# GEnetic counseling Through VIRTUAL visits in Parkinson's Disease (GET VIRTUAL PD)

**Protocol Number: 843748**

**National Clinical Trial (NCT) Identified Number: NCT04527146**

**Principal Investigator: Thomas F Tropea**

**Sponsor: University of Pennsylvania**

**Funded by: NONE**

**Version Number: 2.0**

**21 OCT 2020**

## STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

# CLINICAL RESEARCH PROTOCOL

| | | |
|---|---|---|
| **INVESTIGATIONAL PRODUCT(S):** | | Interactive Multimedia Approach to Genetic counseling to INform and educate in Parkinson's Disease (IMAGINE-PD) |
| **STUDY NUMBER(S):** | **IRB Number** | 843748 |
| | **Other Protocol Identifiers** | NA |
| **PROTOCOL(S) TITLE:** | | **GEnetic counseling Through Virtual visits in Parkinson's Disease (GET VIRTUAL PD)** |
| **REGULATORY SPONSOR:** | | None |
| **FUNDING SPONSOR(S):** | | Department of Neurology |
| **MEDICAL DIRECTOR** | | Thomas F Tropea DO |
| **ORIGINAL PROTOCOL DATE:** | | 6/17/2020 |
| **VERSION NUMBER:** | | V 2.0 |
| **VERSION DATE:** | | 10/21/2020 |

## PRINCIPAL INVESTIGATOR SIGNATURE

| | |
|---|---|
| STUDY SPONSOR: | NA |
| STUDY TITLE: | GET Virtual PD |
| STUDY ID | 843748 |
| PROTOCOL VERSION | v2.0 |

I have read the referenced protocol. I agree to conduct the study in accordance to this protocol, in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

| | | | |
|---|---|---|---|
| Principal Investigator Name | _____ | Signature | _____ |
| Affiliation: | _____ | Date | _____ |

## Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| CFR | Code of Federal Regulations |
| CLIA | Clinical Laboratory Improvement Amendments |
| MP | Monitoring Plan |
| COC | Certificate of Confidentiality |
| CONSORT | Consolidated Standards of Reporting Trials |
| CRF | Case Report Form |
| DCC | Data Coordinating Center |
| DHHS | Department of Health and Human Services |
| DSMB | Data Safety Monitoring Board |
| DRE | Disease-Related Event |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Forms |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FFR | Federal Financial Report |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practices |
| GWAS | Genome-Wide Association Studies |
| HIPAA | Health Insurance Portability and Accountability Act |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonization |
| ICMJE | International Committee of Medical Journal Editors |
| IDE | Investigational Device Exemption |
| IND | Investigational New Drug Application |
| IRB | Institutional Review Board |
| ISM | Independent Safety Monitor |
| ISO | International Organization for Standardization |
| ITT | Intention-To-Treat |

| | |
|---|---|
| LSMEANS | Least-Squares Means |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MOP | Manual of Procedures |
| MSDS | Material Safety Data Sheet |
| NCT | National Clinical Trial |
| NIH | National Institutes of Health |
| NIH IC | NIH Institute or Center |
| OHRP | Office for Human Research Protections |
| PI | Principal Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| DSMC | Data Safety Monitoring Committee |
| SoA | Schedule of Activities |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| UADE | Unanticipated Adverse Device Effect |
| UP | Unanticipated Problem |
| US | United States |

# 1 STUDY SUMMARY

## 1.1 Synopsis

| | |
|---|---|
| **Title:** | **GEnetic counseling Through VIRTUAL visits in Parkinson's Disease** |
| **Short Title:** | GET Virtual PD |
| **Study Description:** | This research tests novel approaches to pre-test counseling and post-test disclosure of genetic information in people with PD. Participants will be randomized to receive different methods of genetic counseling in a factorial design. In both pre- and post-test counseling phases, novel genetic counseling methods will be compared to telephone genetic counseling to demonstrate equivalence. The primary outcomes will be equivalence on genetics knowledge and outcomes scales, and the revised impact of events scale. The purpose is to develop effective and scalable approaches to genetic counseling. This work is crucial for patient safety and will improve access to care through novel genetic counseling approaches. |
| **Objectives:** | The primary objectives of this study are to determine the efficacy of (1) an audiovisual, web-based genetic counseling tool called the Interactive, Multimedia Approach to Genetic counseling to INform and Educate in Parkinson's Disease (IMAGINE-PD), and (2) disclosure of genetic testing results through a real-time, videoconference telegenetics platform compared to telephone counseling. |
| **Primary Endpoints:** | Genetics Knowledge Scale 4 weeks after pre-testing counseling, Revised Impact of Events Scale 3 months after genetic results disclosure, Genetic Counseling Satisfaction Scale (GCSS) immediately after disclosure counseling. |
| **Secondary Endpoints:** | GCOS, GDS, STAI, PDQ-39, C-SSRS, MoCA |
| **Study Population:** | N= 320 (80/counseling group) Parkinson's disease patients seen at the University of Pennsylvania Parkinson's Disease and Movement Disorders Center (PDMDC) who are also enrolled in the PDMDC Genetics Biobanking Protocol (IRB 830237), aged 21 and over. |
| **Phase:** | NA |

| | |
|---|---|
| **Description of Sites/Facilities** | Single-site |
| **Enrolling Participants:** | UPENN PDMDC |
| **Description of Study Intervention:** | For pre-test counseling, an audiovisual, web-based genetic counseling tool called the Interactive, Multimedia Approach to Genetic counseling to INform and Educate in Parkinson's Disease (IMAGINE-PD) will be compared to telephone counseling. Content, layout, and user testing for IMAGINE-PD were developed using the NIH guideline for usability and user testing. Expert input was obtained from movement disorders and neurogenetics specialists. For post-genetic test results disclosure web-based video conference genetic counseling will be compared to telephone genetic counseling. |
| **Study Duration:** | 36 months |
| **Participant Duration:** | 6 months |

