Rush University Medical Center

Title: KICK OUT PD: Karate Intervention to Change Kinematic Outcomes in Parkinson's Disease. **KICK OUT 2:** A Phase Two, Randomized Trial of a Karate Intervention.

Short Title: KICK OUT 2

S#: 18012313

NCT: NCT03882879

Principal Investigator: Jori Fleisher, MD MSCE
Rush University Parkinson's Disease and Movement Disorders Program
Phone: 312-563-2900
Jori_fleisher@rush.edu

ABBREVIATIONS

APDM	
DST	Digit Span Test
PAGEQ	Physical Activity Group Environment Questionnaire
HADS	Hospital Anxiety and Depression Scale
IPAQ	International Physical Activity Questionnaire
I-SWAY	Instrumented-SWAY
I-TUG	Instrumented-Timed-Up & Go
I-WALK	Instrumented- WALK
HY	Hoehn and Yahr Scale
MDS-UPDRS	Movement Disorders Society Unified Parkinson's Disease Rating Scale
MoCA	Montreal Cognitive Assessment
PD	Parkinson's Disease
PDQ-8	Parkinson's Disease Questionnaire – Short Form
PGIC	Patient Global Impression of Change
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SDMT	Symbol Digit Modalities Test
TUG	Timed Up & Go test

I. Project Rationale and Description

I.a. Purpose of the Study

The aim of this study is to test whether and to what degree a community-based karate class tailored for individuals with early- to middle-stage Parkinson's Disease (PD) 1) is feasible; and 2) improves objective mobility and balance, 3) improves patient-reported outcomes in mobility, balance, camaraderie, and overall wellbeing compared with individuals given a standard exercise prescription for PD. The benefits of exercise for general health and wellbeing in older adults are well-established. Balance exercises such as tai chi and yoga, along with resistance training, can improve or maintain physical function in older adults and enhance muscle strength. Furthermore, aerobic activity is critical for maintaining and improving cardiovascular and functional health. Non-contact boxing has seen a surge in popularity among individuals with PD, with components of both aerobic and balance exercise. While participants anecdotally note improvements in stress and physical function, this has only been minimally studied. However, drawing on the enthusiasm for boxing, literature surrounding aerobic and balance exercise in PD, and the combined aerobic, balance, and mindfulness practices that comprise karate, we hypothesized that participation in structured karate programs may offer similar or greater benefits than any of the individual components above. In particular, the aerobic, resistance, and balance aspects of karate may be beneficial for physical and cognitive wellbeing, and the mindfulness exercise may improve overall wellbeing. Therefore, we conducted a pilot, 10 week-long study of a structured karate exercise program for people with early to middle PD during the summer and early fall of 2018. In this single-arm pilot (no control participants), we assessed mobility, gait, balance, falls, attention, quality of life, patient-reported global impression of change, and mood before and after the 10 weeks of karate. Among 15 participants completing 10 weeks of twice-weekly classes, our pilot data highlighted our feasibility: adherence was high (mean attendance 87% of 20 classes), 100% of participants indicated interest in continuing karate classes, and 100% would recommend the program to other individuals with PD, respectively. Additionally, participants experienced a statistically and clinically significant improvement in quality of life, as measured by the Parkinson's Disease Questionnaire-Short Form (PDQ-8), with mean scores improving from 25.3 to 19.3 ($p < 0.01$), significant improvements in measures of working memory and executive function, and a trend toward improvement in the Timed Up and Go mobility measure (9.6 seconds pre-intervention to 9.0 seconds post-intervention, $p = 0.12$). Further data analysis—including qualitative analysis--is underway.

Based on these promising results from the pilot, we are therefore proposing the next step in this line of research, namely, a randomized, controlled trial of a structured karate intervention for individuals with PD. Individuals will receive a one-time, in-person training in best practices for exercise in PD. Due to both the capacity of the karate classes and the scientific approach to detecting changes in PD, subjects will be randomly assigned into either **Arm 1**: immediate participation in the karate class or **Arm 2:** participation in usual exercise for six months followed by karate classes for six months. For participants in **Arm 1**, following the first six months of classes, subjects may choose to continue their participation in karate and in the study, though this will require paying membership fees at the *dojo* (karate studio). For participants in **Arm 2**, following the first six months of usual exercise, participants will then begin 6 months of twice-weekly classes. We will conduct in-person assessments of motor function, attention, and cognition at baseline, six months, and twelve months. We will conduct online assessments of adherence to exercise program, quality of life, anxiety, depression, global impression of change, and group cohesion via bimonthly online surveys. We will assess feasibility with measurement of attendance at each class, and sustainability with the rate of attendance among the participants beyond their first six months of classes.

We hypothesize: 1) Subjects will show improved mobility after 6-months of twice weekly karate classes, as measured by change in Timed Up & Go (TUG)[1] and MDS-UPDRS motor subscore; 2) The majority of subjects will report a positive change from baseline in their overall wellbeing, as measured by a response of "very much improved", "much improved" or "minimally improved" on the Patient Global Impression of Change Scale (PGIC)[2] following 6 months of classes; 3) Feasibility will be high, as measured by $\geq$75% attendance rate and a response of "yes" to either "Would you recommend this program to someone else with PD?" *or* "If available, would you continue to participate in this or a similar karate class?"

Exploratory outcomes will include change in anxiety and depression, as measured by the Hospital Anxiety and Depression Scale (HADS)[3], cognition as measured by the Montreal Cognitive Assessment [4]and measures of attention such as the Symbol Digit Modalities Test (SDMT) and the Digit Span Test (DST)[3]. Additionally, we will assess change in group cohesion or camaraderie using the Physical Activity Group Environment Questionnaire (PAGEQ). Finally, we will offer instrumented gait analysis to all participants at baseline, 6 months, and 12 months, however this component is optional for participants.

