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# Complete Research Protocol (HRP-503)

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## *Template Instructions*

***Sections that do not apply:***

- *In several sections, the addition of checkboxes for **Not Applicable** have been added to the template as responses.*
    - *If an N/A checkbox is present, select the appropriate justification from the list.*
    - *If an N/A checkbox is not present, or if none of the existing checkboxes apply to your study, you must write in your own justification.*
- *In addition:*
    - *For research where the only study procedures are records/chart review: Sections 19, 20, 22, 23, 24, 25, 31, and 32 do not apply.*
    - *For exempt research: Sections 31 and 32 do not apply.*

***Studies with multiple participant groups:***

- *If this study involves multiple participant groups (e.g. parents and children), provide information in applicable sections for each participant group. Clearly label responses when they differ. For example:*

| **Response Example** |
| --- |
| Intervention Group: |
| Control Group: |

***Formatting:***

- *Do not remove template instructions or section headings when they do not apply to your study.*

*If you are pasting information from other documents using the "Merge Formatting" Paste option will maintain the formatting of the response boxes.*

***Amendments:***

- *When making modifications or revisions to this and other documents, use the **Track Changes** function in Microsoft Word.*
- *Update the version date or number **on Page 3.***

## PROTOCOL TITLE:

Response: Repurposing lithium as a disease-modifying therapy in Parkinson's disease: A Phase I trial.

## PRINCIPAL INVESTIGATOR:

Response: Thomas Guttuso, Jr., MD; Department of Neurology; 716-932-6080; tguttuso@buffalo.edu

## VERSION NUMBER/DATE:

Response: Version 4/11-30-23

## REVISION HISTORY

| Revision # | Version Date | Summary of Changes | Consent Change? |
|---|---|---|---|
| 1 | 1/29/20 | Adding 2 MRI scans | yes |
| 2 | 3/30/23 | 1) Adding 15 patients.<br>2) All new patients will receive medium-dose lithium therapy.<br>3) The Week-12 study visit will be eliminated.<br>4) There will be some changes to the blood-based biomarkers assessed. | yes |
| 3 | 5/30/23 | Added language required by CTRC regarding MRI data storage and transmission. | no |
| 4 | 11/30/23 | Parking fee reimbursement for subjects | no |
| | | | |

## FUNDING:

*Indicate any funding for this proposal. This should match the Funding Sources page in Click IRB.*

*Response:* UB Clinical and Translational Science Award (CTSA) under UL1TR001412.

## GRANT APPLICABILITY:

*Indicate whether this protocol is funded by a grant (e.g. NIH, foundation grant). For a grant with multiple aims, indicate which aims are covered by this research proposal.*

*NOTE: This question does not apply to studies funded by a sponsor contract.*

*Include a copy of the grant proposal with your submission.*

*Response: This study is* being funded by a UB Clinical and Translational Science Award (CTSA) under UL1TR001412.

## RESEARCH REPOSITORY:

*Location:* UBMD Neurology

*Address:* 5851 Main Street, Williamsville, NY 14221

*Department:* Neurology

## 1.0 Study Summary

| | |
|---|---|
| **Study Title** | Repurposing lithium as a disease-modifying therapy in Parkinson's disease: A Phase I trial |
| **Study Design** | Open-label |
| **Primary Objective** | Determine if medium-dose lithium aspartate therapy in an additional 15 patients is associated with similar improvements in blood-based therapeutic targets and MRI-based biomarkers as observed in the previous four patients receiving this dosage. |
| **Secondary Objective(s)** | Determine the tolerability of medium-dose lithium aspartate when titrated to a dosage of 30-45mg/day. |
| **Research Intervention(s)/ Investigational Agent(s)** | Lithium aspartate. |
| **IND/IDE #** | IND exempt (#135530) |
| **Study Population** | Parkinson's disease (PD) |
| **Sample Size** | 15 |
| **Study Duration for individual participants** | 25-27 weeks |
| **Study Specific Abbreviations/ Definitions** | Parkinson's disease (PD), Over-the-counter (OTC) |

## 2.0 Objectives*

*2.1 Describe the purpose, specific aims, or objectives of this research.*

Response: *Determine if medium-dose lithium aspartate therapy in an additional 15 patients is associated with similar improvements in blood-based therapeutic*

*targets and MRI-based biomarkers as observed in the previous four patients receiving this dosage.*

*2.2 State the hypotheses to be tested, if applicable.*

*NOTE: A hypothesis is a specific, testable prediction about what you expect to happen in your study that corresponds with your above listed objectives.*

Response: Lithium therapy will engage one or more blood-based therapeutic targets and MRI-based disease-progression biomarkers implicated in PD pathophysiology.