## 1.2 Key Roles and Study Governance

| Principal Investigator | Co-Principal Investigator |
|---|---|
| Thomas F Tropea, DO, Assistant Professor | Alice Chen-Plotkin, MD, Associate Professor |
| University of Pennsylvania Dept of Neurology | University of Pennsylvania Dept of Neurology |
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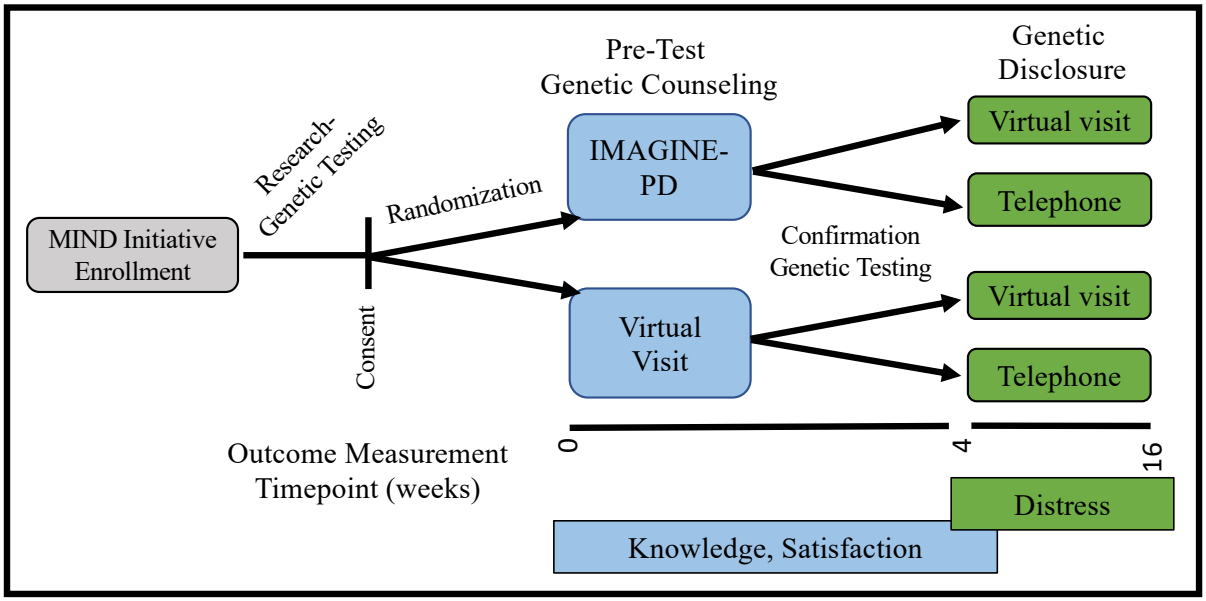
## 1.3 Schema




**Study Schema: Overall Design.**

**Schedule of Events:**

| | |
|---|---|
| Time -30-0 days | Screening (Total n=385) |
| • Screen potential participants by inclusion and exclusion criteria, call to invite to participate<br>• MoCA | |
| Day 0 (Visit 1) | Randomization (N=80/group) |
| • IMAGINE-PD/Virtual, IMAGINE-PD/Telephone, Virtual/Virtual, Virtual/Telephone | |
| Day 0 (Visit 1) | Baseline assessments/ Study Intervention |
| • Obtain informed consent, register in REDCap, train on BlueJeans platform, assign GUID<br>• Pre-Counseling: Demographics, med history, medications, family history, GKS, GDS, STAI, PDQ-39<br>• Administer pre-test genetic counseling via IMAGINE-PD or virtual visit<br>• Observe saliva collection for genetic confirmation testing<br>• Post-Counseling: GCSS | |
| Day 28-56 (Visit 2) | Genetics disclosure visit |
| • Pre-disclosure: GKS (primary outcome)<br>• Administer Post-test Genetic Counseling via virtual visit or telephone<br>• Post-disclosure: GCSS (primary outcome) | |
| Day 90-118 (Visit 3) | Genetics disclosure follow up (3 months post-disclosure) |

| | |
|---|---|
| • IES-R, (Primary outcome), GCOS, GDS, STAI, PDQ-39, C-SSRS | |
| Day 210-238 (Visit 4) | End of study assessment (6 months post-disclosure) |
| • IES-R, GCOS, GDS, STAI, PDQ-39, C-SSRS | |

# 2 INTRODUCTION AND RATIONALE

## 2.1 Study Rationale

The search for a disease-modifying therapy for Parkinson's disease (PD) remains ongoing despite decades of basic research and unsuccessful clinical trials. Novel treatments targeting carriers of pathogenic variants in the glucocerebrosidase (*GBA*) and *LRRK2* genes, the strongest genetic risk factors for PD, show great promise. The frequency of *GBA* and *LRRK2* variants is low in the general PD population (5-10%, and 1-2%, respectively), and therefore identifying eligible patients is a challenge. To achieve this goal, broad genetic testing will become the norm, departing from current practice. Broad genetic testing will capture research-eligible patients and in the future will identify populations of genetic variant carriers for precision-medicine approaches. However, such an expansion in genetic testing raises concerns about the capacity to expand genetic counseling, an essential component of clinical-genetic medical care. The current standard-of-care model, which utilizes a two-visit, face-to-face counseling model, is limited by access to trained genetic counselors to provide pre- and post-genetic testing counseling. Alongside such an expansion in genetic testing, it is essential that we develop novel models for safe and effective communication of genetic information at scale. Alternative genetic counseling and disclosure models involving video or web-based tools are currently being developed or are already in use. However, no studies have examined these approaches in the PD population.