I.b. Background

Parkinson's Disease, the second most common neurodegenerative condition[5] presents a significant health concern and the progressive, incurable course of the disease impacts functional abilities of the patient and quality of life for both the patient and caregivers. Exercise is an established supplement to pharmacologic PD treatment and various modalities have demonstrated benefits in gait, balance, PD symptoms, and quality of life measurements.[6,7,8] Research has encompassed many forms of exercise, including aerobic activities and mindfulness-based practices. Vigorous, aerobic activity has been repeatedly shown to have disease-modifying effects ranging from quality of life to overall cognitive and physical improvement.[8] Mindfulness-based practices, such as tai chi, have seen a recent surge in interest and an overall beneficial effect for participants.[9,10] A notable trial compared resistance training, stretching and tai chi interventions among Parkinson's patients and while both the resistance and tai chi arms showed improvements on multiple measures of physical ability, tai chi demonstrated a significantly greater impact in measures of balance and postural stability.[11] Furthermore, resistance training and tai chi were both correlated with improved patient-reported outcomes and participants in the tai chi group who reported benefits were more likely to continue their exercise programs.[12]

In addition to scholarly efforts, efforts to incorporate various forms of activity into PD care have gained popularity in the community at large, with notable examples including Rock Steady Boxing, a non-contact, PD-focused boxing class that has garnered national media attention. Anecdotal reports of the benefits of these vigorous, goal oriented, exercise classes are numerous; however, it has been minimally studied from the academic perspective. A case series describing six patients attending Rock Steady boxing classes reported at least some improvement in gait, balance, activities of daily living, and quality of life.[13] A randomized trial with 31 patients comparing traditional exercise and boxing demonstrated significant improvements in balance, movement, and quality of life measures among both interventions, with greater gains in gait among the boxing group.[14] Similar to boxing, karate for patients with PD has received some popular attention and media coverage both within the United States and internationally.

Karate is a martial art that incorporates the vigorous activity of aerobic and resistance exercise, mindful practice similar to tai chi, and is taught as large, directed movements in a class-based, communal environment. Karate as an adjunct therapy in PD has not yet been investigated, although one study reports improvements in cognitive speed and subjective mental health among healthy older adults

participating in karate training compared to others in a mindfulness intervention without exercise.[15] The combined benefits of exercise, mindfulness-based practice, and the popularity and promise of these types of interventions lead us to believe that karate is a promising exercise modality for PD patients and warrants further investigation. There is significant opportunity to document the potential benefits of the physical activity and mindfulness components of karate training and begin filling in this gap in the PD and exercise literature.

I.c. Study Design

This is a randomized, single-blinded, crossover-controlled, one-year study of non-contact karate for early- to middle-stage PD. The karate classes are developed for and will include only people with PD. Eligible subjects will attend a baseline study visit at Rush University Medical Center. At that time, the study logistics will be reviewed, informed consent process will occur, and each subject will complete brief, individual pre-intervention assessments including a demographic and medical history questionnaire, followed by assessments of overall mobility, gait, and balance (instrumented Timed up and Go, I-TUG; instrumented 2-minute walk, I-WALK, and instrumented sway test, I-SWAY), PD-specific clinical characteristics (Movement Disorders Society Unified Parkinson's Disease Rating Scale, MDS-UPDRS), overall cognition (Montreal Cognitive Assessment, MoCA), executive function and attention (digit span test, DST, and symbol digit modality test, SDMT), anxiety and depression (Hospital Anxiety and Depression Scale, HADS), physical activity (International Physical Activity Questionnaire, IPAQ) and quality of life (PDQ-8). Instrumented gait analysis will be performed to gather more detailed data on stride length and velocity, number of steps to turn, turn duration, and postural sway.[16]

During recruitment, and confirmed by the Research Coordinator during the baseline visit, each subject will be asked to identify their preference for karate studio (dojo) location: Roscoe Village, Evanston, Glenview, Park Ridge, or Wilmette.

Once all subjects have completed the objective and subjective baseline assessments, the baseline visit will continue with a one-time, in-person, group training highlighting current research on the benefits of exercise for PD. This training will be delivered by the study team in collaboration with an experienced physical therapist familiar with evidence-based recommendations for safe and effective exercise programs for individuals with early to middle stage PD. Participants will leave the training with printed, publicly available materials on exercise for PD as references.

After the training, eligible subjects will be grouped by dojo preference, and randomized 1:1 within each dojo into **Arm 1:** immediate participation in six months of twice-weekly karate classes, or **Arm 2:** usual exercise for six months. After six months, Arm 1 participants may opt to pay for dojo membership and continue classes, and Arm 2 participants will crossover and begin six months of twice-weekly karate classes. Only the Research Coordinator will know which subjects belong to Arm 1 and Arm 2, and she/he will deliver all study-related communication to the subjects.

The karate classes have been specifically designed for individuals with early- to middle-stage PD, focused on incorporating upper and lower limb movements in multiple directions, increasing awareness throughout the body, shifting body weight and rotation, relaxation of the muscles, improving reaction time, using complex repetitive actions to improve coordination, footwork training and centered weight shifts to help with fall prevention, and striking shields for self-defense and stress relief. The PI and study team will provide instruction on PD to all instructors prior to study launch, and will be available and responsive to any questions or concerns throughout the course of the study. The structure of the 6-

month curriculum will be identical at each of the five dojo locations. If a subject misses a class, they may choose to make up a class at one of the other dojo locations.

Every two months, subjects in both Arms will receive an online link to report their attendance at classes, indicate whether their PD medication regimen has changed (as a potential confounder), and complete the IPAQ, HADS, and PDQ-8. In addition, the survey will contain the Physical Activity Group Environment Questionnaire (PAGEQ) to measure camaraderie, and Patient Global Impression of Change (PGIC) for the subject's global impression of change. The online survey will be delivered through a secure online database called Research Electronic Data Capture (REDCap). The purpose of the online surveys is to track adherence to karate classes, adherence to other walking/moderate/vigorous activity, quality of life, anxiety, depression, global impression of change, and group cohesion.

After six months, participants in both arms will have a second in-person study visit in which the pre-intervention assessments will be re-administered (MDS-UPDRS, TUG, IPAQ, MoCA, PDQ-8, HADS, SDMT, DST, and instrumented gait analysis), along with the PAGEQ and PGIC. The PI and co-investigators performing the MDS-UPDRS will be blinded to subjects' assignments. Following completion of all assessments, without the blinded raters present, all participants will be reminded to continue completing the bimonthly online surveys over the upcoming six months, and the Research Coordinator will explain to Arm 2 on the crossing over process into the active intervention (karate classes), and participants will be provided with information on the timing and location of classes. Individuals in Arm 1 will be asked to stay and participate in a brief focus group on the first six months of classes; PI and co-investigators will not be present during the focus group in order to preserve the blind. Subjects will be prompted to share their thoughts on how the intervention impacted their overall wellbeing, balance, and mindfulness; whether the intervention achieved their expectations; whether they intend to continue, and what feedback they would like to provide.

After twelve months, participants in both arms will have a third in-person study visit* in which the pre-intervention assessments will be re-administered (medication regimen, MDS-UPDRS, TUG, IPAQ, MoCA, PDQ-8, HADS, SDMT, DST, and instrumented gait analysis), along with the PAGEQ and PGIC. The PI and co-investigators performing the MDS-UPDRS will remain blinded to subjects' assignments. Following completion of all assessments, all subjects will be asked to stay and participate in a brief focus group to reflect on the entire study. Given the number of subjects, study staff may divide the group into Arm 1 and Arm 2 participants, with concurrently running focus groups in separate rooms to ensure all participants have the opportunity to speak; again, PI and co-investigators performing ratings will not be present to preserve blinding. The script for both groups will be identical.