## 3.0 Scientific Endpoints*

*2.1 Describe the scientific endpoint(s), the main result or occurrence under study.*

*NOTE: Scientific endpoints are outcomes defined before the study begins to determine whether the objectives of the study have been met and to draw conclusions from the data. Include primary and secondary endpoints. Some example endpoints are: reduction of symptoms, improvement in quality of life, or survival. Your response should* ***not*** *be a date.*

Response:

Primary Outcome Measures:

- Clinical Adverse Events assessed at screening, Baseline (BL), and week 24 as well as during a phone call at week 12.
- Blood safety laboratory assessments at screening and week 24 (CBC, CMP, TSH, calcium, ESR, urate, HgA1C and trough serum lithium performed by Kaleida Laboratory Services).
- MRI-based disease-progression biomarkers at BL and week 24:
  - Posterior substantia nigra (pSN), nucleus basalis of Meynert (nbM) and dorsomedial nucleus of the thalamus (DMN-T) free water (FW) levels.
- Blood-based therapeutic targets at BL and week 24:
  - PBMC Nurr1 mRNA levels by real-time polymerase chain reaction (PCR).

Secondary Outcome Measures at BL and week 24:

  - PBMC SOD-1 mRNA levels by PCR, PBMC phosphorylated (p) and total (t) levels of pS9 and t-GSK-3β; pThr308, pS473 and t-Akt (both t and the ratio of p/t will be used for each data point) and plasma interleukin-6 (IL-6) levels by ELISA.
- Trough, steady-state plasma lithium levels assessed by the UB Chemistry Instrument Center utilizing an inductively coupled plasma mass spectrometer (ICPMS) at BL and week 24.
- Clinical Assessments at BL and week 24:
  - Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Part III (Motor Examination).[1]
  - Parkinson's Anxiety Scale.[2]
  - Geriatric Depression Scale-15.[3]
  - Fatigue Severity Scale.[4]
  - Insomnia Severity Index.[5]
  - Parkinson's Disease Questionnaire-8.[6]
- Montreal Cognitive Assessment (MoCA) at screening and week 24.[7]

## 4.0 Background*

*4.1 Provide the scientific or scholarly background, rationale, and significance of the research based on the existing literature and how it will contribute to existing knowledge. Describe any gaps in current knowledge. Include relevant preliminary findings or prior research by the investigator.*

Response:

Background and Preliminary Data:

Parkinson's disease (PD) is the second most common and fastest growing neurodegenerative disorder with a worldwide prevalence that is predicted to more than double over the next 25 years.[8] Although there are several FDA-approved therapies to mask the tremor, stiffness and slowness motor symptoms of PD, no therapies have been shown to slow the progressive worsening of motor symptoms nor the onset of dementia that occurs, on average, within 10 years of diagnosis and represents the most disabling long-term PD sequela.[9-12] In order to identify therapies that can slow disease progression (both motor and cognitive symptom progression) and improve PD patients' prognosis, a.k.a "disease-modifying therapies", such therapies will first need to show positive effects on therapeutic targets and known disease-progression biomarkers.