The goals of this research study are to determine the efficacy of (1) an audiovisual, web-based genetic counseling method called the Interactive, Multimedia Approach to Genetic counseling to INform and Educate in Parkinson's Disease (IMAGINE-PD), and (2) disclosure of genetic testing results through a real-time, videoconference telegenetics platform.

## 2.2 Background

Clinical Genetics of Parkinson's disease

PD was thought to be a sporadic disorder until the late 1990s when genetic mutations responsible for the disease were identified in the synuclein gene (*SNCA*).[1] Since that time significant progress has been made in understanding the genetics of PD. A number of rare mutations have been identified in the genes *Parkin*, *DJ-1*, *Pink1* and *SNCA*, which are highly penetrant causes of PD.[1–4] Additionally, variants with incomplete penetrance have been shown to increase risk of PD in certain populations, including in the gene encoding glucocerebrosidase (*GBA*),[5] the strongest genetic risk factor for PD. It is estimated that PD is 27% heritable based on genetic variants in genome-wide association studies.[6]

Genetic testing is rarely pursued in the clinic because genetics do not currently play a role in the diagnosis or treatment of patients with PD. However, knowing one's genetic status is already of key importance for clinical research purposes, as therapies targeting carriers of *GBA* variants are being studied in Phase I and II clinical trials. Evidence in PD has demonstrated that patients

are interested in learning about their genetic data.[7,8] Moreover, at the University of Pennsylvania (UPenn), my Mentor Alice Chen-Plotkin and I have launched an initiative to approach all PD patients seen in our Parkinson's Disease and Movement Disorders Center (PDMDC) for research consent. The first consecutive 376 PD patients approached through this Molecular Integration in Neurological Diagnosis (MIND) Initiative were surveyed about their interest in participating in genetics research with the potential to learn their own results. Strikingly, 98% indicated interest in participating, as well as interest in knowing their genetic results. It is unknown how many will agree to perform clinical confirmation testing. Expanded access to genetic testing is also occurring on a national level in an effort supported by the Parkinson Foundation called PD Generation, which provides genetic counseling and genetic testing to patients with PD. UPenn is a pilot site for this clinical trial and I am the site investigator. Although interest is high, practical limitations exist with an expansion in genetic testing and counseling in PD.

Novel Genetic Counseling Approaches are Needed in PD

The current genetic counseling model relies on a two-visit, face-to-face, pre-test counseling and post-test disclosure model to ensure informed consent, understanding, healthy psychosocial response, and preventive behaviors.[9] There are many practical limitations to this approach including lack of access to trained genetic counselors, travel and cost restrictions, and the inability to provide effective counseling in the absence of a trained counselor. To address these challenges in other diseases, alternative approaches to genetic counseling have been developed for both pre- and post-test counseling methods by co-Mentor Angela Bradbury. In the domain of pre-test counseling, for instance, the Alzheimer's Prevention Initiative Generation studies utilized video-based pre-test genetic counseling to convey information on *APOE* in Alzheimer's disease risk.[10] Pre-test counseling via a web-based, interactive tool has also been utilized in the Returning Genetic Research Panel Results for Breast Cancer Susceptibility (RESPECT) Study (R01 CA190871: Bradbury).[11]

**Table 1. Change in patient reported outcomes after pre-disclosure and post-disclosure visits by eHealth pre-disclosure delivery as compared to traditional genetic counseling**[11]

| Outcome | Change from BL to post-V1 | Change from BL to post-V2 |
|---|---|---|
| Knowledge | NSS | NSS |
| HADS anxiety | -1.0; p=0.03 | NSS |
| HADS depression | NSS | -1.1, p=0.002 |
| IES cancer worry | NSS | NSS |
| Uncertainty | -1.4, p=0.04 | NSS |

N=216-246, BL = baseline, V1 = pre-disclosure counseling or eHealth alternative (participant choice); V2 = phone disclosure with a genetic counselor (GC), NSS = no statistically significant difference from those who received pre-test counseling with a GC; all p values adjusted for baseline differences between non-randomized groups

Data from RESPECT studies suggest that web-based alternative delivery methods of pre- and post-test cancer genetic counseling are acceptable to many patients and are associated with similar outcomes to traditional pre-test counseling with a genetic provider. To date, 211 (81%) have chosen pre-disclosure education by web-based method. Change in knowledge, anxiety, cancer-specific distress and uncertainty did not differ from baseline to post-disclosure between pre-disclosure education approaches. Further, the web-based approach was not associated with any significant increase in distress or decline in knowledge after receipt of result as compared to those who chose pre-disclosure genetic counselor education (See

**Table 1**).[11] The risks and benefits of alternative forms of pre- and post-test genetic counseling in PD has not been evaluated. As our knowledge of the genetics of PD expands, so too does our need for scalable approaches to counseling that are effective and safe.

## 2.3 Risk/Benefit Assessment

### *2.3.1 Known Potential Risks*

This study provides genetic counseling and testing to all participants. The method of genetic counseling varies between randomization groups. There are no known risks that differ between forms of genetic counseling including web-based, telephone, or virtual visit methods. Potential risks of genetic counseling include anxiety, stress, or discomfort that can arise during genetic counseling. Genetic counseling during this study will be conducted by trained genetic counselors following clinical guidelines genetic counseling in PD. For participants randomized to IMAGINE-PD, participants will have access to a genetic counselor via email for any follow up or clarification questions. The risks of genetic testing are relevant to all participants, which include the potential for emotional, social, or financial consequences of the testing results. Some people may feel angry, sad, anxious, or guilty about the results. There is also a risk of genetic discrimination or of re-identification of deidentified genetic results.

