ClinicalTrial.gov Final Outcomes Report

NCT Number:	04634331
Project Title:	Dual-Task Augmented Reality Treatment for Parkinson's Disease
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Report Date:	10/10/2023

TITLE: Dual-task Augmented Reality Treatment (DART) for Parkinson's disease
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DATE MODIFIED: 1/30/2020

Project Goal: The goal of this project is to evaluate the effectiveness of utilizing a digital therapeutic, Dual-task Augmented Reality Treatment (DART) protocol, for the treatment of postural instability and gait dysfunction (PIGD) in individuals with PD.

Rationale: Postural instability is a cardinal motor symptom of Parkinson's disease (PD), and is often accompanied with non-motor symptoms such as cognitive impairment.[1] Activities of daily living (ADL) frequently involve the simultaneous performance of two or more tasks, such as crossing the street while holding a conversation. The cognitive demands of dual-tasking to perform routine daily activities may lead to increased fall rates relative to healthy peers.[2]

Multi-Modal Training in PD patients: Based on the clear link between cognitive errors and gait instability,[3,4] multi-modal treatment (MMT)[3] was designed to target PD specific declines in these areas of cognitive function and specific gait and posture impairments, such as turning.[5,6] Briefly, MMT training consists of simultaneously training gait and cognition over the course of a 45-minute therapy session. The motor aspect of MMT stresses high velocity, high amplitude training principles with an external focus of attention (i.e. high knee marching, large amplitude stepping to targets, increase gait speed, turning, etc).[7] Considering our recent findings indicating attention and problem solving are particularly impactful on gait performance,[8] the cognitive aspect of MMT stressed these functions by asking patients to spell words backwards (i.e. progress from "cat" to "television") and solve math problems (i.e. progress from "5-2=_" to "3+3+9-11=_").

Multi-Modal Training Improves Gait, Cognition, and Reduces Falls in PD patients: In 2015-27, we conducted a preliminary RCT trial was completed in which MMT was compared to single-modal training (SMT) (i.e. sequential practice of cognitive and motor tasks).[3] There was an interaction effect favoring the MMT group with arm swing amplitude and Serial 7 responses, suggesting that MMT training may be better than SMT training in select motor and cognitive performance.[3] Results indicate that 8 weeks of MMT resulted in a significant reduction in fall frequency in PD patients compared to those in the SMT group whose fall rates remained unchanged.[9]

Delivery of a Digital Therapeutic via Augmented Reality for the Treatment of PIGD: The MMT intervention is well-suited for integration into an augmented reality (AR) platform as it consists of the patient performing a series of cognitive and motor tasks simultaneously while the patient receives knowledge of performance and results from a therapist. The Microsoft HoloLens is an untethered, AR headset used in applications as broad as teaching anatomy, displaying fine art and gaming. With AR, the user maintains contact with the physical world and the people in it. The HoloLens uses AR technology to place holograms, objects made entirely of projected light, into the user's physical environment; hence creating a first-person mixed reality environment. These holograms can be viewed from different angles and distances, can be two-dimensional or three-dimensional, can appear life-like, can move, be shaped, and change according to interaction with users' or the physical environment in which they are projected, depending on the programming. For this study, we will codify the MMT therapy into the DART protocol to create an augmented reality application for use with the HoloLens 2.

APPROACH: We will conduct a RCT comparing the DART protocol with traditional MMT administered by a therapist. It is hypothesized that the DART and therapist-led interventions will be similar in improving lower extremity function and reducing 30-day fall rates. A study flow diagram is provided in Figure 1. A total of 50 PD patients, with a history of falls, will be randomized to the traditional MMT (n=25) or DART (n=25) groups.

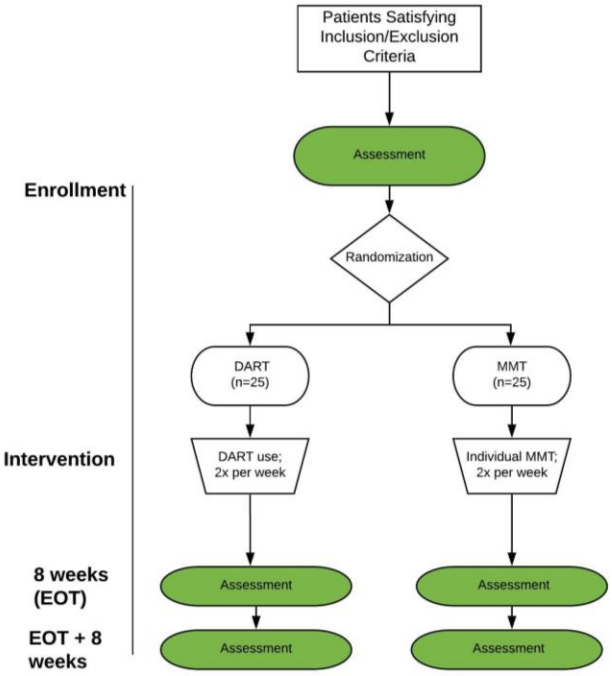

Figure 1: Study flow diagram.

Inclusion criteria:
1) Adult with a diagnosis of idiopathic PD
2) History of at least 2 falls in the past six-months
3) Hoehn and Yahr stage I-III
4) Ability to ambulate >10 minutes continuously

Exclusion criteria:
1) Diagnosis of dementia or any neurocognitive impairment that compromises the ability to provide informed consent,
2) >2 errors on the Short Portable Mental Status Questionnaire,[10]
3) Implanted deep brain stimulation electrodes
4) Musculoskeletal or cardiopulmonary issue that limits one's ability to engage in exercise
5) Neurological disease other than Parkinson's disease that impacts motor or cognitive function
6) Cardiac arrhythmia

Randomization: Participants will be randomized via a RedCap randomization database. The study team has ample experience with the RedCap randomization process, as they are using it for an ongoing, NIH, multi-site trial.