A PD therapeutic target of interest for over 25 years is the nuclear receptor-related 1 protein (Nurr1), [13-15] which is a transcriptional cofactor that upregulates genes essential for dopamine neuron differentiation and survival.[16,17] Loss of dopamine neurons in the brain's substantia nigra (SN) results in dopamine deficiency and the consequent PD motor symptoms upon which the clinical diagnosis is made. Nurr1 levels decrease in the brain by 46% with aging,[18] which is the main risk factor for PD. In PD patients, Nurr1 message is reduced by an additional 61% in central dopaminergic neurons and peripheral blood mononuclear cells (PBMCs) compared to healthy, aged-matched controls, is inversely correlated with intraneuronal alpha-synuclein levels and ameliorates alpha-synuclein-mediated dopamine cell toxicity.[14,19-22] Because alpha-synuclein protein intraneuronal aggregation and inter-neuronal spread is believed to be a principle mediator of the progressive degeneration of neurons in PD,[23] therapies that can increase Nurr1 expression would represent promising disease-modifying therapies. In addition to accumulating and spreading alpha-synuclein, the processes of chronic inflammation and oxidative stress also appear to be critical to the progressive neurodegeneration in PD.[23,24] Experimental models have shown that when Nurr1 levels are depressed, brain cells become vulnerable to insults and die.[20,25] One of the genes under the control of Nurr1 is superoxide dismutase-1 (SOD-1),[26] which is a key brain enzyme to reduce oxidative stress. Nurr1 also decreases the expression of alpha-synuclein and reduces inflammation stemming from the brain's principle macrophage, microglia.[19,27] Thus, increasing Nurr1 expression alone can reduce all three processes critical to progressive neurodegeneration in PD (accumulating alpha-synuclein, chronic inflammation and oxidative stress). Because PBMC gene expression changes have been shown to mirror similar changes in the brain,[28] PBMC Nurr1 and SOD-1 expression represent promising blood-based PD therapeutic targets.

Lithium has multiple neuroprotective actions including suppressing microglial activation, reducing inflammation and oxidative stress, and enhancing autophagy and mitochondrial biogenesis and function.[29-33] Lithium treatment has demonstrated benefit in several Parkinson's disease (PD) animal models.[34-37] Also, the 77% risk reduction of PD in smokers shown in prospective cohort studies has been theorized to be due to the high levels of lithium in tobacco.[38] In addition, lithium treatment increases Nurr1 expression by about 180% and protects against rotenone-induced death in PC12 cells.[39] Additional blood-based PD therapeutic targets that lithium may engage include serum brain-derived neurotrophic factor (BDNF), plasma alpha-synuclein and the inhibited form of glycogen synthase kinases-3β, phosphorylated at serine 9 (pS9-GSK3β), in PBMCs.[40-42]

Because it is unknown if a therapy's ability to engage blood-based therapeutic targets confers any disease-modifying clinical effects in PD, it is more important to determine a therapy's ability to improve known MRI-based disease-progression biomarkers in PD. Previous analyses of a University of Florida (UF) and the Parkinson's Progression Markers Initiative (PPMI) longitudinal PD biomarker cohorts have shown a diffusion-based MRI assessment called free water (FW) in the posterior substantia nigra (pSN) to longitudinally reflect progressive worsening of motor symptoms.[43,44] A more recent PPMI analysis showed increasing FW in the dorsomedial nucleus of the thalamus (DMN-T) and nucleus basalis of Meynert (nbM) to reflect progressive worsening of cognition in PD.[45] FW corresponds to water molecules within a voxel that are not hindered or restricted by the cellular environment and therefore originate from extracellular water.[46] There is pathological evidence that FW reflects tissue atrophy and inflammation,[47,48] which are known to occur in PD. Thus, higher FW levels appear to reflect more advanced tissue degeneration.[43,44,49-51] Thus, a therapy that was shown to slow the longitudinal increases in FW in these brain sites would imply that it was protecting these neurons and, potentially, slowing clinical disease progression. That is, such a therapy would be a highly promising disease-modifying therapy candidate.

Based on the potential disease-modifying effects of the monoamine oxidase inhibitor rasagiline,[52] a recent randomized controlled trial (RCT) assessed rasagiline's effects on pSN FW progression in PD. This RCT showed no significant slowing of pSN FW progression in PD patients randomized to rasagiline compared to placebo for one year.[53] Thus, any preliminary data associating a therapy with slowed or decreasing pSN FW longitudinal changes in PD would be novel and promising.

Preliminary Data:

Based on the above background, we conducted an open-label, randomized, pilot trial assessing the effects of three lithium dosages for six months on both blood-based therapeutic targets and MRI-based disease-progression biomarkers among 16 PD patients. This study was funded by the Buffalo Blue Sky Coin program. Because of the limited amount of funding, MRI scans could only be assessed on seven patients. Nevertheless, this pilot study's results showed the lithium aspartate dosage of 45mg/day to robustly engage the therapeutic targets of PBMC Nurr1 and SOD-1 and also to be associated with longitudinal *reductions* in pSN, DMN-T and nbM FW.