*Covid-19 Procedures for 12 month study visits:
Remaining 12-month data assessments will be administered electronically. Treatment, HADS, IPAQ, PDQ-8, Attendance and Camaraderie, Global Impression of Change, & Post-Intervention questionnaires will be administered over the phone and/or video call. UPDRS will be administered over video call. Cognitive test DST will be administered over the phone. Necessary visual components for the cognitive tests SDMT and MoCA will be emailed to participants to complete and return, and the remainder of these assessments will be administered over the phone. Study team will directly enter all data into REDCap.

Expanding on work begun in the pilot study, the PI and research team will collaborate with an associate professor of Cinema and Television Arts from Columbia College Chicago, IL to develop a documentary to educate others about karate as an interactive form of exercise and its potential benefits on the

symptoms and quality of life of people with PD. To capture the group's journey, portions of the karate classes and study visit focus groups will be videotaped. For a more in-depth look, 2-10 subjects will be followed during the entire study and interviewed to provide a personal narrative of their experiences with the karate classes and living with PD. The interviews will be videotaped.
We will recruit 52 individuals with PD diagnosed by a neurologist, ages 30-90, living in Chicago, and with Hoehn & Yahr (HY) stage 1 (unilateral symptoms, no balance issues), stage 2 (bilateral symptoms, no balance issues), or stage 3 (bilateral symptoms, some postural or balance involvement). Subjects must be able to ambulate independently (i.e., they must not require the use of an assistive device or a care partner to ambulate).

II. Characteristics of the Research Population

II.a. Number of Subjects

Total Number of Subjects: 52; 26 in Arm 1, 26 in Arm 2, assuming up to 25% drop-out.

Our sample size calculation (see table below) is based on the results from the pilot study with the primary outcome being change in TUG. We powered our original study based on existing literature, in which the mean TUG score for individuals with PD is 14.8 seconds with standard deviation of 5.8 seconds, and minimum clinically important difference values for the TUG ranged from 2 seconds to 5 seconds in various studies.[1,17] However, our pilot cohort had a pre-intervention baseline mean TUG of 9.6 seconds, standard deviation of 2.1. As per the tables below, if our new cohort has a similar baseline mean TUG, we would need 12 individuals in each arm to detect a difference of 2 seconds with 90% power, however this may not be plausible (i.e., 9 seconds may be close to the limit of how quickly anyone can complete the TUG task). If, however, participants have a more modest baseline to start, which may be expected when recruiting more broadly than at a tertiary referral center, we yield the second half of the table below. Here, we are extrapolating a baseline mean TUG of 12.5 with SD 4.0 (between our pilot data and the existing literature); with 19 individuals per arm, we would be 90% powered to detect a 3s difference between pre- and post-intervention TUG.

If we assume up to 25% attrition in this group of older adults with a chronic neurodegenerative disease, particularly in a longitudinal study over six months, we need to enroll 52 individuals (26 per arm) to yield a total of 40 completing the study.

Baseline mean TUG	Baseline SD TUG	Minimum clinically Important difference	Power	Sample size per arm
9.6	2.1	2s	.9	12
			.8	9
9.6	2.1	3s	.9	6
			.8	**4**
9.6	2.1	4s	.9	3
			.8	3
9.6	2.1	5s	.9	2
			.8	2
12.5	4.0	2s	.9	43
			.8	32

12.5	4.0	3s	.9	19
			.8	14
12.5	4.0	4s	.9	11
			.8	8
12.5	4.0	5s	.9	7
			.8	6

II.b. Gender of Subjects

There will be no exclusion of subjects based on gender.

II.c. Age of Subjects

Subjects will be 30-90 years of age.

II.d. Racial and Ethnic Origin

There will be no exclusion of subjects based on racial or ethnic characteristics. However, subjects must be fluent in English to participate in the karate classes, as that is the language of instruction, and due to the general lack of appropriately translated neurological and neuropsychological assessments and appropriate normative comparison samples. These factors are critical for accurate administration, scoring, and interpretation of neurological and neuropsychological test data.

II.e. Inclusion Criteria for All Subjects:

1. Each subject must be between 30-90 years of age. A subject may be of either gender, any race/ethnicity.
2. Subjects will be those diagnosed with Parkinson's Disease by a treating healthcare provider
    a. If the subject is seen at Rush University Medical Center, this will be verified via chart review.
    b. If the subject is seen elsewhere, he or she will be asked to have their healthcare provider sign a form confirming the diagnosis of Parkinson's Disease and indicating that the patient can ambulate independently as of the most recent visit, to be sent back to the Research Coordinator for eligibility verification.
3. English speaking.
4. Living within the Chicago area.
5. Subjects may be untreated for Parkinson's Disease, or may be taking any individual PD medication or combination thereof. Subjects may or may not have had Deep Brain Stimulation. Subjects may or may not be receiving physical or occupational therapy. Subjects will be encouraged to maintain their same medication regimen throughout the duration of the study, however if issues arise requiring medication changes, the subject will be prompted to indicate medication changes in the bimonthly online survey, and will not be disqualified from study participation.

II.f. Exclusion Criteria for All Subjects

1. Subjects requiring an assistive device (cane, walker, wheelchair) or the assistance of another person in order to ambulate.
2. Subjects with active psychosis or exhibiting symptoms of a severe psychiatric disorder.
3. Subjects unable to commit to attending, or to travel to, two classes weekly for six months.

4. Subjects previously participating in a karate or other martial arts program, including boxing programs for PD, in the past 30 days.
5. Subjects with atypical parkinsonism, including Progressive Supranuclear Palsy, Multiple System Atrophy, Dementia with Lewy Bodies, Corticobasal Syndrome, drug-induced parkinsonism, vascular parkinsonism, or atypical parkinsonism not otherwise specified, according to the referring healthcare provider.

II.g. Vulnerable Subjects – This study will not include children, prisoners, and homeless persons. The consent form will state that participation in our study will **not** affect their clinical care.

III. Methods and Procedures

Study Visits

Screening Phone Call

Subjects who are interested in participating based on review of printed or electronic recruitment materials will be directed to contact the Research Coordinator by phone, who will provide them with information about the study and the opportunity to ask questions about it in detail; those who express continued interest in participation will be screened for eligibility and ability to attend the scheduled classes, held at one of the five Fonseca Martial Arts dojos in Glenview, Wilmette, Park Ridge, Evanston, or Roscoe Village. Arm 1 will attend classes twice weekly for 6 months, with classes anticipated to run from January through June 2019. Afterwards, Arm 1 subjects may continue classes for a fee between July through December 2019 while subjects in Arm 2 crossover to the active portion and begin their six months of karate classes. Subjects can select from participating in either weekend/weekday daytime classes, or weekday/weekday evening classes, depending on their availability and proximity to each dojo's geographic location. Screening will occur on a rolling basis until the 52 participants are recruited.

