University of Dundee

THE MICHAEL J. FOX FOUNDATION
FOR PARKINSON'S RESEARCH

lite
LRRK2
INVESTIGATIVE
THERAPEUTICS
EXCHANGE

THE MJFF LITE STUDY
PROTOCOL

Title:

The MJFF LRRK2 Investigative Therapeutics Exchange (LITE) Study

The LITE Study

Funder:

The Michael J. Fox Foundation for Parkinson's Research (MJFF)

Global Study Lead:

Esther Sammler, MD PhD

U.S. Sponsor:

Institute for Neurodegenerative Disorders (IND)

U.S. Principal Investigator:

Thomas F Tropea, DO

U.S. Site Investigators:

Ethan Brown, MD and Neha Prakash, MBBS

Study research numbers:

U.S. Protocol ID: 027

U.S. PROTOCOL APPROVAL

The undersigned confirm that the following protocol has been agreed and approved by the Sponsor and that the Principal and Site Investigators agree to conduct the study in compliance with this approved protocol and will adhere to the principles of GCP, the SOPs, and any other applicable regulatory requirements as may be amended from time to time.

Thomas Tropea, DO	Signed by: Thomas Tropea 92A707C4FFF948A...	8/26/2025
U.S. Principal Investigator	Signature	Date

SUMMARY

Study Title	**The MJFF LRRK2 Investigative Therapeutics Exchange (LITE) Study** **The LITE Study**
Study Design	**Cross-sectional, observational**
Study Population	**Parkinson's Disease including genetic (monogenic) and** **Non-genetic (idiopathic) Parkinson's Disease** **Non-Parkinson's Disease**
Sample Size	**Global: 1000** **U.S.: 200**
Planned study period	**2 years**
Clinical phase duration	**Up to 30 days**
Primary	Objective **To identify critical biological markers for LRRK2-driven Parkinson's Disease**

ROLE OF TRIAL SPONSOR AND FUNDER - US

The Sponsor of the LITE study within the United States (U.S.) is The Institute for Neurodegenerative Disorders (IND).

The roles and responsibilities of the Sponsor and Funder will be detailed in the Clinical Research Agreement.

ROLES & RESPONSIBILITIES OF STUDY MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS – U.S.

The U.S. Principal Investigator (PI) will be responsible for the conduct of the study within the U.S. The U.S. Site Investigators (SI) will be responsible for the conduct of the study at their respective site and be overseen by the U.S. PI. A study-specific Site Delegation Log will be prepared by the U.S. sites detailing the duties of each member of staff working on the study.

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP).

LIST OF ABBREVIATIONS

AE	Adverse Event
ASAP	Aligning Science Across Parkinson's
αSyn	Alpha-synuclein
αSyn-SAA	Alpha-synuclein seed amplification assay
CI	Chief Investigator
CRO	Contract Research Organizations
CSF	Cerebrospinal fluid
CTSDMC	Clinical Trials Statistical and Data Management Center
DaT imaging	Dopamine Transporter scan
DNA	Deoxyribonucleic Acid
DRIG	Dundee Parkinson's UK Research Interest Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GBA	Glucocerebrosidase
GCP	Good Clinical Practice
GE	General Electric
GP2	Global Parkinson's Genetics Program
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ID	Identification
IND	Institute for Neurodegenerative Disorders
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator Site File
IU	Indiana University
LITE	LRRK2 Investigative Therapeutics Exchange
LONI	The Laboratory of Neuro Imaging
LRRK2	Leucine-rich repeat kinase 2
LRRK2-PD	Leucine-rich repeat kinase 2-Parkinson's disease
MDS-UPDRS	Movement Disorder Society revision of the Unified Parkinson's Disease Rating Scale

MERQ-PD	Extended Mini Environmental Risk Questionnaire for Parkinson's Disease
MJFF	The Michael J. Fox Foundation for Parkinson's Research
mL	Microliter
MoCA	Montreal Cognitive Assessment
MRC PPU	Medical Research Council Protein Phosphorylation and Ubiquitylation Unit
MRI	Magnetic Resonance Imaging
NIH	National Institutes of Health
OGM	Optical Genome Mapping
PBMC	Peripheral blood mononuclear cell
PD	Parkinson's disease
PI	Principal Investigator
PIS	Participant Information Sheet
PPMI	Parkinson's Progression Markers Initiatives
PROTAC	Proteolysis- targeting chimera
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SI	Site Investigator
SOP	Standard Operating Procedure
SMG	Study Management Group
SNCA	Supreme Nucleotide Complex A
SSC	Study Steering Committee
tbc	To be confirmed
UCSF	University of California, San Francisco
UK	United Kingdom
UPSIT	University of Pennsylvania Smell Identification Test
U.S.	United States
USA	United States of America
WGS	Whole Genome Sequencing
VPS35	Vacuolar Protein Sorting Ortholog 35

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1 PROTOCOL

This protocol is a modification of the core protocol of the LITE study, a multi-national study, to include details of processes to be followed within the U.S.

2 BACKGROUND

2.1 INTRODUCTION TO THE MJFF LRRK2 INVESTIGATIVE THERAPEUTICS EXCHANGE (LITE) INITIATIVE

The MJFF LRRK2 Investigative Therapeutics Exchange (LITE) initiative funded by The Michael J. Fox Foundation for Parkinson's Research (MJFF) is a major new initiative to rapidly expedite the development of therapeutic strategies targeting the Leucine-rich repeat kinase 2 (LRRK2) by bridging basic science advances, translational research and industry-led drug development.

The overarching aim of the LITE initiative is to assemble an expert consortium with representation from underrepresented populations / geographical locations to identify and address knowledge gaps, unmet needs, and research and therapeutic opportunities for LRRK2-driven Parkinson's Disease (PD).

2.2 PARKINSON'S DISEASE

PD is a devastating neurodegenerative condition that affects up to 10 million people worldwide (1). PD remains incurable due to our incomplete understanding of the underlying biological disease processes and the heterogeneity amongst the PD population itself (2). It causes motor symptoms that can include bradykinesia, rigidity, tremor, balance and gait impairment and non-motor symptoms such as cognitive decline, mental health problems, sleep disturbances, and autonomic dysfunction. It can affect all ages, but incidence increases with age. Symptoms progress relentlessly, resulting in a progressive decline in quality of life, independence, escalating care needs and significant economic loss for the individual and society.

PD remains a clinical diagnosis as there is no diagnostic test and treatment is symptomatic. There are currently no treatments that have a proven effect on the course of the disease (disease modification).

2.3 PARKINSON'S DISEASE AND LRRK2

While the underlying cause of PD is largely unknown (idiopathic PD), it has been established that dysregulated LRRK2 cell signaling and lysosomal and other organelle dysfunction are major contributing factors (3). PD due to a pathogenic variant in LRRK2 (LRRK2-PD) is one of the most common monogenic forms – it causes 1-2% of sporadic PD and 4% of familial PD with significantly higher numbers in certain populations (4). LRRK2 is also amongst the 90 genetic loci associated with idiopathic PD (5). While LRRK2-PD closely resembles idiopathic PD, LRRK2-PD has been reported to have a younger age at onset but the penetrance of pathogenic variants in LRRK2 is incomplete and age dependent (4). The reason for this is not well understood and there may be other environmental or genetic modifiers. LRRK2-PD also differs with regards to less frequent presence of pathological α-synuclein in tissues and cerebrospinal fluid (CSF) compared with idiopathic PD (6).

All pathogenic variants increase LRRK2 kinase activity which results in hyperphosphorylation of a subset of RabGTPase (or 'Rab') substrates that orchestrate membrane and vesicle trafficking processes (7, 8). Interestingly, genetic variants mapping to three other Rab proteins (Rab29, Rab32 and Rab39B) and at least 4 other membrane trafficking machinery components (VPS35, VPS13C, DNAJC6, SORL1) have also been linked with PD (9-14). The current hypothesis is that elevated LRRK2 kinase activity and hyperphosphorylation of Rab proteins are responsible for the development of PD by disrupting vesicular trafficking and endolysosomal processes. This suggests that targeting LRRK2 for therapeutic purposes might be of much broader benefit for people with PD and that there may be alternative strategies for disease modification to LRRK2 kinase inhibition with small molecule inhibitors and PROTAC degraders that are currently in clinical trials.