In this pilot trial, 16 PD patients were randomized to "low-dose" or "medium-dose" lithium aspartate (15mg or 45mg/day, respectively) or "high-dose" lithium carbonate therapy titrated to a target trough serum lithium level of 0.4-0.5mmol/L for 24-weeks (clinicaltrials.gov: NCT04273932). Three additional PD patients

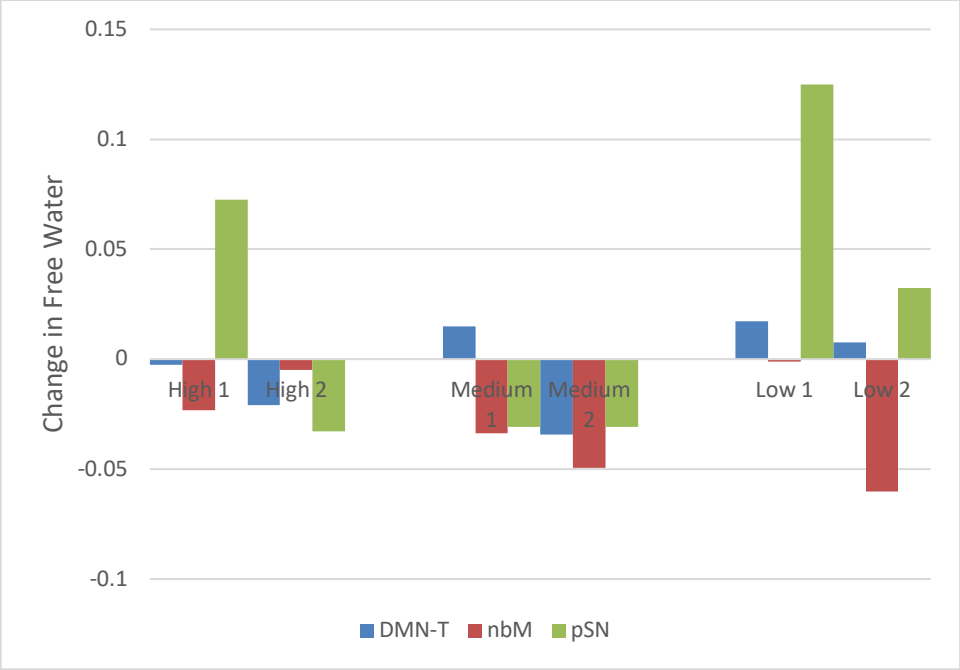
served as controls and did not receive lithium for 24-weeks. Among the six patients receiving medium-dose lithium, two withdrew due to side effects of sedation and brain fog. No other patients reported side effects. One of the patients who withdrew subsequently resumed lithium aspartate at 30mg/day and reported no side effects with a steady-state trough serum lithium level <0.1mmol/L.

Results showed PBMC Nurr1 mRNA levels increased by 420%, 679%, 93% and 139% in the high, medium and low-dose lithium and control groups, respectively, after 24-weeks. Because an *in vitro* study showed that a 180% increase in Nurr1 protected neuronal cells from rotenone-induced death,[39] we defined a "Nurr1 responder" as having a 6-month Nurr1 increase of >200%. With this definition, the Nurr1 responder rates for each lithium dosage and controls were 20%, 75%, 20% and 0%, respectively. Serum lithium levels at six months were 1282, 828, 195 and 0.73µg/L, respectively. In addition, PBMC SOD-1 mRNA increased by 18%, 127%, -1% and 8%, respectively, and by 125% and -21% in Nurr1 responders and non-responders, respectively, after six months. Lithium treatment did not appear to affect PBMC pS9/total glycogen synthase kinase (GSK-3B) ratio levels or plasma alpha-synuclein levels in a dose-response manner.

Thus, the medium-dose lithium group (45mg/day of lithium aspartate) showed the most robust engagement of the PD therapeutic targets Nurr1 and SOD-1 but resulted in severe side effects in 1/3 of the patients. It is unclear why the medium-dose group would show more robust target engagement and more clinical side effects than the high-dose group despite having 35% lower serum lithium levels. We hypothesize that lithium may dissociate from the salt carrier aspartate more readily than from carbonate and/or cross cellular barriers more readily resulting in higher serum and/or intraneuronal "free lithium" levels at equivalent elemental lithium dosages of the two formulations. Because commercial lithium assays typically assess total, not free lithium levels, biological assays like PBMC Nurr1 expression represent a more objective way to compare dose-response relationships among different lithium formulations. This study's findings of numerically higher magnitudes of PBMC Nurr1 and SOD1 mRNA expression associated with medium-dose lithium aspartate versus high-dose lithium carbonate support this hypothesis. In addition, one of the medium-dose lithium aspartate patients who withdrew due to side effects when receiving 45mg/day subsequently reported no side effects when receiving 30mg/day with a steady-state trough serum lithium level <0.1mmol/L. At 45mg/day of lithium aspartate, the highest predicted serum lithium level in this patient would be about 0.15mmol/L, which would be extremely unlikely to produce side effects if derived from lithium carbonate therapy. In support of this hypothesis, a recent study showed 10-100-fold disparate potencies of several different lithium formulations when assessed on an array of biological assays.[54]