Pre-Intervention Study Visit

All subjects will attend a pre-intervention study visit, at which time the study team, including Principal Investigator, Research Coordinator, and research assistants, will review the study design and flow, informed consent process, and each subject will be individually visited by a member of the study team to review and sign the informed consent form (ICF). No reconsenting will be necessary because Phase I participants will not be eligible to participate in Phase II, with the exception of participants who withdrew early from Phase I, who may enroll in Phase II provided that their reason for withdrawal no longer applies and these individuals will need to be newly consented with the Phase II consent document.

Subjects will complete a brief demographic and health questionnaire, including duration of PD diagnosis in years, current medication regimen, baseline activity level, prior involvement with karate or other martial arts, number of falls in the past 12 months, and subjects will complete the Parkinson's Disease Questionnaire-8 (PDQ-8)[18], a brief, validated, PD-specific 8-item measure of quality of life. Subjects will complete the Hospital Anxiety and Depression Scale (HADS). Subjects will also write their response to the open-ended prompt, "What do you hope to achieve in this class?"

Subjects will then meet with a study team member to complete the TUG (see description below) . Subjects will meet with another study team member to complete the MoCA, DST, and SDMT (cognitive testing). Next, the subject will meet with the PI or another study team member in a private room for the motor portion of the MDS-UPDRS to test bradykinesia, tremor, rigidity, and postural stability.

Subjects will then proceed with the instrumented gait, functional mobility and balance analysis.
The use of body wearable inertial motion sensors is a relatively new paradigm in gait, functional mobility and balance analysis. These portable systems allow less costly, less time consuming and noninvasive testing in natural environments compared to traditional marker based approaches (which are conducted in gait laboratories). Gait and functional mobility variables including sit to stand and turn to sit measures using this technology correlate highly with those obtained from traditional optical marker based motion analysis and forceplate approaches.
The instrumented -Timed-Up and Go (i-TUG) and instrumented 2 minute walk (i-WALK) tests will be used for quantitative functional mobility and gait and turn analysis. The TUG is an important functional gait and mobility task and is widely used clinically to determine fall risk. The TUG is also used for our power calculation in this study. The traditional TUG quantifies the time it takes to get up from a chair, walk 3 meters, turn around, walk back and sit down. We will measure a traditional 3 m TUG, and then the distance will be increased to 7 m in the second trial to provide sufficient gait cycles for analysis of the spatiotemporal aspects of gait, turning, sit to stand and stand to sit movement transitions. Intra-subject variability is an indicator of gait instability and fall risk. Stride length and stride velocity variability will be calculated by taking the coefficient of variation of these gait parameters. Comprehensive gait and functional mobility analysis will be performed using the commercially available APDM Mobility Lab™ six inertial sensor system (APDM^{TM}; Oregon). This contains the instrumented Timed up and Go (i-TUG) and instrumented WALK (i-WALK) plug-in that quantitate spatiotemporal aspects of gait, turning, sit to stand, and turn to sit while subjects are in their normal street clothing. These parameters are automatically calculated from previous algorithms developed by the manufacturer. The sensors are attached via velcro straps at the midfoot, at the dorsum of the wrists, on the lumbar trunk at the level of L5, (approximate location of body center of mass) and on the upper trunk 2 cm below the sternal notch. Data streams from the sensors transmit wirelessly to a laptop during test performance. Measured parameters include stride length, velocity, and stride variability; stride length asymmetry, cadence, swing, stance, double limb support time; trunk rotation, turn duration, peak turn velocity, steps to turn; arm, lower leg, and trunk range of motion; peak shank and arm swing velocities, and any asymmetries in these parameters.

The instrumented SWAY (i-SWAY) using one Opal APDM sensor described above will be used to assess balance and postural sway. Subjects will be ask to stand still with their hands across their chests and their feet positioned a set distance apart (scaled to their height) with the sensor applied to the lumbar trunk recording parameters including mean total sway area, path length, jerk, and sway distance in the mediolateral and anteroposterior directions. Postural sway is assessed in standing under the following conditions for 30 seconds for each trial:

1) Eyes open (EO) on a firm support surface with the feet apart
2) Eyes closed (EC) on a firm support surface with the feet apart.
3) Eyes open (EO) on a foam support surface with the feet apart
4) Eyes closed (EC) on a foam support surface with the feet apart

Note that trials 1-4 comprise the modified Clinical test of Sensory Integration and Balance which is widely used clinically to test the sensory systems (vision, proprioception, vestibular) that may be deficient and unable to allow for good postural control in patients with neurological disorders, including PD. The trials will be conducted in a non-random order from 1-4 (in order of greater difficulty). Subjects will be carefully monitored during all trials by the Co-Investigator who is a Physical Therapist and well trained in safe and accurate test administration; she will stand directly next to the subject during the

entire testing protocol. If a subject is not able to complete a trial after an initial demonstration then that trial will be deleted from the protocol. It is anticipated that not all subjects will be able to conduct each trial condition because of their balance deficits and the difficulty of certain trials.

Subjects will perform the 3 m and 7 m i-TUG once, respectively. Subjects will perform the standard 2 minute i-WALK test which will allow us to examine fatigue over time in this longer test and will also allow more accurate calculation of gait variability indices by increasing the number of steps; the subject will walk 25 meters, turn and walk back, and repeat this until 2 minutes has elapsed. Subjects will then complete the i-SWAY as described above. In total, the instrumented gait and balance testing will take approximately 10-15 minutes per subject.

Once all subjects have completed the assessments above, the baseline visit will continue with a one-time, in-person, group training highlighting current research on the benefits of exercise for PD. This training will be delivered by the study team in collaboration with an experienced physical therapist familiar with evidence-based recommendations for safe and effective exercise programs for individuals with early to middle stage PD. Participants will leave the training with printed, publicly available materials on exercise for PD as references.

Depending on participant and study staff availability and schedules, multiple pre-intervention study visits will be held to accommodate all participants.

Intervention
Each karate class will follow a structured curriculum, as shown in Appendix 1, with complexity of movements and movement patterns increasing over the six-month study period. Classes will take place twice weekly, and subjects will be required to attend their assigned class time/location, or make up missed classes at another dojo location, if possible. Each class will last approximately 45-60 minutes. Attendance will be recorded in hard copy by the instructors at each class, with recordings only of the subject's name, not linked to their unique study ID; the attendance log will be shared with the Research Coordinator following the final class. The study staff will be available by phone to answer questions and to support participants and instructors should any questions about protocol or PD safety arise.