### *2.3.2 Known Potential Benefits*

Participating in this study provides genetic counseling and testing for free to participants. This is a service that is not always covered by insurance and could cost a significant amount out of pocket. Learning ones own genetic testing results may provide relief for some people. Additionally, depending on the results of genetic testing, some people may be eligible to participate in other clinical trials that aim to slow progression of disease, which some people may consider to be a benefit.

### *2.3.3 Assessment of Potential Risks and Benefits*

The risk of causing significant depression, anxiety, or suicidality as a result of genetic counseling or testing are very low. Genetic counselors are trained to recognize unsafe conditions and changes in affect related to genetic testing. They will follow established clinical pathways and will alert the PI with concerns. Additionally, secondary outcomes include scales of depression, anxiety, distress, and suicidality, which will be monitored by the study team, overseen by the PI.

# 3 STUDY OBJECTIVES AND ENDPOINTS

Outcomes to be studied include cognitive and affective outcomes, which will be measured via questionnaire-based scales (See **Table 2**). The questionnaires will be administrated electronically utilizing REDCap, a secure online data collection tool. Outcome measures will be collected at multiple time points throughout the study; however, the primary outcomes include Genetics Knowledge Scale at 4 weeks after pre-testing counseling, Genetics Counseling Satisfaction Scale immediately after disclosure counseling, and the Revised Impact of Events Scale 3 months after genetic results disclosure. A data monitoring plan will be in place to ensure patient safety.

# 4 STUDY PLAN

## 4.1 Study Design

The proposed study is a single-center, prospective, factorial, non-inferiority, randomized cohort design to test the equivalence of telephone genetic counseling model to novel forms of pre-test genetic counseling and telegenetic results disclosure in participants with PD carrying a *GBA* or *LRRK2* variant (PD+*gene*+), participants with PD not carrying a *GBA* or *LRRK2* variant (PD+*gene*-), and a group of at-risk *LRRK2 or GBA* variant carriers without PD (PD-*gene*+). Participants will be recruited from a single center at the University of Pennsylvania Parkinson's Disease and Movement Disorders Center. A separate biobanking protocol, called the Molecular Inegration in Neurological Diagnosis MIND Cohort (UPenn IRB # 830237) enrolls subjects with PD and collects optional consent for recontact based on eligibility for additional studies. Subjects enrolled in MIND would be eligible for GET Virtual PD if they elect to allow recontact. Subjects would be recruited to GET Virtual PD after enrolling MIND and after a blood or saliva sample has been collected and research-based genetic testing has been performed, but before clinical-confirmation genetic testing. GET Virtual PD will serve as the follow study to MIND that will allow access to genetic counseling and clinical genetic confirmation testing.

Enrolled participants will be randomized into one of 4 groups based on pre- and post-genetic test counseling: (1)IMAGINE-PD/Virtual, (2)IMAGINE-PD/Telephone, (3)Virtual/Virtual, and (4)Virtual/Telephone, stratified by genetic group. They will receive pre-test genetic counseling through the Interactive Multimedia Approach to Genetic counseling to INform and Educate in Parkinson's Disease (IMAGINE-PD) website or via virtual visit with a genetic counselor. Participants will be asked to complete questionnaires on genetic knowledge, cognitive and affective outcomes prior to and 4 weeks after pre-test genetic counseling. All participants will then have clinical genetics results disclosure via virtual visit or by telephone with a genetic counselor. Patient-reported cognitive and affective outcomes will be measured 6 weeks and 6 months after genetic results disclosure. The hypothesis is that performance on the genetic knowledge scale and the revised impact of events scale will be equivalent between counseling groups at 4 weeks after pretest counseling and 6 weeks post disclosure, respectively.

## 4.2 Scientific Rationale for Study Design

Pretest counseling and post-test disclosure via IMAGINE-PD and telephone will be compared to virtual visits using an established telehealth video-conference platform to demonstrates equivalence between these remote telegenetic methods. Virtual visits were chosen as the comparator group because it is a remote model of genetic counseling that closely mimics in-person counseling, and randomized studies have demonstrated high patient satisfaction and favorable cognitive and affective outcomes with genetic counseling services delivered via video conferencing.[12] Although in-person counseling would be considered standard of care, both telephone and telegenetic counseling can be conducted remotely and are scalable to capture a larger number of people than in-person alone. We also felt that comparing in-person to telehealth or telephone would introduce bias because one group would be evaluated in their homes, while

the other would be conducted in the office, complicating the outcome measures. Finally, given the challenges presented by the current SARS CoV-2 Pandemic, remote models of telegenetic counseling are in even higher demand, and warrant comparison in a research study in this population.

### 4.3 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Appendix Section 12.1.

# 5 STUDY POPULATION

## 5.1 Inclusion Criteria

In order to be able to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to have clinical confirmation genetic testing, and comply with all study procedures and availability for the duration of the study
3. Male or female, over the age of 21.
4. English Speaking

## 5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Prior genetic counseling and/or clinical testing specifically for Parkinson's disease
2. MoCA < 21, or a prior diagnosis of dementia during the screening phase

## 5.3 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

## 5.4 Strategies for Recruitment and Retention

Potential participants are those PDMDC PD patients who have enrolled into the MIND study, had a blood or saliva sample collected, and have indicated that they would be willing to be contacted regarding their potential eligibility for additional studies (see IRB protocol 830237). These participants have all had research-based genetic testing, which is not disclosed to them because they were not conducted in a CLIA approved lab. A non-clinical research staff member will identify subjects with and without PD who carry a *GBA* or *LRRK2* variant from this database. A random sample of PD participants not carrying *GBA* or *LRRK2* variants will also be identified. These lists will be stripped of any genetic information and provided to the clinical research staff. The clinical research staff will initiate contact with potential participants and offer for them to be included in this research study. Subjects will be chosen at random from each of the lists by choosing 5 subjects per list to contact at a time. If a participant in MIND expressly states their interest learning their *LRRK2* or *GBA* status, they will also be invited to participate in

this study at enrollment in MIND to be included in the next set of 5 subjects per list to be contacted.