In addition to the blood-based therapeutic target results, the MRI FW results also supported medium-dose lithium aspartate as the most promising dose for further study. Out of the seven patients who received MRI scans at baseline and after 24-weeks of lithium therapy, six had reliable scan data at both timepoints (Figure 1).

Figure 1: Individual Patient Changes in FW after 24-weeks of High, Medium or Low-Dose Lithium Therapy




FW: free water, DMN-T: dorsomedial nucleus of the thalamus, nbM: nucleus basalis of Meynert, pSN: posterior substantia nigra

Table 1 shows the mean longitudinal FW changes in each of these regions of interest (ROIs) in lithium treated PD patients from this pilot study and well as non-lithium treated PD patients and healthy controls (HCs) from the UF and PPMI longitudinal cohorts (some data provided by Niels Bergsland). It can be seen that the medium-dose lithium treated group was the only group showing mean longitudinal *reductions* in FW in all three ROIs, which is in contrast to the known natural history of FW progression in PD seen in the UF and PPMI cohorts. These findings suggest that medium-dose lithium therapy is associated with improved neuronal integrity and/or reduced inflammation in these important PD ROIs.

**Table 1: Mean FW Longitudinal Changes from Pilot Lithium/PD Trial, UF and PPMI Longitudinal Cohorts**

| | **Mean Change in DMN-T FW** | **Mean Change in nbM FW** | **Mean Change in pSN FW** |
|---|---|---|---|
| **High-Dose Lithium** (24-Week Changes) | -0.0117 (*n*=2) | -0.0140 (*n*=2) | 0.0198 (*n*=2) |
| **Medium-Dose Lithium** (24-Week Changes) | -0.0098 (*n*=2) | -0.0416 (*n*=2) | -0.0307 (*n*=2) |
| **Low-Dose Lithium** (24-Week Changes) | 0.0123 (*n*=2) | -0.0306 (*n*=2) | 0.0787 (*n*=2) |
| **PD from UF** (1-Year Changes) | --- | --- | 0.038[44] (*n*=25) |
| **Aged-Matched HCs from UF** (1-Year Changes) | --- | --- | 0.001[44] (*n*=19) |

| | | | |
|---|---|---|---|
| **PD from PPMI** (1-Year Changes) | 0.0100 ± 0.030[45] (*n*=130) | 0.0025 ± 0.041[45] (*n*=130) | 0.0180 ± 0.055[43] (*n*=103) |
| **Aged-Matched HCs from PPMI** (1-Year Changes) | 0.0005 ± 0.024[45] (*n*=58) | -0.0085 ± 0.034[45] (*n*=58) | 0.0070 ± 0.030[43] (*n*=49) |

FW: free water, PD: Parkinson's disease, UF: University of Florida, PPMI: Parkinson's Progression Markers Initiative, DMN-T: dorsomedial nucleus of the thalamus, nbM: nucleus basalis of Meynert, pSN: posterior substantia nigra, HC: healthy control.

In summary, this pilot study showed medium-dose lithium therapy to have the most robust therapeutic target engagement of PBMC Nurr1 and SOD-1 mRNA expression and the most robust improvements in known MRI disease-progression biomarkers but to also have a high rate of side effects. Also, these results stem from only four and two patients receiving this lithium dosage with blood-based and MRI biomarker data, respectively. If similar results were found in a larger number of PD patients treated with medium-dose lithium therapy in a manner to improve clinical tolerability, such preliminary data would form a strong grant application to the Michael J Fox Foundation and/or the NIH to support a larger RCT.