Bimonthly online survey
Using the survey functionality of the HIPAA-secure, password-protected REDCap electronic database, all participants in both arms will automatically receive a personalized email every two months directing them to indicate how frequently they have attended karate classes (Arm 1) or how frequently they have engaged in exercise as discussed at the initial study visit (Arm 2), whether their PD medication regimen has changed (as a potential confounder), and complete the IPAQ, HADS, and PDQ-8. In addition, the survey will contain the Physical Activity Group Environment Questionnaire (PAGEQ) to measure camaraderie, and Patient Global Impression of Change (PGIC) for the subject's global impression of change.

Six-month study visit
Following six months of classes for Arm 1, and six months of usual exercise for Arm 2, the study team will contact subjects to schedule a six-month study visit, consisting of a repeated TUG, HADS, PDQ-8, SDMT, DST, MoCa, medication regimen and falls questionnaire, PAGEQ, PGIC, and MDS-UPDRS

examination. Each subject in Arm 1 will receive their initial response to the "What do you hope to achieve in this class?" prompt, and will be asked to reflect in a written, open-ended manner on whether they feel that they achieved their goal. Individuals in Arm 1 will be reminded that they may continue to attend karate classes, but the usual class fee per the dojo will no longer be waived. Individuals in Arm 2 will be informed that they may now begin karate classes at their dojo of choice for the following six months. This 6-month study visit is different than the 6-month follow-up call that was part of the initial KICK OUT PD pilot study; this six-month study visit is conducted in person, not by phone, and involves retesting of all of the measures from the initial, baseline visit. There will not be a 6-month follow up call in the new KICK OUT 2.

Twelve-month study visit

Following twelve months of classes for those individuals in Arm 1 opting to continue, and six months of classes for participants in Arm 2, the study team will contact subjects to schedule a twelve-month study visit, consisting of a repeated TUG, HADS, PDQ-8, SDMT, DST, MoCa medication regimen and falls questionnaire, PAGEQ, PGIC, and MDS-UPDRS examination. Each subject will receive their initial response to the "What do you hope to achieve in this class?" prompt, and will be asked to reflect in a written, open-ended manner on whether they feel that they achieved their goal. In addition, subjects will indicate their response to the following questions regarding feasibility: "Would you recommend this program to someone else with PD?" and "If available, would you continue to participate in this or a similar karate class?" Following completion of all assessments, all subjects will be asked to stay and participate in a brief focus group to reflect on the entire study. Given the number of subjects, study staff may divide the group into Arm 1 and Arm 2 participants, with concurrently running focus groups in separate rooms to ensure all participants have the opportunity to speak. The script for both groups will be identical.

As noted above, due to the Covid-19 outbreak, remaining 12-month data assessments will be administered electronically for participants. Treatment, HADS, IPAQ, PDQ-8, Attendance and Camaraderie, Global Impression of Change, & Post-Intervention questionnaires will be administered over the phone and/or video call. UPDRS will be administered over video call. Cognitive test DST will be administered over the phone. Necessary visual components for the cognitive tests SDMT and MoCA will be emailed to participants to complete and return, and the remainder of these assessments will be administered over the phone. Study team will directly enter all data into REDCap.

Documentary

Portions of the karate classes and 12-month study visit, and potential in-depth interviews, will be videotaped by the Columbia filmmakers using personal equipment. Subjects may choose to not participate in the documentary project which means subjects will not participate in the in-depth video interviews, and they will not be included in individual or group video shots during the focus groups and karate classes.

Assessments: Subjects who agree to be part of the study and sign the Informed Consent Form will be asked to complete a series of assessments to determine their current neurological status and overall wellbeing. There is no known risk associated with participation in these assessments, and they are a part of routine clinical care for these conditions. These tests are typically experienced as interesting to subjects. Administration of these assessments may take up to 60 minutes per subject at the pre-intervention study visit, 6-month study visit, and 12-month study visit. Administration of the bimonthly

online survey assessments may take up to 20 minutes. All or some of the following assessments and self-report measures may be administered but are not limited to:

- *Demographic/disease questionnaire:* This brief, one-page questionnaire will ask for the subject's name, , age, gender, race, ethnicity, PD duration in years, prior exposure to karate or martial arts classes, baseline activity level, and number of falls in the past 12 months. There will be one open-ended question asking, "What do you hope to achieve in this class?"

- *Hoehn and Yahr Scale (HY):* A system used for describing how Parkinson's symptoms progress and the relative level of disability. There are five stages: Stage 0 – No signs of disease; Stage 1 – Unilateral disease; Stage 1.5 – Unilateral plus axial involvement; Stage 2 – Bilateral disease, without impairment of balance; Stage 2.5 – Mild bilateral disease with recovery on pull test; Stage 3 – Mild to moderate bilateral disease; some postural instability; physically independent; Stage 4 – Severe disability; still able to walk or stand unassisted; Stage 5 – Wheelchair bound or bedridden unless aided.[19]

- *Timed Up and Go (TUG)*: A well-validated, brief measure of mobility. Administered by a study team member with a stopwatch who has previously measured out the distance between a standard arm chair and a taped line on the ground 10 feet (3 meters) away, subjects sit in a standard arm chair and are instructed that when the team member says "Go", they should stand up from the chair, walk at their normal pace to the line, turn, walk back to their chair at a normal pace, and sit down again. The study team member will record the TUG results in seconds using a stopwatch. This is a recommended test of balance in PD.[20]

  Instrumented- Timed Up and Go (i-TUG): study team member will follow same procedure as TUG described above. For the first trial, subjects will be instructed to walk 3 meters. During the second trial, the distance between the arm chair and a taped line will be increased to 7 meters.
- *Instrumented- WALK (i-WALK):* a test to examine fatigue over time and will also allow more accurate calculation of gait variability indices by increasing the number of steps. The subject will walk 25 meters, turn and walk back, and repeat this until 2 minutes has elapsed.

- *Instrumented- SWAY (i-SWAY):* a test to assess balance and postural sway. Subjects will be asked to stand still with their hands across their chests and their feet positioned a set distance apart (scaled to their height) with the APDM sensor applied to the lumbar trunk recording parameters including mean total sway area, path length, jerk, and sway distance in the mediolateral and anteroposterior directions.

- *Hospital Anxiety and Depression Scale (HADS):* Brief, 14-item highly validated scale for measuring anxiety (7 items) and depression (7 items), where scores of >8 for either anxiety or depression indicate probable symptoms.[3] The HADS was selected due to its use in prior peer mentoring studies and strong psychometric profile

- *Modified Unified Parkinson's Disease Rating Scale (MDS-UPDRS)*: The motor subscale will be conducted by the PI or study staff, assessing rigidity, resting/postural/intention tremor,

bradykinesia, gait, and balance.