2.4 PARKINSON'S DISEASE AND ALPHA-SYNUCLEIN AGGREGATION

The current gold-standard diagnosis for PD is based on clinicopathological criteria that include neuronal loss in the substantia nigra pars compacta and Lewy-body pathology related to alpha-synuclein (α-Syn) aggregation (9). However, histopathological findings in some genetic forms of PD challenge this definition since a proportion of PD patients with *LRRK2* carrier status do not have Lewy-body pathology while there is no data so far for other monogenic forms including Rab32 and VPS35 associated PD (6). More recently, a seed amplification assay to detect misfolded α-Syn in CSF has further highlighted the dichotomy between *LRRK2* mutation carriers compared to idiopathic PD; as α-Syn seeding was positive in 93% of idiopathic PD compared to only 78% of *LRRK2* pathogenic variant carriers with PD and less so in those with hyposmia and female sex (15). For VPS35 and Rab32 associated PD, no seed aggregation assay (SAA) data exists. Thus, the role of the α-Syn SAA in CSF and in the future also in blood (e.g. plasma) for patient stratification in LRRK2-driven PD requires further investigation.

2.5 EXISTING LRRK2 BIOMARKERS

Other examples of existing biological markers relate to measuring LRRK2 dependent Rab substrate phosphorylation as a read out for LRRK2 kinase activity in blood (16-22), perturbed endolysosomal vesicular trafficking as measured by urinary bis(monacylglycerol) phosphate (23-25), LRRK2 Serine 935/910 phosphorylation biomarker sites for target engagement for Type 1 inhibitors (26, 27) and possible insights into LRRK2 confirmation as well as mitochondrial DNA damage in blood (28). While these and other markers inform on LRRK2 pathway activation and have utility in target engagement, they don't correlate with disease state or progression and may lack sensitivity and / or specificity for detecting LRRK2-driven PD.

2.6 LRRK2 AND LYSOSOMAL DYSFUNCTION

Much evidence points towards perturbed LRRK2 signaling resulting in dysregulated organelle homeostasis and this will likely be the key for defining LRRK2-driven disease signatures that may correlate with clinical phenotype and genotype. As these organelles (e.g. lysosomes, mitochondria, endosomes and Golgi) make up only a small fraction of a cell's content, it is challenging to interrogate changes in their molecular content under disease conditions using conventional clinical samples. To address this, we have developed novel methodologies such as the 'Tagless LysoIP' method for molecular profiling of lysosomal content in clinical samples' to immunoaffinity enrich organelles such as lysosomes from peripheral blood for subsequent mass-spectrometry based analyses (29, 30). Such data will then be leveraged for biomarker discovery and a better understanding of the underlying disease pathology.

Thus, there is a knowledge gap and great need for novel LRRK2 pathway biological markers to refine and enhance patient stratification strategies, differentiate between manifesting and non-manifesting mutation carriers, measure progression and assays of pharmacodynamic effects of LRRK2-focused drugs, in clinical studies. With the MJFF LITE initiative, the LITE study will address these gaps and deploy known and novel state of the art targeted and untargeted approaches to biological samples from well characterized participants to define LRRK2-driven biological signatures. Importantly, this could also help to explore and translate molecular signatures related to LRRK2 and lysosomal prototypes in the large group of idiopathic people with PD in order to stratify these for molecular pathway-specific trials. Moreover, the MJFF LITE initiative will be a unique resource, as its members collectively follow a trial-ready cohort.

2.7 THE LITE STUDY

The proposed LITE study is the translational pillar of the LITE Initiative and is designed as an observational, multi-center international study with the additional option for follow up. The LITE study aims to discover and test new biological markers for LRRK2-driven Parkinson's disease (PD) in various genetic (monogenic) PD and non-genetic (idiopathic) PD populations, people at risk for PD and healthy controls, and correlate these with clinical and imaging features of disease state and progression. To achieve this, the LITE study will leverage novel organelle enrichment methodologies (such as LysoIP for enriching lysosomes from clinical samples), assays for LRRK2 kinase pathway activation and other markers of lysosomal dysfunction in conjunction with sophisticated mass-spectrometry technology in different biofluids the recently, United States (U.S.) Food and Drug Administration endorsed, alpha-synuclein seed amplification (αSyn-SAA) biomarker as well as other more explorative analysis. For comparison, country-specific (age- and sex-matched) idiopathic PD participants and healthy participants will be recruited.

Participants will be comprehensively assessed at baseline and will be offered to opt in to stay in touch regarding future research opportunities, obtaining additional information or clarification related to their participation in the LITE study and potentially attend follow-up appointments.

U.S. Participants will be enrolled in the Parkinson Progression Markers Initiative (PPMI) and may have completed demographic, clinical (motor, neuropsychiatric and cognitive), skin biopsy, CSF, DNA isolation, genetic testing, and imaging assessments. Results from those assessments will be shared from the PPMI study from the most recent visit. Participants, without a recent visit, may conduct additional clinical assessments as part of the LITE enrollment. Participants will donate biological samples including blood (e.g. plasma and different immune cell populations such as: Peripheral blood mononuclear cells (PBMCs), neutrophils and monocytes), and may donate urine, skin swabs, and breath samples for comprehensive biological sample analysis.

The expected outcome is to define biological pathways and other markers for LRRK2-driven PD that can be applied for patient stratification, quantification of different states of disease progression and target engagement in clinical trials.

2.8 LITE AND OTHER INITIATIVES

The LITE study will be aligned with several existing initiatives, including the Aligning Science Across Parkinson's (ASAP) Collaborative Research Network (CRN) (https://parkinsonsroadmap.org/research-network/#), the Parkinson's Progression Markers Initiatives (PPMI, https://www.ppmi-info.org) and the Global Parkinson's Genetics Program (GP2, https://gp2.org) creating a point of collaboration across organizations. This includes efforts to harmonize where possible protocols, data collection and processing within the LITE study across the other clinical initiatives (e.g. PPMI), undertake efforts to co-enroll participants and thereby leveraging existing data and biological samples (e.g. from participants enrolled in PPMI) and the GP2 analysis platform for the comprehensive genetic analysis of the LITE study participants. To allow this, participant IDs will be linked across relevant programs, only pseudonymized data will be linked.

3 STUDY DESIGN

Cross-sectional, observational, multi-center, international study to identify critical biological markers for LRRK2-driven PD with the additional option for follow up.

4 STUDY POPULATION

The LITE study sites have been selected based on their respective patient population, geographical location, expertise, and infrastructure.

The study population for the LITE study will focus on monogenic (genetic) PD due to genetic variants predominantly (but not exclusively) in LRRK2, VPS35, Rab32, as well as the genetic risk factor GBA1 as there is experimental data to support convergence of the underlying molecular pathways on either LRRK2 kinase activity or lysosomal dysfunction. We will also recruit participants with an increased risk for developing PD due to carrier status of PD relevant genetic mutations in these genes (non-manifesting carriers) to address whether there is a biological signature that differentiates those with and without PD and, additionally, individuals with a positive family history of PD. Additionally, the LITE study will recruit individuals with idiopathic PD and healthy controls for comparison but in a country-, age- and sex matched fashion with unequal recruitment ratio (Fig 1).

4.1 PARKINSON'S DISEASE GROUP (GROUP I)

A. **Genetic PD:** PD participants carrying a pathogenic or probable pathogenic variant in LRRK2, VPS35, Rab32, GBA1 as well as any other monogenic forms.
B. **Idiopathic PD:** PD participants who do not or are not known to carry carrying a pathogenic or probable pathogenic variant in LRRK2, VPS35, Rab32, GBA1 as well as any other monogenic forms.