*4.2 Include complete citations or references.*

Response: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## 5.0 Study Design*

*5.1 Describe and explain the study design (e.g. case-control, cross-sectional, ethnographic, experimental, interventional, longitudinal, observational).*

Response:

We will enroll 15 additional PD patients within five months. Eligible patients will have PD for <4 years diagnosed by a movement disorder specialist (Drs. Guttuso or Sirica), be 45-80 years old, have normal thyroid and renal function at the screening visit, have no previous exposure to lithium therapy, have no history of brain surgery, have no hx of brain imaging findings suggesting another neurological condition besides PD, have no use of tobacco or THC products for >1 year, have stable PD medications for >30 days without current need for adjustments in the investigator's opinion, and have stable psychiatric and diuretic medications for >60 days with no anticipated need for changes for at least 24 weeks.

All patients will receive medium-dose lithium aspartate therapy (30-45mg/day) for 24 weeks ensuring that the study will be completed within 12 months. The following dose titration will be used in order to minimize side effects: 10mg bid x 1 week, then 15mg bid x 1 week, then 20mg bid x 2 weeks, then 20mg qAM and 25mg qhs thereafter. Patients will be contacted weekly over the first 4-6 weeks to assess for side effects that are likely to be due to lithium, such as sedation, dizziness or confusion. If side effects occur and are bothersome to the patient, the dose will be decreased incrementally to a minimum of 30mg/day. Such a design will enable identification of the maximum tolerated dose for study in a future trial and maximize the number of patients receiving the most promising dose (45mg/day) identified in the previous pilot clinical trial. Blood-based biomarkers and MRIs will be assessed at baseline and 24 weeks.

The primary blood-based biomarker outcome measure will be change in PBMC Nurr1 mRNA expression from baseline to 24 weeks, which will be compared with the data from the three control PD patients from the pilot study using ANCOVA. PBMC mRNA expression will be assessed by quantitative real-time PCR using TaqMan probes to match the pilot study's methodology. Based on the

22% standard deviation among the three control patients and the 540% treatment effect size for the primary outcome from the pilot study results, only two patients would be needed to detect a difference with 95% power at a 2-tailed alpha of 0.05. Secondary outcome measures will include 24-week changes in PBMC SOD-1 expression, PBMC pS9/total glycogen synthase kinase-3B (GSK-3B) and pThr308, pS473 and t-Akt and plasma interleukin-6 (IL-6) levels. Blood-based biomarkers will be assessed by Luciana Frick, PhD. Statistical analyses will be performed by Greg Wilding, PhD.

The primary MRI outcomes will be 24-week MRI changes in DMN-T, nbM and pSN FW. Using ANCOVA, these outcomes will be compared with the known natural history of such changes in PD derived from the UF and PPMI longitudinal cohorts summarized in Table 1. In addition, secondary comparisons will be made between changes in these lithium-treated patients and age-matched and disease-duration-matched PD subsets from PPMI.

Exploratory clinical outcomes will include changes in Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III (Motor Examination) with subjects in the "on" state,[1] Montreal Cognitive Assessment (MoCA),[7] Parkinson's Anxiety Scale,[2] Geriatric Depression Scale-15,[3] Fatigue Severity Scale,[4] Insomnia Severity Index[5] and Parkinson's Disease Questionnaire-8.[6] Adverse events and medication compliance will be assessed at a three month phone call. Trough serum lithium and safety labs including HgA1C will be assessed at each visit. Because both baseline and on-treatment lithium levels will mostly be below the level of detection using conventional clinical laboratory services (i.e. Kaleida or Quest), these assays will be performed by the UB Chemistry Instrument Center under the direction of Valerie Frerichs, PhD. A protocol was developed by Drs. Guttuso and Frerichs for these assays for the pilot study that provided reliable results able to detect baseline lithium levels in all patients prior to initiation of lithium therapy.