- *Montreal Cognitive Assessment (MoCa):* a screening instrument designed to help health professionals detect mild cognitive dysfunction. It assesses numerous cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation.

- *Patient Global Impression of Change (PGIC)*: This single-item rating scale asks subjects to rate their overall response to the intervention using a 7-point rating scale, with the options of "very much improved", "much improved", "minimally improved", "no change", "minimally worse", "much worse" and "very much worse". Recommendations for assessing importance of this scale include reporting the percentages of subjects endorsing each of the 7 response options.

- *Physical Activity Group Environment Questionnaire (PAGEQ):* a measure of group cohesion used in sports psychology. This conceptual model of cohesion is a modified version of the GEQ (Group Environment Questionnaire). PAGEQ is divided into two levels of perceptions: an individual's perspective of a group as a whole (collective) and an individual's attraction to a group (personal). These two levels are further defined by social and task aspects. All these components are categorized into four constructs: Group Integration-Social (GI-S), Group Integration-Task (GI-T), Individual Attractions to the Group-Social (ATG-S), and Individual Attractions to the Group-Task (ATG-T).

- *Parkinson's Disease Questionnaire- Short Form (PDQ-8):* A validated and shortened version of the PDQ-39, with 8 items each representing one domain of the PDQ-39, also with a summary index score standardized to a scale of 0-100, with higher scores signifying worse quality of life; this scale is recommended for use in PD by the Movement Disorder Society.

- *Symbol Digit Modalities Test:* This uses a reference key while the examinee has 90 seconds to pair specific numbers with given geometric figures. Responses can be written or oral, and for either response mode, administration time is 5 minutes. The WPS AutoScore Test Form simplifies scoring. SDMT allows the opportunity to compare written and spoken responses from the same individual. The Manual provides separate norms for written and oral administrations of the test. Norms for adults are separated by age group and level of education.

- *Digit Span Test:* This tests the number of digits a person can absorb and recall in correct serial order after hearing them or seeing them. Here the person has to remember a small amount of information for a relatively short time, and the order of recall is important. To test the auditory digit span of a person, the administrator says numbers slowly in one second intervals, in a monotone voice. For example, the administrator will say 6-1-5-8 and have the person repeat it back in the order it was given or the reverse order. If the person is able to say a 4 digit sequence back correctly 75% of the time on the first try, it will be considered a short term memory of 4, and is the same for each higher digit. The average in our society for a seven-year old to adult is 7.

III.b. Data Analysis and Data Monitoring

Oversight of the data will be maintained by the Principal Investigator. The Principal Investigator will

review study procedures annually and report any concerns in the IRB continuation application. This is a Level I, Low, Minimal Risk study; therefore, there is minimal risk of unanticipated problems with the exception of breaches in confidentiality. The data for the study will be entered into a secured database using an electronic data capture program, Research Electronic Data Capture (REDCap).[22] The database will be stored on a secure password-protected server and not on individual desktop computers. The code sheet will be password protected and the password will be updated annually. Breaches of confidentiality will be reported to the IRB immediately with the "Reportable Event/Unanticipated Problem Form."

Data will be exported from REDCap in de-identified format for statistical analysis, with all PHI stripped from the dataset prior to analysis by statisticians. We will summarize categorical variables by frequencies and percentages and will assess continuous variables for normality, summarized by mean/standard deviation, or median/interquartile range. We will report the basic descriptive statistics of the cohort, including baseline demographics, TUG, MDS-UPDRS, HADS, PDQ-8, IPAQ, SDMT, MoCa, and DST. We will report on attendance, defined as the percentage of classes attended, in each arm once active. We will analyze the change in TUG, MDS-UPDRS, HADS, PDQ-8, IPAQ, SDMT, DST, MoCa, and PAGEQ respectively, from baseline to six months, comparing Arm 1 and 2 (active vs. control), and again at twelve months to determine whether longer participation yields additional benefits, using paired *t*-tests or nonparametric Wilcoxon sign rank tests, as appropriate. We will report on the percentage of subjects endorsing each of the 7 PGIC response options at six and twelve months, between Arms, respectively. We will report the descriptive statistics concerning whether subjects' individual predefined goal for the class was achieved (binary outcome), and will present de-identified qualitative comments noted in the feedback at the study visit focus groups. We will report descriptive statistics on continued interest and likelihood of recommending the program to someone else with PD. We will analyze descriptive statistics on continued involvement in karate/martial arts, and will again report the percentage of subjects endorsing each PGIC response option.

The qualitative data from the study visit focus groups will be audio-recorded and transcribed, with all identifying information stripped from the transcripts. Once transcribed, the audio recordings will be destroyed. The qualitative data will be analyzed using a grounded theory approach to identify pertinent themes, with data stored as password-protected files behind the Rush firewall, accessible only to study staff.

All video footage will be the sole property of the PI. Videos will have identifying information (i.e. image of patient's face, first name). Video files will be stored and password-protected behind the Rush and the Columbia firewalls. The video along with the data collected from the focus groups and karate classes may be used as part of the dissemination of the study results and for educational purposes.

The PI, co-investigators, and/or study staff will review all data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. To maintain blinding, the Research Coordinator will maintain a codesheet linking the subject ID numbers and subject names, which will be password-protected. The PI will only break the blind in the event of a safety concern. The data will be reviewed on a quarterly basis:

- Subject accrual (including compliance with enrollment criteria)
- Status of all enrolled subjects
- Adherence data regarding study visits and procedures

Safety data (AEs and SAEs) will be reported to the Principal Investigator and reviewed per occurrence and in accordance with the IRB's regulations. Any significant findings (i.e. protocol deviations) will be reported to the IRB in accordance with requirements and will be documented accordingly.

III.c. Data Storage and Confidentiality

All subjects will be assigned unique ID numbers. All research data files will be stored at the Rush University Parkinson's Disease and Movement Disorders Program in secured file cabinets, including hard copies of case report forms, informed consent forms and informed consent documentation checklists. Data will be entered into a secured database (REDCap). The database will be stored on a secure password-protected server and not on individual desktop computers. The code sheet will be password protected and the password will be updated annually. Hard copies of case report forms and informed consent documentation checklists will be labeled with the study ID only and maintained in individual files by study ID number. Signed informed consent forms, containing subject names, will be stored separately in the regulatory binder, which will be stored in a locked file cabinet in the PI's office. Class attendance records will be maintained using name only, not subject ID, by the class instructors. These records will then be given to the Research Coordinator following the final class, who will then link the attendance information with the subjects' data using the code sheet. Attendance information will be entered into REDCap. Subject records will be kept for ten years in accordance with Rush policy, after which time, the hard copies/source documents will be destroyed, and the database will remain in its electronic format but with identifying information removed, anonymizing the data.

