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14. ABSTRACT

Due to unanticipated delays in obtaining necessary institutional review board (IRB) approvals by several IRB agencies involved, including University of Vermont, Oregon Health & Science University (OHSU), Department of Veteran Affairs, the WCG IRB (single IRB agency approved by the DOD) and, WCG IRB, and the Office of Human Research Oversight (ORHO), the implementation of the data entry module of ORMIS-PD (part of aim 1) in the human subject research for collection of the data as part of aim 2 was delayed until May 2023. Accordingly, the project team filed and was grant a no-cost extension of 1 year from September 1st, 2023, to August 30th, 2024. From June to August 2023, a total of 10 patients have been recruited at both sites with a plan to finish the planned recruitment over the first 9 months of the no-cost extension period

Building on the work done so far in the ORMIS-PD project, the project team applied for and was awarded s $1.2 million award from the DOD's Investigator Initiated Research Award for a project titled "Cognitive Functions Impairment as a Novel Paradigm for Delineating Cognitive Dysfunction in Parkinson's Disease (PD-CFI)".

15. SUBJECT TERMS
Parkinson's disease (PD), informatics, clinical decision support tool, neurotoxin-associated PD

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Table of Contents

	Page
Introduction……..…….…..	**1-2**
Body…….	**3-5**
Key Research Accomplishments…….…….	**6**
Reportable Outcomes……	**7**
Conclusion……	**8**
References……	**9-10**
Appendices……	**11-12**

Introduction

Diagnosis of PD is made in clinic by primary care clinicians, neurologists, and movement disorders specialists based on the presence of key motor features, such as the presence of asymmetric limb bradykinesia with rigidity and/or rest tremor, when accompanied by one or more of the non-motor features. However, such clinical diagnosis has low sensitivity and specificity, especially in primary care and general neurology clinics, where movement disorders expertise may not be readily available, and due to the lack of any Clinical Decision Support (CDS) tool. The latest Movement Disorders Society clinical diagnostic criteria for PD (MDS-PD criteria) attempt to classify patients in two levels of diagnostic certainty, that is, “clinically established” and “clinically probable” PD. Although this classification scheme has high sensitivity and specificity, it is difficult to use for a clinician for an individual patient in clinic, given that it follows a complex algorithm of presence of parkinsonism, absence of nine absolute exclusion criteria, presence of at least 2 out of 4 supportive criteria, and absence of red flags or presence of red flags counterbalanced with supportive criterion. In addition, the clinical heterogeneity of PD is quite remarkable, sometimes referred as “many faces of Parkinson’s disease”, which has been formally recognized to represent distinct subtypes of PD, specifically, “mild-motor-predominant”, “intermediate”, and “diffuse malignant”, linked with varying rates of progression. This heterogeneity of PD diagnosis, clinical phenotypes and progression are directly linked with underlying complexity of PD pathophysiology. For example, although alpha-synuclein (α-Synuclein) protein misfolding and accumulation in the form of Lewy bodies is considered a pathophysiological hallmark of PD, a variety of genes and / or proteins are also implicated in PD, including, Leucine-rich repeat kinase 2 (LRRK2), glucocerebrosidase (GBA), Parkinson juvenile disease protein 2 (PARKIN), PTEN-induced kinase 1 (PINK1), Vacuolar protein sorting-associated protein 35 (VPS35), tau, and beta-amyloid 42 (Aβ42), among others. In terms of biomarkers, several fluid and imaging biomarkers have been associated with PD, including α-Synuclein, tau, phosphorylated-tau, Aβ42 in cerebrospinal and blood, as well as magnetic resonance and nuclear imaging modalities.

An important context of heterogeneity of clinical and pathophysiological differences of PD is in US veterans. Specifically, PD is considered a presumptive condition for service connection for veterans if they served in specific areas for certain duration and is also eligible for service-connection if veterans develop it in exposure to herbicide agents, burn pits and in-service traumatic brain injury (TBI). This is supported by studies showing elevated risk of PD in association with pesticide or traumatic brain injury, which can occur in military service. Furthermore, one study has shown that the clinical features (tremor at rest, rigidity, finger taps, rapid alternating movement and facial expression) and neuroimaging features (18F-FP-CIT PET uptake) are different in PD participants exposed to Agent Orange compared to PD participants without Agent Orange exposure. However, further data on such differences in clinical phenotypes, prognosis and pathophysiology between neurotoxin-associated PD and idiopathic-PD are limited or non-existent.