4.2 PARTICIPANTS WITHOUT PD (GROUP II)

A. Participants without PD and without increased genetic risk for PD
B. Participants without PD and with increased genetic risk for PD due to carrier status of a genetic variant(s) (non-manifesting carriers of genetic PD variants)
C. Participants without PD and a multi-incidence family history of PD or a first degree relative of genetic PD

Group	**PD diagnosis**	**Genetic variant**	**Family association**	**Global target** **Total: 1000**	**U.S. target** **Total: 200**
I A	YES	YES	possibly	350	120
I B	YES	NO	NO	150	20
II A	NO	NO	NO	150	20
II B	NO	YES	possibly	150	40
II C	NO	NO	YES	200	0

Table 1: Summary of group characteristics

Recruitment to individual groups may go over target to meet the total target.

4.2.1 NON-PD PARTICIPANTS

Group II A (no PD and no genetic carrier status for PD)

The reasons to include healthy controls and to perform all assessments and biomaterial collections in the same way as for the PD subgroups and non-manifesting pathogenic variant carriers are as follows: This is one of the first global initiatives to systematically and comprehensively collect standardized data and biomaterial from people with and without PD carrying relevant pathogenic variants in PD genes. As known from multi-site studies, we expect differences in some clinical assessments due to country-specific characteristics (e.g., cognitive tests due to different education levels and smell tests due to different cultural odor specification such as in Asian countries). Additionally, this study explores new LRRK2-specific biomarkers not only in patients with PD but also in patients with probable pathogenic mutation carriers and in non-manifesting mutation carriers. Therefore, we need the same clinical and biomaterial data from healthy controls for comparison to estimate whether any findings are disease- and/or mutation- and/or population-specific. Importantly, the control group will add valuable information also for the design of future studies and clinical trials. These might include but are not limited to: learning about the variability of phenotypic and biomarker characteristics and whether these are unspecific (also in healthy elderly) or disease- and/or mutation-specific.

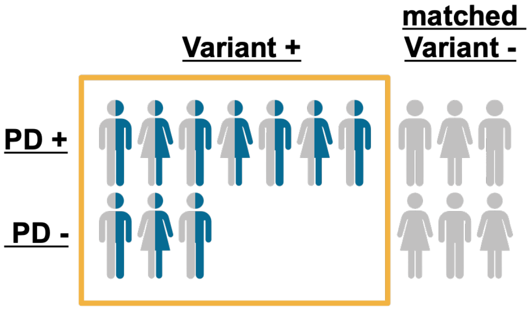
Group IIB (no PD but non-manifesting carrier status of PD relevant genetic variants)

In addition to the healthy control group, there will also be a group of people without PD who have an increased risk for developing PD in the future because they carry a genetic risk variant(s) for PD. Their PD risk is significantly higher compared to those without genetic carrier status although not everybody will go on to develop PD – incomplete, age dependent penetrance of e.g. LRRK2 G2019S. It will be important to understand whether this group differs from healthy controls (Group IIA) or those with genetic PD (Group I A).

Group IIC (no PD but a positive family history of PD)

We are recruiting people without PD (healthy controls) who have a first-degree relative with genetic PD 'proxy' case or a multi-incident family history of PD. This is because of our recruitment strategy, especially for non-manifesting carriers, where we are inviting family members of people with known mutation carrier status.

Depending on the outcome of the genetic testing result, participants who have a first-degree relative with PD may be reallocated to Group IIB as healthy, non-manifesting carriers of PD-associated genetic variants.



Variant priority:

LRRK2 G2019S > R1441G/S > G2385R > R1628P > others

VPS35 D620N

Rab32 S71R

GBA1

Others

Figure 1: Unequal site recruitment ratio of LITE

5 SAMPLE SIZE JUSTIFICATION

5.1 GLOBAL TARGET

Since the overall goal is to identify a clinical and biomarker-based **"LRRK2-driven Signature"** in a graded concept (LRRK2 vs. another monogenic PD-relevant carrier status vs. idiopathic, manifesting vs. non-manifesting participants), we must account for confounders such as site-, age-, and sex-specific differences. Based on findings from the PPMI cohort (similar confounders as in the present study) using unbiased proteomic approaches, meaningful signal detection is possible in 200-250 PD participants and 100 controls (*19*). Thereby, we estimate that globally 500 PD patients (350 genetic - including different PD genes-and 150 idiopathic PD), 150 healthy control participants, 150 non-manifesting variant carriers, and 150 'proxy' cases is the minimum required number to recruit for our purposes.

5.2 U.S. TARGET

The target number for recruitment in the U.S., see table 1, is based on feasibility with regards to what our sites can realistically achieve within the recruitment window and number of known participants with relevant genetic variants.

6 AIM AND OBJECTIVES

The LITE working hypothesis is that LRRK2 plays an important role in PD and offers the prospect of applying precision medicine and disease modification to PD.

The overall aim of the LITE study is to identify critical biological markers for LRRK2-driven PD.

This will be achieved by pioneering novel lysosomal enrichment methodologies to profile the molecular content of lysosomes in clinical samples from the LITE study participants and integrate lysosomal with other biological, genetic, clinical and imaging data. This will allow us to refine patient stratification strategies to identify those who would best respond to LRRK2 targeting treatments and develop robust assays that can be used to test pharmacodynamic effects of LRRK2-targeting drugs in future clinical trials.

The LITE study objectives are:

(i) collect relevant biological samples, clinical and other data from a large and diverse cohort of carriers of variants in relevant genes (including but not limited to LRRK2, VPS35, Rab32, GBA) with and without PD, people with idiopathic PD, healthy controls and at-risk individuals.

(ii) deploy novel organelle enrichment strategies (e.g. tagless LysoIP) and other markers for LRRK2 kinase activation and lysosomal dysfunction and correlate these with markers of pathological α-synuclein aggregation in blood and CSF as part of the core analysis.

(iii) undertake explorative biomarker discovery research using skin biopsies, skin sebum, and breath.

(iv) perform sophisticated untargeted and targeted mass-spectrometry and other analysis in all available biological specimens and analysis thereof that will be made available to the PD research community.

(v) establish a clinical trial-ready cohort of patients with LRRK2-driven PD.

7 OUTCOMES

Key outcomes will be measures of LRRK2- and lysosome-specific (dys-)function and analytes related to neurodegeneration, e.g. abnormal α-synuclein aggregation. Detailed demographic, clinical, genetic, imaging, biological and other explorative data will be collected to test specific hypotheses in subsequent analyses. In addition, data quality metrics, including compliance with study procedures, quality metrics related to the biological samples, and completeness of data collection, will be monitored on an ongoing basis.

8 GLOBAL RECRUITMENT

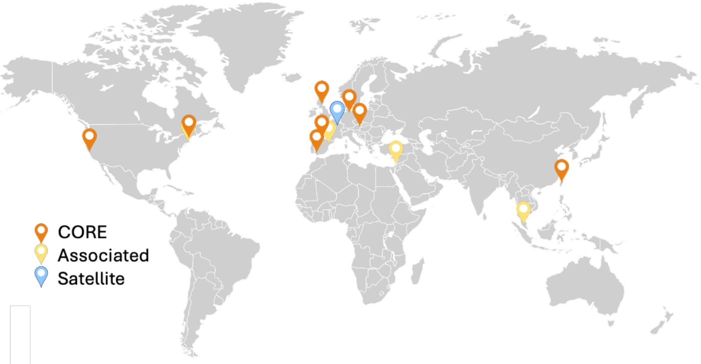
The LITE study is a global initiative led by the University of Dundee with 8 clinical sites which will recruit participants with and without manifest PD who are carriers of relevant genetic variants in PD genes (including but not limited to *LRRK2*, *VPS35*, *RAB32*, *SNCA* and *GBA*) while taking into account population and country-specific differences in PD pathogenic variants in these genes. Monogenic PD is much rarer than the common idiopathic form of the condition and there are significant population specific differences. The collaborating LITE sites have been carefully chosen as they look after larger cohorts of these rare types of potential participants for prospective biosample collection and recruitment. Additionally, LITE will leverage existing samples and data from the Parkinson's Progression Marker Initiative and other collections (such as the sample set referred to above from Israel - associated LITE site). Please see the overview of global recruitment sites below.