We anticipate enrolling 3 subjects per week. Subjects will not be reimbursed for participating. To ensure enrollment of historically underrepresented groups, lists will include race and sex, and recruitment calls will ensure inclusion of women and non-white participants in each recruitment round. No vulnerable populations will be included in this study.

# 6 STUDY INTERVENTION

## 6.1 Study Intervention(s) Administration

### *6.1.1 Study Intervention Description*

**Virtual telemedicine and telephone genetic pretest and disclosure counseling:** The virtual visits and telephone visits will be conducted by a certified genetic counselor to provide all counseling in accordance with guidelines set forth by the National Society of Genetic Counselors. The counseling visit will be conducted in real-time by telephone or via an established and secure audiovisual conferencing telemedicine platform (BlueJeans or Penn's approved telemedicine platform) within the PennChart/EPIC electronic medical record dashboard. See Genetic Counseling SOP for additional information.

**IMAGINE-PD:** The Interactive, Multimedia Approach to Genetic Counseling to INform and Educate in Parkinson's Disease (IMAGINE-PD) is a novel, interactive, web-based, audiovisual, self-guided, genetic counseling tool in the development phase through the UPenn Clinical Research Computing Unit (CRCU), which has expertise in research computing and development. Essential genetic counseling themes, outlined by a senior certified clinical genetics counselor in accordance with national guidelines, are presented in a web-based format, utilizing videos, text, pictures, and audio. The content was refined using a binned and tiered approach, previously described.[13] User testing was conducted with PD patients and movement disorders physicians according to best practices.[14,15] Feedback was incorporated and prototype was created. This version underwent usability testing according to NCI usability guidelines,[15] and feedback was incorporated to create a final version. Participants can interact with IMAGINE-PD at their own pace, with the ability to move backward and forward, repeat sections, and have the ability to submit questions to the genetic counselor via e-mail. Web analytics will be provided by the CRCU.

## 6.2 Genetic testing

All participants will have completed enrollment in the MIND protocol (UPenn IRB protocol #: 830237), and research-based *GBA* and *LRRK2* testing will be completed. A random selection of *GBA* or *LRRK2* variant carriers (gene+) and non-carriers (gene-) with PD (PD+), and a small sample of *GBA* or *LRRK2* variant carriers (gene+) without PD (PD-) will be selected by research staff not involved in clinical data collection. Gene+ groups will have variant confirmation testing in a CLIA-approved lab (outside vendor: Fulgent Genetics). Only the variant identified in research-based testing will be examined. No further testing will be conducted on this sample. For gene- groups research-based *GBA* and *LRRK2* mutation screening will be conducted in exactly the same manner as was previously performed. This will be conducted in collaboration with Vivianna Van Deerlin, MD PhD at the University of Pennsylvania. This is not a CLIA approved test. Participants will be made aware of the possibility of having confirmation testing in a CLIA-approved lab or in a non-CLIA lab,

however, they will only learn which test was conducted at the disclosure visit to prevent partial unblinding of their results prior to confirmation testing and genetic counseling visit.

The results will be communicated to the patient via virtual visit or telephone, based on randomization. After the visit the genetic counselor will prepare a summary letter, including information specific to the results from that patient. This will be mailed to the patient. See Genetic Counseling Guideline for further description.

### 6.3 Assignment of Global Unique Identifier (GUID)

The GUID is a computer-generated alphanumeric code that is unique to each research participant. It protects identifiable information allowing de-identified data to be integrated and tracked over time across multiple projects, databases, and biobanks.

### 6.4 Measures to Minimize Bias: Randomization and Blinding

Subjects will be randomized 1:1:1:1 into each of the 4 factorial-design groups: IMAGINE-PD/Virtual, IMAGINE-PD/Telephone, Virtual/Virtual, Virtual/Telephone. Participants and investigators will be blinded to the genetic testing results (research or clinic confirmation test) until the disclosure visit. The non-clinical researcher from the MIND study who will provide blinded lists of potential participants will not be involved in study conduct, data collection, patient interaction, or have access to any clinical data collected in the GET Virtual PD study.

### 6.5 Study Intervention Compliance

The CRCU will provide web-analytics demonstrating time spent one each page, total time spent on the website, number of clicks, and times visited to the site. This information will be used to infer compliance with observing the pre-test counseling via IMAGINE-PD.

