipt of data from collaborating institutions will commence upon receipt of HRPO approval.

KEY RESEARCH ACCOMPLISHMENTS AS OF 31 MARCH, 2012

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.

- *We continue to actively establish collaborative relationships with San Francisco Bay Area sleep medicine clinics.*
- *In addition to formal sleep clinics, we are continuing to survey neurologists in the region in order to identify additional physicians who may potentially treat patients with iRBD in their practices.*
- *Subject recruitment materials have been developed. They were approved by the El Camino Hospital IRB on February 1, 2012. They were submitted to USAMRC ORP HRPO on March 5, 2012.*

2. Develop a secure database to track subject recruitment and enrollment efforts
    - *A secure relational database is in development.*

3. 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.*

4. 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
    - *Data collection protocols, forms, and an operations manual are in development.*
    - *Clinical databases are in development.*

5. <u>Establish digital EKG collection in the APDC cohort:</u> 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 plans to implement EKG recordings as part of their comprehensive annual clinical assessment under the APDC study protocol. Transfer of de-identified EKG data to the Parkinson's Institute will commence upon IRB approval.*

6. Establish a study steering committee: *A steering committee meeting will be planned after IRB reviews have been completed.*

7. 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
    - *iRBD subject enrollment is pending final approval by USAMRMC ORP HRPO*
    - *Data transfers from PARS and APDC are pending final approval by USAMRMC ORP HRPO*

8. Data analysis: Analysis of digital EKG data for 15 HRV parameters; descriptive analyses for each cohort, and preliminary explorations of associations between HRV, hyposmia and other putative pre-motor features
    - *Pending data acquisition after approval by USAMRMC ORP HRPO.*

REPORTABLE OUTCOMES

None at this time.

CONCLUSIONS

Substantial progress has been made in laying the foundations for this project. Important next steps for the project include the following:

1. Continue efforts to develop efficient and thorough case ascertainment methods to facilitate rapid cohort enrollment upon IRB approval
2. Ongoing development of relational tracking database
3. Develop operations manual
4. Ongoing development of clinical database
5. Prepare to enroll iRBD cohort study subjects, contingent on USAMRMC ORP Human Research Protections Office approval
6. Prepare to receive de-identified data from collaborating sites (PARS; APDC/BBDP)
7. Establish a study steering committee; precise timing of convening the committee meeting will be dependent on the status of IRB reviews

REFERENCES

None

APPENDICES

None