For comparison, country-specific (age- and sex-matched) idiopathic PD participants (without pathogenic variants in known PD genes) and healthy participants will be recruited.

The focus is on recruiting carriers of PD relevant genetic variants with and without the disease and additionally, as much as possible age and sex matched healthy controls and people with idiopathic PD.

Recruitment to groups will stop when the country's recruitment target has been met for that group.

CORE LITE SITES	Country
Barcelona Garrido, Marti	Spain
Dundee Esther Sammler	UK
Lübeck Klein, Brüggemann	Germany
New Haven Tom Tropea	US
San Francisco Tom Tropea	US
San Sebastian Javier Ruiz-Martinez	Spain
Sevilla Pablo Mir, Pilar Gómez Garre	Spain
Taipei Chin-Hsien Lin	Taiwan
Vienna Zimprich, Brücke	Austria



Associated LITE SITES	Country
Kuala Lumpur Tan & Lim	Malaysia
Tel Aviv Alcalay	Israel

Satellite LITE SITES	Country
Paris Baille	France

Figure 2: Overview of current global LITE sites: Core LITE sites are those committed to prospective recruitment into LITE and completion of all study activities (clinical assessments, core imaging and comprehensive biological sample collection). **Associated LITE sites** significantly contribute to the overarching aims of the LITE initiative (e.g. contribution of existing relevant biological sample collections) and may become core LITE sites. **Satellite sites** support the overall participant identification and recruitment efforts. Additional sites may be added during the course of the study.

8.1 PARTICIPANT IDENTIFICATION AND SCREENING – U.S.

Participants already enrolled or concurrent with a baseline visit for the Parkinson Progression Markers Initiative (PPMI) in the U.S. will be screened for eligibility to co-enroll in LITE.

PPMI participants from all U.S. PPMI sites will be screened (by the Indiana University PPMI Screening Core) based on existing data collected as part of PPMI enrollment or ongoing data collection. Individuals meeting criteria for co-enrollment in LITE will be invited to participate at either of the two U.S. PPMI-LITE sites during 1) their baseline or next PPMI annual visit if they are already an active PPMI participant at the U.S. LITE sites or 2) within ideally 3 but not more than 6 months before or after their next PPMI annual Clinical visit if they are not a participant at one of the U.S. LITE sites. The IU Screening Core will contact identified participants to discuss the opportunity, and if interested, they will be referred to 1 of 2 enrolling sites to further discuss the protocol and next steps.

8.2 INELIGIBLE PARTICIPANTS

Where an individual is found to be ineligible by the U.S. PPMI-LITE site for study participation, they will be thanked and the reasons for the ineligibility fully explained. Any queries or questions will be answered by an appropriate member of the study team.

9 PARTICIPANT ELIGIBILITY

Participants will be considered eligible for the LITE study if they fulfill the inclusion criteria and none of the exclusion criteria as defined below. The SI or delegated study staff will confirm eligibility after consent has been given.

9.1 PARKINSON'S DISEASE GROUP

- INCLUSION CRITERIA FOR ALL PARTICIPANTS WITH PD

  - Age ≥18 years
  - Able to provide informed consent
  - Enrolled in or baseline eligible for PPMI with a diagnosis of PD (co-enrollment in LITE can occur at PPMI Baseline visit or any PPMI follow up visit)

- EXCLUSION CRITERIA FOR ALL PARTICIPANTS WITH PD

  - A clinical diagnosis of dementia as determined by the prior PPMI visit cognitive diagnosis designation.
  - Clinical evidence of atypical parkinsonism (e.g., multiple-system atrophy or progressive supranuclear palsy) or evidence of drug-induced parkinsonism.
  - Previously obtained Magnetic Resonance Imaging (MRI) scan with evidence of clinically significant neurological disorder (in the opinion of the Investigator).
  - Any other reason (medical or psychiatric condition or lab abnormality) that, in the opinion of the investigator, would render the participant unsuitable for study enrollment.
  - Participation in a clinical trial testing an investigational medicinal product for PD that could interfere with the study investigations, e.g. LRRK2 or lysosome targeting investigational products (Ips) (in the opinion of the investigator).

9.1.1 ADDITIONAL INCLUSION AND EXCLUSION CRITERIA FOR PD SUBGROUPS

- **Genetic PD**

  Confirmation of carrier status of a pathogenic or probable pathogenic variant in LRRK2, VPS35, Rab32, GBA1 or other monogenic form of PD.

- **Non-Genetic PD (Idiopathic PD)**

  Absence of carrier status of a pathogenic or probable pathogenic variant in LRRK2, VPS35, Rab32, GBA1 or other monogenic form of PD.

9.2 NON-PARKINSON'S DISEASE GROUP

- INCLUSION CRITERIA FOR ALL PARTICIPANTS WITHOUT PD

  - Age ≥18 years
  - Able to provide informed consent
  - Enrolled in PPMI or baseline eligible (co-enrollment in LITE can occur at PPMI Baseline visit or any PPMI follow up visit)

- ○

EXCLUSION CRITERIA FOR ALL PARTICIPANTS WITHOUT PD

- Symptomatic PD syndromes due to either drugs (e.g., metoclopramide, flunarizine, neuroleptics) or metabolic disorders (e.g., Wilson's disease), encephalitis
- Clinical evidence of atypical parkinsonism (e.g., multiple-system atrophy or progressive supranuclear palsy).
- A clinical diagnosis of dementia as determined at the prior PPMI visit cognitive diagnosis designation.
- Previously obtained Magnetic Resonance Imaging (MRI) scan with evidence of clinically significant neurological disorder (in the opinion of the Investigator).
- Any other reason (medical or psychiatric condition or lab abnormality) that, in the opinion of the investigator, would render the participant unsuitable for study enrollment.

9.2.1 ADDITIONAL INCLUSION AND EXCLUSION CRITERIA FOR NON-PD SUBGROUPS

NO PD AND NO GENETIC CARRIER STATUS FOR PD ('HEALTHY CONTROLS')

- Absence of carrier status of a pathogenic or probable pathogenic variant in LRRK2, VPS35, Rab32, GBA1 or in any other clearly PD related gene. Research testing conducted as part of PPMI.
- Absence of a first degree relative with PD (e.g., biological parent, sibling, child) or multi-incident family history of PD

NO PD BUT NON-MANIFESTING PATHOGENIC VARIANT CARRIER STATUS

- Confirmation of carrier status of a pathogenic or probable pathogenic variant in LRRK2, VPS35, Rab32, GBA1 or other monogenic form of PD. Research testing conducted as part of PPMI.

NO PD BUT POSITIVE FAMILY HISTORY OF PD

- First degree relative with PD (e.g., biological parent, sibling, child) or multi-incident family history of PD
- Unknown genetic carrier status of a pathogenic or probable pathogenic variant in LRRK2, VPS35, Rab32, GBA1 or other monogenic form of PD.

10 OBTAINING INFORMED CONSENT

10.1 CONSENT PROCESS

The procedures and requirements of the study, together with any potential hazards/risks, and the freedom to withdraw from participation in the study at any time, will be explained to each potential participant as part of the consent process. The consent process will take place in a space that allows for privacy and confidentiality and should allow for enough time for the individual to consider participation and ask any questions. Consent will be obtained by the SI or delegated study staff. Each participant will sign an informed consent to document the agreement to participate in the study.

The Site Coordinator and SI may schedule a teleconference meeting with the PPMI participant in advance of travelling to review the informed consent, allow time to answer questions, and electronically sign an informed consent form.