DART Platform and Intervention: Patients randomized to the DART group will be asked to complete 16 sessions (2x per week for 8 weeks) with the HoloLens version of the MMT protocol (e.g. simultaneously completing functional and cognitive based tasks that are progressively increased in difficulty based on biometric outcomes). Two initial familiarization sessions with a physical therapist (PT) will be completed with the DART protocol; the remaining 14 sessions will be largely self-administered by the participant without direct supervision from a PT. Considering this is the first effort to evaluate an AR digital therapeutic for the treatment of PIGD in PD, additional precautions will be undertaken to ensure patient safety and integrity and completeness of data. The DART protocol is designed to be self-administered by the patient, however, all training will take place in the Alberts lab and Dr. Rosenfeldt, a neurologically trained physical therapist, will be present to address any potential technical issues and to ensure the safety of the patient. Based on performance and completion rates of the assigned modules, Drs. Rosenfeldt and Alberts will progress the complexity of training.

MMT Intervention: Patients in the therapist-led group will attend in clinic one-on-one MMT sessions with a licensed PT (Dr. Rosenfeldt). She will deliver the MMT intervention over 8 weeks (twice per week) using the exact model she used in our recent RCT.[3]

Data Collection: Three assessments of motor and non-motor function will be completed for all participants: enrollment, EOT, and EOT + 8 weeks; the primary motor and non-motor outcomes are identical to those from our clinical trial[3] and are provided in Table 1. To most closely resemble daily life, assessments will be conducted in the "on-medication" state (PD medication 1 hour prior to testing). Med-reconciliation will be completed at each assessment and levodopa equivalent daily doses (LEDDs) will be determined. Demographic variables will be recorded in RedCap

Table 1: Primary and Secondary Outcome Measures	
Primary Outcome	Description
Gait velocity	Self-selected walking speed on the CAREN system during single- and dual-task conditions
MDS-UPDRS III	Clinical assessment of PD motor symptoms
30-day fall rate	Fall history
Secondary Outcome	Description
Spatiotemporal gait variables	Ex: Cadence, step length, step width, arm swing on the CAREN system during single- and dual-task conditions
Postural sway	Measure of balance on the CAREN system during single- and dual-task conditions
Timed-Up-and-Go (TUG)	Total trial time, turning velocity and duration under single- and dual-task conditions
Cognitive performance	During single- and dual-task conditions
PIGD items of MDS-UPDRS III (items 9-13)	Gait and posture
System Usability Scale	Usability of HoloLens and DART protocol technology.
Activities-specific balance confidence scale (ABC)	Balance confidence during daily tasks
Neuro-QOL	Quality of life scale for individuals with neurological disease

Our primary outcomes are gait velocity, MDS-UPDRS III scores, and 30-day fall rate. Gait parameters will be evaluated for all participants using the Computer Assisted Rehabilitation Environment (CAREN) system (Motekforce Link, Netherlands). To assess baseline cognitive function over a range of cognitive domains, a series of cognitive tests will be administered in a seated position in random order: N-back (working memory), Serial 7 subtraction (attention), Digit Recall (working memory), Controlled Oral Word Association (COWA, verbal fluency), and visual Stroop test (executive function). The cognitive test will then be administered during gait to assess the effects of DART and MMT on dual-task motor and cognitive performance. The MDS-UPDRS III is a global scale of motor function for PD.[11] Fall history will be gathered retrospectively over a 30-day period prior to baseline, over the last 30 days of the intervention, and 30 days prior to the 8-week follow-up evaluation.

Secondary outcomes are listed in Table 2. Spatiotemporal gait variables will be collected on the CAREN system similarly to our previous studies.[3,8,12] Postural sway will be recorded from the force platforms of the CAREN system. Consistent with our previous PD studies, we will use an instrumented TUG to determine transfer, gait, and turning variables.[5,6] The same cognitive tasks that were conducted on the CAREN system, will be administered in a seated position to assess cognition alone. The difference in cognitive performance between single- and dual-task conditions will be used to assess dual task loss. The System Usability Scale will be used to determine the usability of the HoloLens system and DART protocol at the end of the intervention period for those who were randomized to the DART group. The System Usability Scale was successfully used by Meldrum and colleagues when assessing virtual reality in a novel

setting.[13,14] The Neuro-QOL and ABC scale will be used as self-administered questionnaires to measure quality of life and balance confidence, respectively.

Power and Statistical Analysis: The primary outcomes for both groups will be the number of falls over the course of 30 days, MDS-UPDRS III scores, and gait velocity during dual-task conditions from baseline to EOT and EOT + 8 weeks. Biomechanical data will be gathered using the same paradigm as our clinical trial[3] with the CAREN system in the Alberts' laboratory.[3,8,12,15,16] Statistical models will include time (3-levels baseline, EOT, EOT+8) and group (2 levels - DART and therapist-led MMT) and their interaction. Criterion for equivalency is 1) both interventions show significant improvements between baseline and EOT time points and 2) the improvement in primary outcomes measures from the DART intervention is within 10% of the therapist-led MMT. A power analysis was performed using data from our previous therapist-led MMT,[3,9] where the effect was reduced by 10% in the biomechanical and fall frequency outcome measures. Results indicated a sample size of N=17-30 in each group was required to achieve a power of 70-80% at a significance level of 5% (alpha=0.05) (RStduio 2017-power-paired-test)[17]; therefore we selected N=25 for each group to achieve a power of 80%.

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