# 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Discontinuation from IMAGINE-PD or virtual/telephone genetic counseling does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- All planned subsequent study interventions

## 7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- If any clinical adverse event (AE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

The reason for participant discontinuation or withdrawal from the study will be recorded in the study log. Subjects who sign the informed consent form and are randomized but do not receive the counseling or clinical confirmation testing may be replaced. Subjects who sign the informed consent form and are randomized and receive the genetic counseling and/or clinical confirmation testing, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

## 7.3 Lost To Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 8 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

# 8 STUDY ASSESSMENT AND PROCEDURES

## 8.1 Efficacy and Safety Assessments

Below are assessments to be performed. See Schedule of events for timing of assessments.

| | Primary Objective/ Endpoint | Description |
|---|---|---|
| Primary Outcomes | Knowledge/Genetics Knowledge Scale (GKS) | A genetics knowledge questionnaire will be adapted from questionnaires previously administered to PD research studies.[7,8] Topics will include general and PD-specific genetics knowledge, genetic testing attitudes and beliefs, interest in genetic testing and counseling. |
| | Test-related distress/Revised Impact of Events Scale (IES-R) | The Revised Impact of Events Scale is a 22 item, 5-point, self-report scale measuring the affective impact of routine or acute life stress or trauma over the past 7 days. The scale is scored as the mean of non-missing items (88 points), and in domains of intrusion (32 points), avoidance (32 points), and hyperarousal (24).[16] The IES has been used to evaluate the impact of disclosure of *APOE* genetic status in The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) longitudinal study.[17] |
| | Satisfaction/Genetic Counseling Satisfaction Scale | The Genetic Counseling Satisfaction Scale (GCSS) short-form will be adapted to be applicable to both in-person and web-based interactions. It is a 6-item scale that uses a 5-point Likert-type response.[18] |
| Secondary Outcomes | Geriatric Depression Scale (GDS) | The Geriatric Depression Scale (short version) is a 15-item, "Yes/No", validated, self-report measure of depression in older adults.[19] |
| | State-Trait Anxiety Inventory (STAI) | The State-Trait Anxiety Inventory is a 20 item, 4-point, well-validated self-report scale measuring aspects of both state- and trait-anxiety.[20] |
| | Parkinson's Disease Questionnaire- 39 (PDQ-39) | The PDQ-39 is a disease-specific health status measure that assess multiple dimensions of daily living. It is a validated, self-report measure for people with PD.[21] |
| | Columbia Suicidality Severity Rating Scale (C-SSRS) | The Columbia Suicidality Severity Rating Scale is a method to prospectively monitor suicidal ideation and behavior, which can be self-administered. The *Baseline/Screening* version will be used at first visit and the *Since Last Visit* version will be used for all subsequent assessments.[22] |
| | Genetic Counseling Outcome Scale (GCOS) | The Genetic Counseling Outcome Scale (GCOS) is a validated, 24-question self-report questionnaire measuring outcomes after genetic counseling.[23] |
| | Montreal Cognitive Assessment (MoCA) | The Montreal Cognitive Assessment is a 30-point, well-validated cognitive screening tool. Cut-off values have been validated in the PD population.[24] |

Table 2. Summary of outcome measures.

## 8.2 Adverse Events and Serious Adverse Events

### *8.2.1 Definition of Adverse Events (AE)*

An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. Intercurrent illnesses or injuries should be regarded as adverse events.

A pre-existing condition should be recorded as an adverse event if the frequency, intensity or the character of the condition changes.

### *8.2.2 Definition of Serious Adverse Events (SAE)*

Serious Adverse Events (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that, in the view of either the investigator or the sponsor, is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.
- required intervention to prevent permanent impairment or damage (for devices only)

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

### *8.2.3 Classification of an Adverse Event*

#### *8.2.3.1 Severity of Event*

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.

- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious"

#### *8.2.3.2 Relationship to Study Intervention*

All adverse events (AEs) must have their relationship to genetic counseling assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be considered.

- Related – The AE is known to occur with the genetic counseling, there is a reasonable possibility that the genetic counseling caused the AE, or there is a temporal relationship between the genetic counseling and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the genetic counseling and the AE.

Not Related – There is not a reasonable possibility that the administration of the genetic counseling caused the event, there is no temporal relationship between the genetic counseling and event onset, or an alternate etiology has been established

#### *8.2.3.3 Expectedness*

The PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for genetic counseling.

### *8.2.4 Time Period and Frequency for Event Assessment and Follow-Up*

Safety will be assessed by monitoring and recording potential adverse effects using the CTCAE at each study visit. Participants will be monitored by study outcome measures. If CTCAE

grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible.

At each contact with the subject, the investigator will seek information on adverse events by non-directive questioning and, as appropriate, by examination. Adverse events may also be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. Information on all adverse events will be recorded in the source documentation. To the extent possible, adverse events will be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event.

As much as possible, each adverse event or follow-up information will be evaluated to determine:

1. Severity grade (CTCAE Grade 1-5)

2. Duration (start and end dates)

3. Relationship to the study treatment or process – [Reasonable possibility that AE is related: No (unrelated/ not suspected) or Yes (a suspected adverse reaction)]. If yes (suspected) - is the event possibly, probably or definitely related to the investigational treatment?

4. Expectedness to study treatment or process – [Unexpected – if the event severity and/or frequency is not described in the investigator brochure (if applicable) or protocol].

5. Action taken with respect to study or investigational treatment or process (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)

6. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)

7. Whether the event is serious

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

### *8.2.5 Adverse Event Reporting*

**Reporting Period**

Adverse events will be reported from the time of informed consent until study completion.

The investigator will report AEs and SAEs to the IRB/EC of record and other local regulatory groups per the local requirements.

### *8.2.6 Serious Adverse Event Reporting*

The study clinician will immediately report to the IRB any serious adverse event, whether or not considered genetic counseling related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that genetic counseling caused the event.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable.

### *8.2.7 Reporting Events to Participants*

For all events, AE and SAE, participants will be informed via mailing at the end of the study. Any AE or SAE deemed study intervention related will be included in the informed consent for subsequent participants.