Only the PI and research staff will have access to the database and hard copies of study documents. Data will be stored in a format suitable for research inquiries by the PI who might make use of the data in a retrospective manner for other Rush-based research studies. If a particular researcher/collaborator has an interest in a study population, then the PI will review the database to identify eligible subjects that meet the study inclusion criterion and the potential participant(s) will then be contacted by a member of this study team whom the subject has already met to see if they are interested in participating in the particular study. If a participant is interested, he or she will be referred to that Rush study team and will be scheduled for a separate consent procedure with the individual Rush researcher for that particular study and at that point the participant can choose whether to participate or not in that particular study. The results of the Karate for PD study may be published in a book, journal, and other media or used for teaching purposes. However, all published data will be made anonymous.

IV. Risk/Benefit Assessment

IV.a. Risk

There are no known risks from participating in neurological or neuropsychological tests. Subjects may experience mild boredom or cognitive fatigue; however, most individuals with like symptoms find the tests interesting and are able to tolerate up to two-hour duration of testing well. There is, however, a risk of falls or injury associated with participation in any exercise, including karate, for which subjects assume the risk and liability as they would with participation in any voluntary exercise activity. The risks will be minimized to the extent possible by 1) having all instructors undergo basic instruction in principles of PD by the PI prior to the first class; 2) having all classes held at quieter times in the dojo, so as to avoid overcrowding and risks of falls or freezing of gait in crowded, busy situations; 3) having small instructor to subject ratios to allow for maximal supervision and guidance; 4) having study staff available by phone to answer any questions or address concerns.

Another possible risk is the loss of confidentiality by participating in the documentary because the subject's image may be captured. However full names will not be used during interviews with the subjects who agree to answer questions about their experiences with the karate classes.

IV.b. Potential Benefit to Subjects

Potential benefits to subjects include the following: 1) cognitive and physical improvements in PD symptoms related to both vigorous physical activity and mindful exercise; 2) benefits of mindful exercise on quality of life; 3) the enjoyment of participating in a new activity in a social environment with other individuals with PD; 3) the satisfaction of learning a new skill; 4) the knowledge that by participating, subjects are contributing to the understanding of how karate impacts individuals with PD; 5) the altruistic benefit of contributing to the development of a fun, novel intervention for themselves and potentially others. Additional benefits include the opportunity to be active in the community and form relationships with peers. The positive effects on subjects with PD also have the potential to impact the wellbeing of their families and caregivers, as this karate class offers a new option for fun, therapeutic activity. The potential benefits to society include furthering the involvement of individuals with chronic diseases in community activities and the potential physical benefits may help modify the disease progress for the many affected by PD.

V. Subject Identification, Recruitment, and Consent/Assent

V.a. Method of Subject Identification and Recruitment

Individuals will be recruited via posted fliers, print and electronic newsletter postings, and social media postings from the Rush University Parkinson's Disease and Movement Disorders Program, electronic newsletter postings in the Rush University Medical Center Research Newsletter, Rush clinical trials website, via electronic and printed copies of fliers sent to Rush University Medical Center (1725 W Harrison St Ste 755 Chicago, IL 60612) including the departments of Neurological Sciences, Neurosurgery, Geriatrics, Internal Medicine, Family Practice, Psychiatry, Physical Medicine and Rehabilitation, and other relevant departments caring for people with PD; Rush Oak Park Hospital (520 S Maple Ave Oak Park, IL 60304), Northwestern University (710 N Lake Shore Dr Abbott Hall, 11th Fl Chicago, IL 60611), University of Chicago (5841 S Maryland Ave MC 2030 Chicago, IL 60637), University of Illinois-Chicago (1801 W Taylor St Ste 4E Chicago, IL 60612), Jesse Brown Veterans Affairs Hospital (820 S Damen Ave Chicago, IL 60612), Captain James A. Lovell Federal Health Care Center (3001 Green Bay Rd North Chicago, IL 60064), Edward Hines Jr. VA Hospital (5000 5th Ave Hines, IL 60141), Evanston Hospital (2650 Ridge Ave., Evanston, IL 60201), Glenbrook Hospital (2100 Pfingsten Road, Glenview, IL 60026), Highland Park Hospital (777 Park Ave. West, Highland Park, IL 60035), Skokie Hospital (9600 Gross Point Road, Skokie, IL 60076) including general neurologists and movement disorder specialists. Information will be disseminated to PD patients at monthly support group meetings and other educational and research fairs, in-person and via emailed recruitment fliers, as opportunities arise. Information will also be sent to all Chicago senior centers, Area Agencies on Aging, AARP Illinois, and libraries and recreation centers near each dojo. Recruitment fliers will be shared with the Parkinson Foundation for possible distribution through their electronic newsletters and social media avenues to increase reach to other potential subjects throughout the Chicago area. We will also post to clinicaltrials.gov within 30 days of starting enrollment.

V.b. Process of Consent

At the time of the pre-intervention study visit, the study team, including Principal Investigator, Research Coordinator, and research assistants, will review the study design and flow, informed consent process, and each subject will be individually visited by a member of the study team to review the informed consent form (ICF), engage in capacity assessment as described below, and assuming capacity, sign the ICF, witnessed by the study team member. The study team member will complete an ICF documentation checklist, as well.

V.c. Subject Capacity

Capacity to consent will be assessed by the designated trained research staff member and/or the PI. Throughout the consent process, the study staff member will assess the participant's comprehension by asking the participant to verbally summarize key elements of the consent form particularly the sections of the consent form that explains that they are being asked whether they agree to be contacted for other studies, as well as aspects of the consent form that explain the inclusion of PHI in the database, how their confidentiality will be protected, and how their data will be stored for future use. Subject's capacity is not expected to fluctuate significantly during the 6-months of the study, and would not be expected to be significantly impaired in early to middle stage PD.

During the consent process, subjects will have the opportunity to indicate whether they wish to be contacted for participation in future studies conducted by researchers at Rush and their collaborators. Subjects who agree to participate in the program will also have an opportunity to authorize having their Personal History Information (PHI) shared with our collaborators. PHI data will **NOT** be shared unless written authorization is obtained from the subject. Subjects will be given a copy of the signed IRB approved Informed Consent Form for their future reference. Signed consent forms will be stored in a locked cabinet in the PI's office at Rush, separate from the study data.

V.d. Debriefing Procedures

Subjects will be debriefed about the aims and study hypotheses following administration of all study procedures. This will occur after the end of the intervention in order to avoid introducing bias into subjects' responses to questions.

V.e. Documentation of Consent

A Consent Process Documentation Form will be included in the subjects' research chart that will document the informed consent process that took place.