These complexities in clinical diagnosis, progression, and underlying pathophysiology of PD, including potential differences between neurotoxin-associated PD and idiopathic PD, highlight the *critical need* to develop innovative approaches and novel CDSS for improving diagnosis accuracy and predicting prognosis in clinical care and research. In particular, the development of new knowledge resources such as the Parkinson Progression Marker Initiative (PPMI), together with advances in application of computer technologies in medicine, such as biomedical ontologies and machine learning, make this an opportune time to develop novel data-driven techniques for addressing these unmet needs for PD. PPMI is a unique resource for cohort-based studies of different phenotypes and patterns of clinical progression and biomarkers. However, conventional single hypothesis-driven approach to using the PD database requires

manual processing and significant amount of researcher time, which is inherently limited in its approach and impact. To translate the PPMI database for broader and more meaningful discovery and applicability to individual participants in a personalized manner and on a scalable basis, we need a comprehensive informatics-based approach with machine learning component. There are significant mapping and integration challenges that need to be addressed for integrated analysis of individual participants and the PPMI database. A critical gap in this respect is the lack of a comprehensive domain ontology for movement disorders, which can enable a formal knowledge model for data input, semantic data integration, and support analytical queries for predictive modeling in PD. As preliminary work, we have developed Parkinson and Movement Disorders Ontology (PMDO) for addressing this gap.

As part of the Early Investigator Research Investigator (EIRA) grant, we are developing the Ontology-based, Real-time, Machine learning Informatics System for Parkinson's Disease (ORMIS-PD) tool for automated diagnostic classification and prognostication of an individual PD patient, and then implementing it for testing potential differences in diagnostic and prognostic differences in PD patients between two groups, one group with Agent Orange exposure (neurotoxin PD) and another group without Agent Orange exposure (idiopathic PD), at two sites, namely, UVMMC and Portland Veterans Affairs Medical Center (PVAMC). This will be done by collecting the clinical information of PD patients using the ORMIS-PD and then comparing the ORMIS-PD generated diagnostic and prognosis measures between the two groups.

Body

- The subtask 1 of major task 2, major task 3, and major task 4 each have now been completed. The subtask 2 of major task 2 completed. The subtask 2 of major task 3 was 75% completed.

- We revised the inclusion criterion to include any disease duration and a lower minimum age cut-off of 40 years.

- A no-cost extension (NCE) was submitted by the project team in August 2023 for a duration of one year, which was approved by the DoD. We have accordingly revised the timeline for other major tasks and associated subtasks as shown in the tables below.

Projected Quarterly Enrollment

Original Plan	**Year 1**				**Year 2**			
Target Enrollment (Per quarter)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Site 1 - UVMMC			10	15	15	10		
Site 2 – PVAMC/OHSU			10	15	15	10		
Target Enrollment (cumulative)	0	0	20	50	80	100		

Latest Plan	**Year 1**				**Year 2**				**Year 3 (NCE)**			
Target Enrollment (Per quarter)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Site 1 - UVMMC								5	8	25	25	
Site 2 – PVAMC/OHSU								3	7	25	25	
Target Enrollment (cumulative)	0	0	0	0	0	0	0	10	15	50	100	