It is the responsibility of the SI (or as delegated to the person obtaining consent) to ensure that the participant understands what she/he/they are agreeing to and that informed consent is obtained before the participant is involved in any protocol-defined procedures. Each participant will be provided with a signed copy of the consent form(s).

10.2 ADDITIONAL CONSENT PROVISIONS FOR COLLECTION AND USE OF PARTICIPANT DATA AND BIOLOGICAL SPECIMENS IN ANCILLARY STUDIES

Consent from participants will be gained for:

- contact by U.S. PPMI-LITE site for further follow up for the LITE study, for example, if changes to protocol occur and further information is required from participants already completed
- use of their data in future research
- use of their specimens in future research

11 STUDY PROCEDURES

Study procedures will be performed according to the Schedule of Procedures, Appendix 1. Study procedures which identify any clinically significant incidental findings, see section 11.8 for details.

Study procedures will be carried out according to study specific guidelines.

11.1 TIMING OF PROCEDURES

Study procedures will occur in a single visit. There will be about 1 hour of study procedures per visit, specifically related to LITE. LITE participants can be co-enrolled at a PPMI visit, during which PPMI assessments will be conducted, some of which overlap with LITE requirements. However, the additional assessments to be conducted specifically for LITE will take an additional 1 hour beyond the PPMI visit. All LITE study activities outside of PPMI will occur on the same day. However, if a LITE visit occurs outside of a PPMI visit, all assessments will be collected within 6 months, preferably 3 months of an annual and in-person PPMI visit.

11.2 PRE-VISIT REQUIREMENTS

Prior to the participant's first visit a member of the research team will discuss the visit with the participant and the requirements for fasting and not bathing. The participants will have to fast and abstain from bathing (optional) as below prior to giving consent. This is to minimize the number of visits required for the participants. Participants may attend a visit unfasted/abstained from bathing if wished, to discuss the study in person before agreeing to the pre-visit requirements.

11.2.1 FASTING

The research blood samples must be collected in a fasted state (i.e., minimum of 8 hours since the last meal/food intake). If fasting is not possible, then participants will be advised to eat a low-lipid diet.

11.2.2 NOT BATHING (OPTIONAL)

Participants will be asked to avoid skin products in the region – the back of the neck - where the swabs will be taken for at least 12 hours and avoid bathing for 24 hours if possible.

11.3 GENERAL ACTIVITIES

Clinical data collected under the PPMI protocol may be requested and shared with LITE investigators. Additional assessments and samples (see below) will be reviewed after completion by the study staff.

11.4 CLINICAL ASSESSMENTS

- Vital signs, including weight and height, concomitant medications, and collection of adverse events

11.5 QUESTIONNAIRES

- Extended Mini Environmental Risk Questionnaire for Parkinson's Disease (MERQ-PD): captures information pertaining to environmental risk factors, with additional questions on co-morbidity risk factors for PD (e.g. inflammatory bowel disease) and lifestyle factors (e.g. caffeine)

11.6 BIOLOGICAL SAMPLES

All samples will be collected, processed, and stored as per laboratory manual. The laboratory manual will also provide additional information on core sample sets that need to be collected for LITE by Core sites.

11.6.1 BLOOD

The required blood volume for completing all the LITE study assessments as listed below is around 80 (max 100) ml. The research blood samples will be collected in a fasted state (i.e., minimum of 8 hours since the last meal/food intake) to ensure the quality of samples for future analyses. If fasting is not possible, then participants should be advised to eat a low-lipid diet.

11.6.2 URINE

Urine collected and stored in the PPMI biorepository may be requested by the LITE study investigators by request. Samples may be requested from the visit closest to the LITE visit or other PPMI visits.

11.6.3 CEREBROSPINAL FLUID

CSF collected and stored in the PPMI biorepository may be requested by the LITE study investigators by request. Samples may be requested from the visit closest to the LITE visit or other PPMI visits.

11.6.4 SKIN BIOPSIES

Skin biopsies collected and stored in the PPMI biorepository may be requested by the LITE study investigators by request. Samples may be requested from the visit closest to the LITE visit or other PPMI visits.

11.6.5 SKIN SWABS (OPTIONAL)

- Up to 6 skin swabs will be taken from the upper back.

Participants will be asked to avoid skin products in the region where the swabs will be taken for at least 12 hours and avoid bathing for 24 hours if possible. Swabs should be taken in the morning. This procedure is optional for U.S. participants.

11.6.6 BREATH SAMPLE (OPTIONAL)

- Up to 3 samples of breath will be collected.

Participants will be asked to fast for at least 2 hours before the breath sample collection to minimize potential dietary influences. Breath samples will be collected using supplies for breath collection according to the study laboratory manual. This procedure is optional for U.S. participants.

11.7 CORE IMAGING

Usable MRI and DaTSCAN^{TM} data collected in the PPMI study LITE participants will be available for the LITE study via download from the PPMI imaging data repository.

11.8 INCIDENTAL FINDINGS

Study procedures which identify any clinically significant incidental findings will be communicated to the participant who will be informed of the result and instructed to follow up with their primary care physician. Should there be a safety concern warranting a referral for medical or psychiatric follow-up, the Investigator should provide the participant with the appropriate referral as necessary. The sites will follow their standard procedures for clinically urgent and non-urgent medical situations identified during study visits.

11.9 END OF STUDY

The end of study will be defined as last participant last visit.

12 U.S. SAMPLE MANAGEMENT

Biological sample collection, local processing and storage will be described in a study laboratory manual. All research samples will be identified using participant IDs. Samples will be collected and processed locally before being transferred for analysis at the collaborating laboratories or for storage to the biorepository at Indiana University School of Medicine (IU), in Indiana, U.S. All samples will be pseudonymized prior to leaving the study site.

Samples will be appropriately labeled in accordance with the study procedures to comply with applicable U.S. privacy and confidentiality regulations, including the Health Insurance Portability and Accountability Act (HIPAA). Biological samples collected from participants as part of this study will be transported, stored, accessed, and processed in compliance with applicable U.S. federal and state regulations, including FDA, NIH, and institutional biospecimen policies, as well as any applicable Institutional Review Board (IRB) requirements.

12.0 GENETIC ANALYSIS

DNA collected and stored in the PPMI biorepository may be requested by the LITE study investigators. Genetic data, including whole genome sequencing may be available on request for LITE participants. A DNA sample may be requested by the LITE team to be sent to the **University of Lübeck** (Germany) where further research-based genetic analyses including long read whole genome sequencing can be performed. Additionally, a whole blood sample may be provided to the **University of Lübeck** (Germany) for optical genome mapping (OGM), upon request.

All data generated for research purposes will be securely stored and analyzed in a **coded (pseudonymized)** format. Since these analyses are conducted to research standards (not clinical-grade), findings may not be validated or actionable.

12.1 BLOOD MULTIOMICS, CSF, URINE, SKIN BIOPSIES, SKIN SWABS, BREATH

All samples collected for LITE will be transferred, after collection, processing and appropriate storage locally, in batches to the biorepository at Indiana University, Indiana, U.S.

Samples will then be distributed for analysis to the University of Dundee, UK and collaborating academic and industry (Contract Research Organizations, CRO) laboratories including but not limited to:

- Amprion, San Diego, California, United States: CSF, skin biopsy, plasma (by request and not in duplicate of samples and analyses already conducted as part of PPMI or related studies for which existing data can be requested)
- Professor Perdita Barran, University of Manchester: Sebum
- Institute of Neurogenetics, University of Lubeck, Germany: DNA, Blood for DNA/RNA analysis
- University of Dundee: multi-omics and targeted assays of most biological samples

Samples will not be transferred prior to a Material Transfer Agreement being in place with the respective laboratories and biorepository. All samples will be pseudonymized prior to transfer and no participant identifiable data will be transferred with the samples. The IU Biorepository will also store samples for future research.