V.f. Costs to the Subject

Subjects will not receive any inducements before, or rewards or compensation (i.e. cash, taxi fares, medical care, gifts, etc.) after the study. Subjects will be provided with a traditional uniform for class. Subjects will be provided with a parking validation voucher for each study visit. There will be no other costs to subjects associated with participation in this study for the first 6-months of classes; if individuals in Arm 1 opt to continue participating in karate classes beyond six months, they will need to pay the membership fee at the dojo.

VI. References

1. Dal Bello-Haas V, Klassen L, Sheppard MS, Metcalfe A. Psychometric Properties of Activity, Self-Efficacy, and Quality-of-Life Measures in Individuals with Parkinson Disease. *Physiother Can*. 2011;63(1):47-57. doi:10.3138/ptc.2009-08

2. ECDEU assessment manual for psychopharmacology : Guy, William : Free Download & Streaming : Internet Archive. https://archive.org/details/ecdeuassessmentm1933guyw. Accessed January 16, 2018.

3. Snaith RP, Zigmond AS. The hospital anxiety and depression scale. *Br Med J Clin Res Ed*. 1986;292(6516):344.

4. Nazem S, Siderowf AD, Duda JE, et al. Montreal cognitive assessment performance in patients with Parkinson's disease with "normal" global cognition according to mini-mental state examination score. *J Am Geriatr Soc*. 2009;57(2):304-308. doi:10.1111/j.1532-5415.2008.02096.x

5. Vincent P. Calabrese MD. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*. January 2018. http://n.neurology.org/content/projected-number-people-parkinson-disease-most-populous-nations-2005-through-2030. Accessed January 23, 2018.

6. Grazina R, Massano J. Physical exercise and Parkinson's disease: influence on symptoms, disease course and prevention. *Rev Neurosci*. 2013;24(2):139–152.

7. Goodwin VA, Richards SH, Taylor RS, Taylor AH, Campbell JL. The effectiveness of exercise interventions for people with Parkinson's disease: A systematic review and meta-analysis. *Mov Disord*. 2008;23(5):631–640.

8. Ahlskog JE. Does vigorous exercise have a neuroprotective effect in Parkinson disease? *Neurology*. 2011;77(3):288–294.

9. Kwok JYY, Choi KC, Chan HYL. Effects of mind–body exercises on the physiological and psychosocial well-being of individuals with Parkinson's disease: A systematic review and meta-analysis. *Complement Ther Med*. 2016;29:121-131. doi:10.1016/j.ctim.2016.09.016

10. Bega D, Zadikoff C. Complementary & Alternative Management of Parkinson's Disease: An Evidence-Based Review of Eastern Influenced Practices. *J Mov Disord*. 2014;7(2):57-66. doi:10.14802/jmd.14009

11. Li F, Harmer P, Fitzgerald K, et al. Tai Chi and Postural Stability in Patients with Parkinson's Disease. *N Engl J Med*. 2012;366(6):511-519. doi:10.1056/NEJMoa1107911

12. Li F, Harmer P, Liu Y, et al. A randomized controlled trial of patient-reported outcomes with tai chi exercise in Parkinson's disease. *Mov Disord*. 2014;29(4):539-545. doi:10.1002/mds.25787

13. Combs SA, Diehl MD, Staples WH, et al. Boxing training for patients with Parkinson disease: a case series. *Phys Ther*. 2011;91(1):132–142.

14. Combs SA, Diehl MD, Chrzastowski C, et al. Community-based group exercise for persons with Parkinson disease: a randomized controlled trial. *NeuroRehabilitation*. 2013;32(1):117–124.

15. Jansen P, Dahmen-Zimmer K, Kudielka BM, Schulz A. Effects of karate training versus mindfulness training on emotional well-being and cognitive performance in later life. *Res Aging*. 2017;39(10):1118–1144.

16. Pal G, O'Keefe J, Robertson-Dick E, Bernard B, Anderson S, Hall D. Global cognitive function and processing speed are associated with gait and balance dysfunction in Parkinson's disease. *J Neuroengineering Rehabil*. 2016;13(1):94. doi:10.1186/s12984-016-0205-y

17. Huang S-L, Hsieh C-L, Wu R-M, Tai C-H, Lin C-H, Lu W-S. Minimal detectable change of the timed "up & go" test and the dynamic gait index in people with Parkinson disease. *Phys Ther*. 2011;91(1):114-121. doi:10.2522/ptj.20090126

18. Jenkinson C, Fitzpatrick R. Cross-cultural evaluation of the short form 8-item Parkinson's Disease Questionnaire (PDQ-8): results from America, Canada, Japan, Italy and Spain. *Park Relat Disord*. 2007;13(1):22-28. doi:10.1016/j.parkreldis.2006.06.006

19. Goetz CG, Poewe W, Rascol O, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. *Mov Disord Off J Mov Disord Soc*. 2004;19(9):1020-1028. doi:10.1002/mds.20213

20. Bloem BR, Marinus J, Almeida Q, et al. Measurement instruments to assess posture, gait, and balance in Parkinson's disease: Critique and recommendations. *Mov Disord*. 2016;31(9):1342-1355. doi:10.1002/mds.26572

22. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inf*. 2009;42(2):377-381. doi:10.1016/j.jbi.2008.08.010

Appendix 1: Sample Karate Class Curriculum

Curriculum Sample:

Warm-ups:

Single knee ups
Double knee ups
Alternating knee ups
Knee swings (inside-out)
Knee rotations
One leg squat, with other leg doing toe taps (forward, backward, side)
Squats with arms extended
Hip circles
Body rotation
Arm side swings

Arm circles
Rotator cuff

Strikes from Ready Stance (feet shoulder width apart, knees slightly bent):
Deep breathing with palms extended
Double palm strike
Single palm strike (alternate arms)
Single punching (alternate arms)
Rising block (two count)
Rising block (one count)
Downward block (same arm with other hand on hip)
Downward block (alternating arms)
Knee strike (alternate legs)
Front snap kick (same leg)
Front snap kick (alternating)

Strikes from Fighting Stance (switch feet and repeat):
Jab (stationary)
Reverse (stationary)
Jab-Reverse (stationary)
Jab with front foot step
Reverse with front foot step
Jab-Reverse with single front foot step

Stance Work:
Front stance (moving forward)
Front stance (moving backward)
Double palm strike slowly (two count, then one count)
Front punch (two count, then one count)
Rising block (two count, then one count)
Downward block (two count, then one count)
Knee strike (forward only)
Front snap kick (forward only)

Mitt/Paddle Work:
Jab (mitt stationary and flashing for reaction)
Reverse (mitt stationary and flashing for reaction)
Jab-Reverse (mitt stationary and flashing for reaction)