Specific Aim 1: Develop ORMIS-PD through integration of clinical data capture with MDS-PD criteria, PPMI data, and machine learning algorithm.	**Original Timeline (Months)**	**% Completed**	**Latest Timeline (Months)**
Major Task 1 Create PMDO-driven ORMIS-PD Data Entry Module	0-6	90%	6-36
Subtask 1 – Expand PMDO with all clinical data elements relevant to the proposed study.	0-6	100%	0-6
Subtask 2 – Design and implement dynamic user interface for data capture	0-6	100%	0-12
Subtask 3 – Integrate user interface with data repository	0-6	0%	28-33
Major Task 2 Create ORMIS-PD Knowledge Base Module	6-18	75%	6-36
Subtask 1 – Model the MDS-PD criteria in PMDO schema	6-18	100%	6-18
Subtask 2 – Integrate PPMI data in the data repository using PMDO	6-18	50%	18-33
Major Task 3 Create ORMIS-PD Analytics Module	6-18	50%	12-33
Subtask 1 – Implement statistical algorithm diagnostic classification on MDS-PD criteria and calculate GCO score	6-18	75%	12-30
Subtask 2 – Implement graph network machine learning algorithm for computing GCO trajectory	6-18	25%	21-33

Specific Aim 2: Compare differences in ORMIS-PD generated diagnostic classification and prognosis measures between neurotoxin-associated PD and idiopathic PD.	**Original Timeline (Months)**	**% Completed**	**Latest Timeline (Months)**
Major Task 4 Clinical Research Study at UVMMC and PVAMC sites	0-24	25%	0-36
Subtask 1 – IRB Application and Approval	0-6	100%	0-14
Subtask 2 – Identification of eligible patients through chart review	6-18	Ongoing	21-33
Subtask 3 – Reach out to patients by phone for potential recruitment before the clinic visit	6-18	Ongoing	21-33
Subtask 4 – Consent of interested patients for participation in the study using the informed consent form in tandem with clinic visit	6-18	Ongoing	21-33
Subtask 5 – Capture patient's history and clinical examination findings in the ORMIS-PD data entry module in tandem with clinic visit	6-18	Ongoing	21-33
Subtask 6 – Transfer de-identified patient information from UVMMC and PVAMC sites to CWRU site through a secure and encrypted electronic transfer	6-18	Ongoing	34-34
Subtask 7 – Monthly virtual meetings among the UVMMC, PVAMC, and CWRU sites to review progress and troubleshoot any issues with ORMIS-PD data entry module	0-24	Ongoing	0-36
Major Task 5 Data Analysis and Publication	0-24	25%	12-36
Subtask 1 – Data analysis for statistical testing of outcome measures between neurotoxin-associated PD and idiopathic PD groups	18-24	0%	33-36
Subtask 2 – Scientific abstract and manuscript development for the study findings	18-24	25%	12-36

Key Research Accomplishments

- We started implementation of the data entry module of ORMIS-PD (part of aim 1) successfully in the human subject research at both sites.
- We finished creation of the data analytic module of ORMIS-PD for computing the MDS-PD diagnostic classification on the collected data.
- An undergraduate student Deepika Muthuswamy worked on non-human subject research project relevant to this project, with funding from the Binter Center's Laud Family Undergraduate Parkinson's disease Summer Fellowship Research Award. The title of Deepika's project was "A Machine Learning Model of Global Composite Outcome Measure in Parkinson's Disease".

Reportable Outcome

- Version 2.0 of the ORMIS-PD application, including data entry module and data analytics module, is now available for free for registered users at weblink http://www.ormis.org. A brief video demonstrating both modules is available at weblink http://www.tcrpd.org/ormispddemo/

- PD-CFI project for the DOD's Investigator Initiated Research Award, September 2022. Please see attached a copy of the technical abstract of the appendix item # 1.

- Principal investigator passed the Clinical Informatics board certification examination as of January 2023. Please see attached a copy of the certificate in appendix item # 2.

Conclusions

Having successfully built and implemented the data entry and data analytic modules of ORMIS-PD as part of aim 1 and aim 2, we are now working towards completion of recruitment of a total of 100 patients at the two sites of the project. In parallel, we are developing the knowledge base module by incorporating the PPMI database as proposed in aim 1 and additionally incorporating a machine learning algorithm (based on the PPMI data) in the data analytics module for implementing the GCO score and trajectory. By the end of one year NCE, we are committed to finishing this project by completing all the tasks.

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Appendices

Appendix # 1…… 11

Appendix # 2…… 12