12.2 CORE BIOLOGICAL SAMPLES ANALYSIS

Analysis of the core outcomes will be carried out by specialist laboratories including academic collaborator laboratories and commercial laboratories. A sample transfer agreement will be put in place to allow this. All samples will be pseudonymized with study participant ID and no identifiable participant data will be included. Biological research samples will be shipped and stored at the biorepositories. From there, samples will be distributed to the appropriate laboratory for analysis of study outcomes. The respective laboratory is listed below if known at this point or tbc if not.

Below is an outline of the different biomatrices and prioritized core analysis for LITE:

- **Tagless OrganelleIPs:** From fresh peripheral blood, different cell populations will be isolated and processed for organelle enrichment (e.g., via a novel tagless LysoIP methodology (Saarela, 2024 #88) (see lab manual) or other organelleIPs to enrich other organelles). This will yield enriched organelle (e.g., lysosomal) and whole-cell lysate fractions enabling the profiling of organelle (e.g., lysosomal) content versus the rest of the cell. Analysis includes predominantly targeted and untargeted multiomics (proteomics, metabolomics and lipidomics).
- **αSyn-SAA in CSF, skin and plasma:** samples may be accessed by request and not in duplicate of samples and analyses already conducted as part of PPMI or related studies for which existing data can be requested.
- **Targeted and untargeted multiomics in plasma:** samples may be accessed by request and not in duplicate of samples and analyses already conducted as part of PPMI or related studies for which existing data can be requested.
- **Targeted and untargeted multiomics in PBMCs, monocytes and neutrophils**
- **Targeted and untargeted multiomics in urine:** samples may be accessed by request and not in duplicate of samples and analyses already conducted as part of PPMI or related studies for which existing data can be requested.
- **Targeted and untargeted multiomics in CSF**: samples may be accessed by request and not in duplicate of samples and analyses already conducted as part of PPMI or related studies for which existing data can be requested.
- **DNA from blood for extended genetic testing:** samples may be accessed by request and not in duplicate of samples and analyses already conducted as part of PPMI or related studies for which existing data can be requested.
- **RNA from blood for RNA sequencing:** to explore transcriptomic datasets (Provider: University of Lubeck).
- **Whole blood for Optical Genome Mapping (OGM):** to explore large-scale structural variants in human genomes (Provider: University of Lubeck).
- **Skin sebum for mass-spectrometry analysis (optional for US participants)** as an explorative marker for PD (35). (Lab: MRC PPU, University of Dundee and University of Manchester, UK).
- **Differential white blood cell count:** to account for the percentage of monocytes as these are the peripheral blood mononuclear cell type with the highest LRRK2 expression (*local provider*).
- **PBMCs** for cryopreservation, GBA1 assays, other LRRK2 relevant assays, and as surplus biorepository resource.
- **Breath 'biopsy' (optional for US participants)** to analyze volatile organic compounds (VOCs) and other biomarkers in exhaled breath. Unpublished data on breath non-volatile compounds show promise in identifying a PD-specific signature and could be highly relevant in LRRK2 biomarker research as LRRK2 is highly expressed in the lung.

- **Skin biopsies for generation fibroblasts and induced pluripotent stem cells (IPSCs):** samples may be accessed by request and not in duplicate of samples and analyses already conducted as part of PPMI or related studies for which existing data can be requested.

12.3 SAMPLE SHARING AND STORAGE FOR FUTURE USE

LITE specific specimens will be stored indefinitely for future research at the biorepositories at a central biorepository. For the U.S., the respective biorepository is Indiana University School of Medicine, Indianapolis, U.S. may be used for ethically approved research. Access for future use of those specimens will be via a Specimens and Data Access Committee.

Sample sharing will be aligned with the principles of Good Clinical Practice (GCP) in research and in line with data protection laws with academic and industry partners to accelerate novel biomarker discovery and assist the development of novel treatment strategies. The reason for the indefinite storage is the highly dynamic field of PD research, in which new aspects often emerge only over time.

Research specimens will be made available to academic and industry researchers to conduct analyses through an application and approval process involving the MJFF LITE Steering Committee. If approved samples will be redistributed from the biorepositories to the collaborating partner, pseudonomized study data may be released with samples. A sample and data transfer agreement will be put in place prior to any transfer.

13 DATA MANAGEMENT

13.1 DATA HANDLING AND RECORD KEEPING

A Participant ID number will be assigned to all participants. The Participant ID number will be used to identify a participant on all study related documentation and specimens. Participants already enrolled in PPMI will have their PPMI ID linked to their LITE ID. This will allow for data connection between LITE participants in PPMI using the dual study IDs for these participants. The PPMI Participant ID number will be used to identify a participant on all study related documentation (e.g., clinical database, biological specimens).

Additional data collected for this study will be maintained and stored indefinitely at the study Cores on secure, password protected systems. All study information (data and samples) will be accessed only by those who require access as pertains to the individual's role in the study. All organizations responsible for data storage and review will observe the highest precautions to ensure data integrity and security.

Data collected for this study may be transferred and shared across participating PPMI Cores including the Clinical Trials Statistical and Data Management Center (CTSDMC) at the University of Iowa, Indiana University PPMI Cores (Indianapolis, IN), the Site Management Core at the Institute for Neurodegenerative Disorders (New Haven, CT), and the Statistical Core at the University of Iowa (Iowa City, IA) for conducting analyses as pertains to the study including, but not limited to, enrollment, compliance, study outcomes and, in combination from the data received from other PPMI Program studies

All data obtained during the conduct of PPMI will be sent to the Laboratory of Neuro Imaging (LONI) in Los Angeles, California to be stored indefinitely for research purposes. Research data will be made available by request to the LITE study from previously completed PPMI visits. Researchers will be required to comply with the PPMI data agreement to access data. All personally identifiable information will be removed before it is shared in LONI outside the study.

LITE specific research biosamples will be shipped to Dundee for the conduct of LITE activities by the biorepository, and stored indefinitely for research purposes at the Biorepository Cores at Indiana

University School of Medicine. All personally identifiable information will be removed before biosamples are shared with the biorepository or outside the study.

13.2 13.2 ACCES TO DATA

The PIs (Principal Investigator) and site investigators (SIs) at all institutions involved in the study will permit study related-monitoring, audits, Research Ethics Committee review, and regulatory inspection. In the event of an audit or inspection, the PI and/or SIs will allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all study records and source documentation. Please refer to the U.S. PPMI -LITE study operations manual.

13.3 DATA COLLECTION TOOLS

13.3.1 CLINICAL AND ASSESSMENT DATA

The SI or delegated staff will be responsible for maintaining accurate and complete source documents for each participant in the study. Source documents will include, but are not limited to: medical information, laboratory data, imaging results, study questionnaires and the results of any other tests or assessments. The questionnaires will be completed by the participants and act as source data, the completed forms will be filed in the Investigator Source File (ISF). Only source documents completed for the LITE study will be filed in the ISF.

An electronic Case Report Form (eCRF) will be provided by the Institute of Neurogenetics, University of Lubeck. The study system will be based on the protocol for the study. Development and validation of the study database and quality control will be done according to University of Lubeck Standard Operating Procedures (SOPs). The eCRF will not collect more information than is required to meet the aims of the study and to confirm the eligibility and safety of the participant.

The eCRF will allow the collection of data related to consent and eligibility review, general activities, clinical assessments and questionnaires. Data previously collected at a PPMI visit will not be included in the LITE eCRFs and will be available via PPMI data repository.

The SI may delegate eCRF data entry but is responsible for completeness, plausibility, and consistency of the eCRF. Delegated study staff will be trained on the protocol, data entry conventions, and definitions prior to eCRF use. These delegated team members will enter the data required by the protocol into the eCRFs following training in the definitions and methods used in completing the eCRF. Any queries will be resolved by the PI or delegated member of the study team.

Data verification, cleaning and data extraction will be performed as per Institute of Neurogenetics, University of Lubeck local SOPs. The University of Lubeck team will perform plausibility checks and contact participating sites if any discrepancies occur. The eCRF will have restricted fields to ensure high data quality. All electronic data will be stored on secure University of Lubeck or cloud-based servers which have restricted access and have disaster recovery systems in place. Documentation related to data management activities, such as eCRF completion guidelines, training records, and query resolution logs, will be retained in the Trial Master File (TMF) and ISF, as appropriate.