### *8.2.8 Reporting of Pregnancy*

Pregnancy, in and of itself, is not regarded as an AE. Genetic counseling may have different implications for pregnancy women, we exclude pregnant women at study enrollment, however, would not exclude pregnant women from subsequent study visits at the discretion of the study participant.

## 8.3 Unanticipated Problems

### *8.3.1 Definition of Unanticipated Problems (UP)*

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### *8.3.2 Unanticipated Problem Reporting*

Unanticipated problems (UPs) such as:

- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team
- Breach of confidentiality
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study
- Premature closure of a study (e.g., due safety, lack of efficacy, feasibility, financial reasons, etc.)

should be reported by the investigator to the Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;

- A detailed description of the event, incident, experience, or outcome;

- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported as any other SAE.

- Any other UP will be reported to the IRB within 3 months of the investigator becoming aware of the problem.

All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 3 months of the IRB's receipt of the report of the problem from the investigator.

### *8.3.3 Reporting Unanticipated Problems To Participants*

For all UPs participants will be informed via mailing at the end of the study. Any UP deemed study intervention related will be included in the informed consent for subsequent participants.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 Statistical Hypotheses

The primary hypotheses are: (1) Scores on the Genetics Knowledge Scale (GKS) will not differ between virtual pre-test genetic counseling and IMAGINE-PD methods, and (2) Scores on the genetic counseling satisfaction scale and test-related distress scale (IES-R) will not differ between telephone and telegenetic results disclosure methods. The primary analyses of knowledge will be measured by the GKS at 4 weeks after pre-test counseling; Satisfaction by the GCSS score between genetic counseling groups immediately after pretest and disclosure counseling; and test-related distress by the IES-R score at 3 months between post disclosure. The null hypothesis is that these methods differ.

Secondary hypotheses include IES-R at 6 months between genetic counseling groups, scores on affect, outcomes, and quality of life scales at 3 and 6 months.

## 9.2 Sample Size Determination

The difference in IES-R between groups after genetic disclosure counseling is used to determine sample size. A clinically significant difference in IES-R score is not defined. Sample size is determined from previously reported normative data of the IES-R in a community sample of N=154 non-PTSD ex-service members, demonstrating a mean of 1.82 (SD=1.05).[16] A range of equivalence limits, the difference in standard deviation beyond which a significant difference would be considered relevant, are demonstrated in **Table 3** at alpha = 0.05 and power of 80%.[25] A sample size of N=80/counseling group (divided between PD+*gene*+ (45%), PD+*gene*- (45%), and PD-*gene*+ groups (10%)), with an expected attrition of 15-20%, would allow for analysis of the primary outcome at a conservative 0.5-0.75 SD equivalence limit, and allow genetic and PD-subgroup analysis.

| Equivalence limit (SD) | Per Group | Total Sample Size |
|---|---|---|
| 0.5 | 80 | 320 |
| 0.75 | 36 | 132 |
| 1 | 20 | 80 |

Table 3. Sample Size Estimates.

## 9.3 Populations for Analyses

Analyses will be conducted for all randomized participants *in the* Intention-to-Treat (ITT) Analysis Dataset, as well as the Per-Protocol Analysis Dataset defined a subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model (e.g., participants who complete the 3-month study visit).

## 9.4 Statistical Analyses

### *9.4.1 General Approach*

Descriptive statistics will be presented as percentages for binary variables, and as means with standard deviations or median with IQR depending on the distribution of the data. For inferential tests, the Type I error will be set at 0.05 using two-tailed tests. Covariates will be determined based on their significance as independent predictors of outcome, although age and sex will be included in all models. Check on normality will be performed through data visualization as well as using appropriate statistical tests of normality (eg Shapiro-Wilks test). Transformation of non-normally distributed continuous variables will be performed, and models will be compared to non-transformed models using non-parametric tests.

### *9.4.2 Analysis of the Primary Efficacy Endpoint(s)*

The primary endpoint is the score on the IES-R scale, which will be treated as a continuous variable. The primary outcome will be difference in IES-R score between the counseling groups at 3 months post disclosure. A linear regression model accounting for baseline differences in age, sex, and other relevant covariates will be used. Missing data will be handled in 2 ways: an analysis of available data, and using an imputed dataset. Imputation will be performed via multiple imputation using the MICE (Multivariate Imputation via Chained Equations) package. Imputation in this package uses linear and logistic regression to predict missing values. MICE assumes missing values are missing at random, and overall missingness pattern will be assessed using this package. Results will be reported as means with standard errors. Assumptions for each statistical model will be tested. Results will be analyzed using 2 approaches: data transformation and using nonparametric statistical tests, where necessary. Bonferroni correction will be used to correct for multiple-testing comparisons.

### *9.4.3 Analysis of the Secondary Endpoint(s)*

All secondary outcome variables will be treated as continuous variables. The hypotheses will be difference between counseling method groups at all study timepoints. A linear regression model accounting for baseline differences in age, sex, and other relevant covariates will be used. Missing data will be handled in 2 ways: an analysis of available data, and using an imputed dataset. Results will be reported as means with standard errors. Assumptions for each statistical model will be tested. Results will be analyzed using 2 approaches: data transformation and using nonparametric statistical tests, where necessary. Bonferroni correction will be used to correct for multiple-testing comparisons.

### *9.4.4 Safety Analyses*

No statistical analysis will be performed on safety endpoints. The Columbia Suicidality Rating Scale will be monitored at each visit. Any concerning result will trigger appropriate referral for mental health counseling or medical care.

#### *9.4.5 Baseline Descriptive Statistics*

Counseling groups will be compared on baseline characteristics, including MoCA, Age, Sex, Disease Duration, vitals, and all secondary endpoint measurements. Parametric or non-parametric tests will be used to compare means or frequencies within groups.