13.4 BIOLOGICAL SAMPLE DATA

Raw data results as well as analyzed data from biological samples carried out at collaborating laboratories (e.g. University of Luebeck, University of Manchester) and contract research organizations will be transferred to the data & imaging repository using secure data transfer systems, unless previously collected at a PPMI visit.

Additionally, analyzed data and results may also be transferred to the PPMI data repository.

Integrated data analysis will be coordinated by the University of Dundee and the LITE steering committee as well as relevant research collaborators.

All biological sample data will only be identified by participant ID number and no identifiable data will be transferred.

13.5 IMAGING DATA

Usable MRI and DaTSCAN™ data collected in the PPMI study LITE participants will be available for the LITE study via download from the PPMI imaging data repository.

13.6 ARCHIVING

Archiving study documents will be the responsibility of individual sites. Each site will archive their own Study Master File in accordance with their institutional policies and applicable regulations. All essential study documents must be retained for a minimum of 5 years following the Last Participant Last Visit (LPLV) at that site or longer, if required by local regulations, contractual obligations, or Sponsor requirements. U.S. sites will utilize a standardized electronic trial master file managed by the Institute for Neurodegenerative Disorders through a third-party provider, Florence.

Archiving practices will follow Sponsor and site Standard Operating Procedures (SOPs). Medical records and other source documents will be maintained in compliance with applicable U.S. federal and state regulations, including FDA regulations for record retention (21 CFR 312.62 and 21 CFR 812.140), and HIPAA requirements for protected health information.

The IND team will be responsible for arranging the archiving and maintenance of the electronic Trial Master File for the U.S. PPMI-LITE sites. All archived documents must remain accessible for inspection by regulatory authorities upon request Pseudonymized Study.

DATA SHARING

All data collected for this study will be pseudonymized (Participant ID) and stored indefinitely in a secure, password-protected database. All study information (data and samples) will be accessed only by those who require access as pertains to the individual's role in the study. All organizations responsible for data storage and review will observe the highest precautions to ensure data integrity and security.

No personally identifiable information will be shared outside the study site unless explicit consent has been given. It is the responsibility of the Principal Investigator and site investigators (SIs) to assure that the confidentiality of participants, including their personal identity and personal medical information, will be maintained at all times. If participants choose to take part in this study, they agree that their pseudonymized clinical data may be shared with MJFF (the study funder) and MJFF affiliated organizations.

13.6.1 DATA SHARING – GP2

The Global Parkinson's Genetics Program (GP2) is a resource program of the Aligning Science Across Parkinson's (ASAP) initiative focused on improving the understanding of the genetic architecture of Parkinson's disease (PD) and making this knowledge globally relevant. GP2 is made up of member organizations around the world that are coming together to create a global research community dedicated to rapidly addressing emerging research needs in PD. GP2's work is aimed at using genetic knowledge to accelerate the path to the development and deployment of therapeutic strategies for PD.

In support of the mission, GP2 collects diverse cohorts from around the world through collaboration and openly sharing data, processes, and results.

The LITE study clinical data set will be shared with GP2 and made available along with the genetic results to collaborators of GP2 according to their access requirements.

13.6.2 DATA SHARING – BRIDGE ANALYTICS DATA REPOSITORY

Bridge Analytics, San Francisco, USA, is a company devoted to supporting the mission of making it easier for researchers to access and analyze existing data that can drive clinical and scientific impact of disorders and diseases impacting the central nervous system. Pseudonymized data from the LITE study will be sent regularly (e.g., monthly, quarterly, annually) to long-term data repository owned by Bridge Analytics. The purpose of this data sharing is to make the data available to qualified researchers in the future, enabling the advancement of general research and knowledge of disease. Data deposited will be stripped of identifying information before transferring to Bridge Analytics as described in the "Privacy and Confidentiality" section of this protocol. Access to the data is controlled and requires researchers to agree to terms of use that include maintaining confidentiality and not redistributing the data. Data may be retained indefinitely to maximize its potential for future research. Future transfer of data to other data repositories may occur where these repositories meet the above criteria for secure storage and access. Bridge Analytics may access data collected in a PPMI visit from the PPMI LONI data repository.

14 STUDY ANALYSIS

14.1 ANALYSIS PLAN

In order to translate our understanding of the basic biology into specific therapies and biomarkers for future trials, the LITE study focuses on the standardized collection of clinical, genetic, imaging and other data as well as data from biological samples from LRRK2 and other genetic PD manifesting and non-manifesting carriers and matched idiopathic PD and healthy controls. The deep phenotyping of these samples through the use of targeted assays (multiomic mass-spectrometry analysis of OrganelleIPs in particular of lysosomes, LRRK2 pathway and PD relevant targeted and untargeted studies, alpha-synuclein aggregation assays etc.) and unbiased approaches (proteomics, metabolomics, lipidomics) of the collected biosamples will shed light on the mechanisms and targets that play a role in these genetically-driven forms of PD. Importantly, this could also help to explore and translate molecular signatures related to the LRRK2-driven prototypes to the large and heterogenous group of people with idiopathic PD in order to stratify these for molecular pathway-specific trials. Moreover, this consortium will be a unique source following a trial-ready cohort. Importantly, clinical data and specimens will be made available to researchers to conduct analyses through an application process to the steering committee. Special focus will be given to the following analyses:

(I) Identify molecular / biological signatures that differ between LRRK2-associated PD, other monogenic and idiopathic PD,

(II) Identify molecular / biological signatures that differ between manifesting and non-manifesting monogenic (e.g. LRRK2) carriers

(III) Compare molecular signatures between different types of PD (monogenic, genetic risk and idiopathic PD) and use these signatures to stratify the heterogenous group of idiopathic PD for LRRK2-driven disease.

(IV) Translate a “LRRK2-driven Signature” as defined by the minimal required data- and bio-sample set to idiopathic (and other) PD subtypes enabling stratification of idiopathic PD for “LRRK2-targeting” trials

14.2 GENETICS

All participants may have a blood sample taken for genetic analysis to identify PD related variants and disease related genetic signatures. Relevant samples will be analyzed by GP2 at Psomagen, United States for research grade whole genome sequencing and the University of Luebeck, Germany for additional genetic analysis.

14.3 CLINICAL AND ASSESSMENT DATA

An integrated clinical and assessment data analysis will be carried out by the Universities of Lubeck and Dundee.

14.3.1 14.4 MRI AND DATSCAN IMAGING

Usable MRI and DaTSCAN™ data collected in the PPMI study LITE participants will be available for the LITE study via download from the PPMI imaging data repository.

14.4 DATSCAN™ IMAGING

DaT SPECT scan semiquantitative analysis, image receipt and QC will be done by the CORE imaging provider (XingImaging). Data and imaging collected as part of PPMI for individuals co-enrolled in LITE in the US will be analyzed together with additional DaT SPECT data collected at other non-US LITE sites. Image collection for non-US LITE sites will be performed by qualified imaging centers setup by the Core imaging provider per the Technical Operations Manual (TOM). No new DaT SPECT will be obtained in the US as part of LITE study activities.

All workflows are already established within the MJFF-funded PPMI study.

15 RISKS TO PARTICIPANTS

15.1 BLOOD SAMPLING

Risks associated with venous blood draw include pain and bruising at the site where the blood is taken. Sometimes people can feel lightheaded or even faint after having blood drawn. To avoid such events, blood drawing will be performed in a sitting or lying position.

15.2 SKIN SWABS

A skin swab is a non-invasive and low-risk procedure. Participants may experience some irritation or discomfort at the site of the swab.

15.3 BREATH SAMPLE

This is a low-risk and non-invasive procedure. Participants may experience discomfort and dizziness during or after the breath biopsy due to hyperventilation and fatigue

16 POTENTIAL BENEFITS TO PARTICIPANTS

There are no direct anticipated benefits to study participants in this study. However, new information may be generated by the study that will support development of better treatments and diagnosis for PD.

16.1 CLINICALLY RELEVANT FINDINGS AND SHARING PERSONAL RESEARCH INFORMATION

If an assessment, lab, or imaging study reveals a clinically significant abnormality (e.g., MRI structural lesion, abnormal laboratory result), the SI will inform the participant of this result and, with their consent, instruct follow up with his or her primary or secondary care provider. Should there be a safety concern warranting a referral for medical or psychiatric follow-up, the investigator team will provide the participant with the appropriate referral as necessary. The standard clinical care pathways for clinically urgent and non-urgent medical situations identified during study visits will be followed. Participants will be made aware that this may involve their primary or secondary health care providers.

In addition to the standard of care/clinically relevant results described above, personal research findings may be returned in the future. No personal research findings will be routinely returned to participants unless they opt in to receive such information..

There may also be research results (for example, information about a diagnosis made by the Investigator) that could impact individual decisions about the participant's clinical care. At the discretion of the Site Investigator these research findings may be discussed with the participant.

17 COSTS FOR PARTICIPATION

Assessments and tests will be provided at no cost to the study participant.

18 PARTICIPATION IN CLINICAL TRIALS / CO-ENROLLMENT IN OTHER STUDIES

Participation in another observational study or some device studies may be compatible with co-enrollment in the LITE study. However, participation in a clinical trial testing a novel IMP may not be compatible with eligibility for the LITE study (e.g., if someone is taking part in a double-blind, placebo-controlled trial testing a new disease-modifying treatment for PD, it would not be clear whether any potential changes in the biological samples are because of the investigational medicinal product or not). The final decision regarding eligibility is made by the PI/SI.

19 PAYMENT AND REIMBURSEMENT FOR PARTICIPATION

Participants and, if necessary, a caretaker, will be reimbursed for travel costs to LITE sites in the U.S. and, if required, for accommodation. Participants who require travel to the U.S. LITE sites or incur other costs associated with a study visit will be reimbursed according to the study reimbursement guidelines. Participants will receive funds via the ClinCard system depending on policies and participant preference.
Participants will be offered compensation for completed study visits based on the type of visit and depending on site-specific guidelines with regards to reimbursement

20 PARTICIPANT WITHDRAWALS

Study participants will be informed during the consent process that they have the right to withdraw from the study at any time without prejudice and may be withdrawn at the Investigator's discretion at any time. Any data and samples that have already been collected prior to the study participant's withdrawal cannot be removed.

21 ADVERSE EVENTS

21.1 DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant.
Serious Adverse Event (SAE)	A SAE is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalization or prolongation of existing hospitalization • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect

Term	Definition
	Other 'important medical events' may also be considered serious if they jeopardize the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

To avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

21.2 ADVERSE EVENT REPORTING REQUIREMENTS

Study staff will be instructed to inform the participants about potential adverse events. The participants are provided PPMI-LITE team contact information, detailed in the informed consent form, allowing them to directly contact the study team. Only AEs assessed by the SI and/or PI to be associated with study participation will be recorded, AEs will be recorded on the AE Log in the eCRF. Details of AEs will be recorded in the participant's research record. AEs will be recorded from the time a participant consents to join the study until the participant's last study visit. Participants will be requested to contact the study team if they experience any adverse events for up to 10 days post last visit. Participants with unresolved AEs/SAEs at the end of the study will be followed up until 30 days after participant's last visit.

Adverse events will be reported by the site as required by the site's Institutional Review/Ethics Board and to the Radiation Safety Committee, as applicable.

21.2.1 SERIOUS ADVERSE EVENT REPORTING REQUIREMENTS

Serious adverse events pertaining to any study procedure will be reported.

SAEs will be reported to the Sponsor, the Investigator will comply with his/her local Institutional Review Board (IRB)/Ethics Board, and Radiation Safety Committee (as applicable), regarding the reporting of adverse experiences.

21.2.2 ASSESSING RELATIONSHIP OF ADVERSE EVENTS

The assessment of the relationship of an AE a study procedure is a clinical decision based on all available information at the time the event is being documented. The following definitions of the relationship between the AE (including SAEs) and the study procedure should be considered:

- Unrelated - No possible relationship
- Unlikely - Not reasonably related, although a causal relationship cannot be ruled out.
- Possible - Causal relationship is uncertain
- Probable - High degree of certainty for causal relationship
- Definite - Causal relationship is certain

21.2.3 ASSESSING INTENSITY/SEVERITY OF ADVERSE EVENT

In addition to assessing the relationship of the adverse event to the study procedure, an

assessment is required of the intensity (severity) of the event. The following classifications should be used:

- Mild: A mild AE is an AE, usually transient in nature and generally not interfering with normal activities.
- Moderate: A moderate AE is an AE that is sufficiently discomforting to interfere with normal activities.
- Severe: A severe AE is an AE that incapacitates the participant and prevents normal activities. Note that a severe event is not necessarily a serious event. Nor must a serious event necessarily be severe.

22 MONITORING AND SITE MANAGEMENT

A member from the LITE initiative executive committee is part of the LITE study's Steering Committee with additional independent members as well as patient and public engagement representatives. The Steering Committee, or designee will monitor all procedures for safety, GCP, and regulatory compliance. The study will be managed and overseen in an ongoing manner to verify:

(a) The rights and well-being of human participants are protected.

(b) The reported study data are accurate, complete, and attributable.

(c) The conduct of the study follows the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

The Sponsor may Monitor and/or audit the study for compliance.

23 PUBLIC AND PATIENT ENGAGEMENT

Patient and public engagement is an essential part of the LITE initiative and all MJFF funded initiatives. Members from the Dundee Parkinson's UK Research Interest Group (DRIG) – people living with or affected by PD – have been involved in the protocol development and their feedback has been incorporated into the study documents. DRIG representatives will be part of the LITE Study Steering Committee. Additionally, the LITE study documents have undergone a quality by design assessment by the MJFF with the aim to make the study as patient centric as possible.

24 PRIVACY AND CONFIDENTIALITY

It is the responsibility of the SI to consider the participant's privacy and confidentiality when completing study visits and related protocol activities.

The SI must assure that the confidentiality of participants, including their personal identity and personal medical information, will be maintained at all times. Participants will be identified by participant ID numbers on data forms and other study materials, the central laboratory, and central biorepository.

The SI will permit the study monitor or designated representative to review signed informed consent(s) and that portion of the participant's medical record that is directly related to the study (or provide certified copies of source documentation upon request). This shall include all study relevant documentation including participant medical history to verify eligibility, laboratory test result reports, admission/discharge summaries for hospital admissions occurring while the participant is in the study. Only study staff requiring access to related study documentation will have permission to view identifiable information.

25 REFERENCES

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26 APPENDIX 1: SCHEDULE OF PROCEDURES

Procedures *(International sites should indicate if any study procedures **are not** being carried out at that site)*	**Participants consented for all procedures**[a]
Consent and Eligibility Review	
Informed consent	X
Eligibility review	X
General Activities	
Family History of Dementia	X
Treatments including concomitant medications	X
Collection/reporting of adverse events (AEs)	X
Core Clinical and Biological Samples	
Clinical lab blood sample[1]	X
Research blood samples including genetics	X
Skin swab	X
Breath sample	X
Core Clinical Assessments (including physical, neurological examination and cognitive tests) (information obtained from PPMI Clinical Data Collection may be requested)	
Vitals signs – Pulse, supine & standing blood pressure, and temperature	X
Weight & height	X
Questionnaires (information obtained from PPMI Clinical Data Collection may be requested)	
Risk factor and exposure questionnaires (MERQ-PD)	X

[a] Visits can be split across multiples days as necessary to accommodate all procedures, all of which should be completed within 30 days of visit 1

[1] Includes blood for PMBC collection as well as differential white blood cell count