#### *9.4.6 Planned Interim Analyses*

NA

#### *9.4.7 Sub-Group Analyses*

All Primary and Secondary endpoints will be compared using age and sex as covariates in each multivariate model. PD and Gene groups will also be compared.

#### *9.4.8 Tabulation of Individual Participant Data*

NA

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1 Regulatory, Ethical, and Study Oversight Considerations

### *10.1.1 Informed Consent Process*

#### *10.1.1.1 Consent/Assent and Other Informational Documents Provided To Participants*

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant in electronic form and documentation of informed consent is required prior to starting intervention/administering study intervention via electronic consent.

#### *10.1.1.2 Consent Procedures and Documentation*

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures

being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

### *10.1.2 Study Discontinuation and Closure*

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed.

### *10.1.3 Confidentiality and Privacy*

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB) or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited

to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB or Institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be kept in REDCap and transmitted to a local, secure database.

For participants who have clinical testing at Fulgent Genetics, their information including their name, date of birth, and genetic status will be shared with Fulgent and may be stored in the internal laboratory database during and after the conclusion of the study. This follows the standard-of-care for clinical genetic testing. After the study, Fulgent Genetics will not release information without the participant's express written consent, as specified by HIPAA guidelines and CLIA certification guidelines.

### *10.1.4 Future Use of Stored Specimens and Data*

Fulgent Genetics may store the sample and data in an internal laboratory database as is the standard-of-care for clinical genetic testing. Fulgent Genetics will not perform additional analyses of the data without the express written consent of the participant and/or their physician. Fulgent Genetics may perform additional studies on the specimen collected for medical research and/or education, after it is anonymized, unless the participant contacts the lab directly to refuse and withdraw this consent.

### *10.1.5 Safety Oversight*

Safety oversight will be under the direction of a Safety Monitor (SM) composed of an individual with the appropriate expertise, including movement disorders neurology or neurogenetics. The ISM should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The SM will receive reports of safety data in the event of an AD or SAE.

### *10.1.6 Clinical Monitoring*

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- The PI and Co-PI will conduct monitoring, on a yearly basis through a targeted review of certain data.

### *10.1.7 Quality Assurance and Quality Control*

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be analyzed by the Investigator.

### *10.1.8 Data Handling and Record Keeping*

#### *10.1.8.1 Data Collection and Management Responsibilities*

Data collection is the responsibility of the clinical trial staff under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data will be recorded in the electronic case report form (eCRF) derived from source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse events) and clinical laboratory data will be entered into REDCAP, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly into REDCap.

Genetic data will be recorded in REDCAP for the study, and externally in the Fulgent Genetics internal laboratory database. The participants' data will be stored at Fulgent with the same management guidelines used for standard-of-care in clinical genetic testing.

#### *10.1.8.2 Study Records Retention*

Study documents should be retained for a minimum of 2 years after the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations.

### *10.1.9 Protocol Deviations*

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or protocol requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation. All deviations must be addressed in study source documents, reported to IRB, per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

### *10.1.10 Publication and Data Sharing Policy*

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers up to 10 years after the completion of the primary endpoint by contacting the Investigator

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

### *10.1.11 Conflict of Interest Policy*

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

### 10.2 Additional Considerations

NA

### 10.3 Protocol Amendment History

| Version | Date | Description of Change | Brief Rationale |
|---|---|---|---|
| 1.0 | 6/15/2020 | Initial Protocol | |
| 2.0 | 10/7/2020 | Updated protocol with Fulgent Genetics sample labeling | After samples are received at MIND, the ones going to Fulgent will be re-labeled. Fulgent Genetics will receive participants' name & date of birth with their saliva samples. Fulgent will perform the clinical confirmation testing and will have access to the participants' identifiable, labeled genetic results as well as their genetic information in their database. This is the standard-of-care in clinical genetic testing. |
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# 12 APPENDIX

## 12.1 Schedule of Activities (SoA)

| Procedures | Screening Day -30 to 0 | Study Visit 1, Day 0 | Study Visit 2 Day 28-56 | Study Visit 3 Day 90-118 | Study Visit 4 Day 210-238 |
|---|---|---|---|---|---|
| Informed consent | | X | | | |
| Demographics | | X | | | |
| Medical History[a] | | X | | | |
| MoCA | X | | | | |
| Randomization | | X | | | |
| Pretest Counseling (Virtual or IMAGINE-PD) | | X | | | |
| Genetic Testing | | X[d] | | | |
| Genetic Test Disclosure (Virtual or Telephone) | | | X | | |
| Genetics Knowledge Scale | | X[b] | X[b] | | X |
| Geriatric Depression Scale | | X | | X | X |
| State Trait Anxiety Scale | | X | | X | X |
| Parkinson's Disease Questionnaire-39 | | X | | X | X |
| Genetic Counseling Satisfaction Scale | | X[c] | X[c] | | |
| Revised Impact of Events | | | | X | X |
| Columbia Suicidality Rating Scale | | | | X | X |
| Genetic Counseling Outcomes Scale | | | | X | X |
| Complete Case Report Forms (CRFs) | x | X | X | X | X |
| Adverse Events Review | | X | X | X | X |

**[a]Medical History includes medical history, medication review, family history review. [b]Prior to genetic counseling. [c]After genetic counseling. [d]Fulgent or in-house testing for confirmation tests.**

# 13 ATTACHMENTS

## 13.1 Genetic Counseling Checklists

## 13.2 Saliva Collection Standard Operating Procedure

## 13.3 Telephone Outreach Script

## 13.4 Case Report Forms

## 13.5 Genetic Counseling Letters

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