The MRI protocol will include a 3D T1-weighted image that will be optimized with the new Philips 3T scanner. Similarly, a multi-shell diffusion weighted imaging acquisition will also be optimized for free water imaging. We will use a sequence with a longer repetition time (6400ms) in order to avoid aliasing T1 effects.[55] In addition, a b=0 image will be acquired with opposite phase encoding to facilitate susceptibility-induced geometric distortions. 3D T1-weighted images will be corrected for intensity inhomogeneity using the N4 tool and subsequently segmented using the SIENAX tool[56] to obtain partial volume estimate maps of the grey matter. The nbM will then segmented as previously described.[57] Briefly, a histologically defined map of the nbM[58] will be brought into the native 3D T1-weighted image space for each scan via non-linearly warping with Advanced Normalization Tools.[59] In addition, each 3D T1-weighted image will be processed using the FreeSurfer 6.0 pipeline[60] along with the thalamic nuclei segmentation submodule.[61] Outputs will be visually inspected for errors and misclassification. Manual corrections to the FreeSurfer output (e.g., introduction of white matter control points, editing of brain mask, white matter mask) will be made as appropriate. For obtaining a mask of the DMN-T, the following individual nuclei will be combined into a single segmentation: paratenial, reuniens (medial ventral), mediodorsal medial magnocellular and mediodorsal lateral parvocellular. pSN regions of interest (ROI) will be obtained using previously published methodology.[44] Briefly, the b=0 image will be aligned to MNI space using an affine registration. Next, the pSN will be drawn using ROIs that include 10 voxels that span two axial slices on each image. The dorsal slice will contain a rectangular

region of interest of six voxels (2 × 3) and the ventral region of interest will consist of a square region of interest of four voxels (2 × 2). The resulting ROIs will then be brought back into native space using the corresponding inverse transformation. Finally, the nBM and DMN-T maps will be brought into the diffusion space using boundary based registration[62] between the 3D T1-weighted image and the b=0. The maps of the nBM, DMN-T, and pSN in diffusion space will be used to obtain free water values within each ROI.

The diffusion-weighted imaging acquisition will be corrected for susceptibility-induced and eddy current/subject movement-induced distortions using a combination of the FSL tools topup [63] and eddy.[64] Next, the corrected diffusion weighted data will be processed with the free water elimination model[65] implemented in DIPY (https://dipy.org) to obtain free water maps. Occipital FW changes will serve as an internal quality control since this ROI is known to have relatively small longitudinal FW changes over 1 year in PD. For example, data from PPMI showed 1-year pSN and occipital FW changes in PD to be 11.6% and 0.25%, respectively. In the lithium/PD pilot study, 24-week occipital FW changes ranged from -8% to 5% among the six patients with valid MRI scans. In the proposed study, patients with occipital FW changes of at least 14% from baseline to Week 24 will be excluded from the MRI outcome analyses as such changes would indicate an MRI acquisition anomaly at either visit.

# 6.0 Study Intervention/Investigational Agent

1.1 Description: *Describe the study intervention and/or investigational agent (e.g., drug, device) that is being evaluated.*

Response:

Lithium aspartate (OTC dietary supplement).

*6.1 Drug/Device Handling: If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.*

- *If the control of the drugs or devices used in this protocol will be accomplished by following an established, approved organizational SOP (e.g., Research Pharmacy SOP for the Control of Investigational Drugs, etc.), please reference that SOP in this section.*

Response:

Lithium aspartate 5mg capsules will be purchased from e3 Pharmaceuticals, Inc. and manufactured in an NSF-certified facility in accordance with Good Manufacturing Practices (GMP). All study lithium will be stored at room temperature in a locked cabinet at the study site. All study lithium will be confirmed to not expire prior to being dispensed to study subjects.

*6.2 If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:*

- *Identify the holder of the IND/IDE/Abbreviated IDE.*
- *Explain procedures followed to comply with sponsor requirements for FDA regulated research for the following:*

| | ***Applicable to:*** | | |
|---|---|---|---|
| ***FDA Regulation*** | ***IND Studies*** | ***IDE studies*** | ***Abbreviated IDE studies*** |
| ***21 CFR 11*** | ***X*** | ***X*** | |
| ***21 CFR 54*** | ***X*** | ***X*** | |
| ***21 CFR 210*** | ***X*** | | |
| ***21 CFR 211*** | ***X*** | | |
| ***21 CFR 312*** | ***X*** | | |
| ***21 CFR 812*** | | ***X*** | ***X*** |
| ***21 CFR 820*** | | ***X*** | |

Response:

The FDA has issued IND exemption for lithium carbonate use in PD (IND #135530).

## 7.0 Local Number of Subjects

*7.1 Indicate the total number of subjects that will be enrolled or records that will be reviewed locally.*

Response: 15 additional patients (total of 34 including the 19 who have completed the study).

*7.2 If applicable, indicate how many subjects you expect to screen to reach your target sample (i.e. your screen failure rate).*

Response: 20

*7.3 Justify the feasibility of recruiting the proposed number of eligible subjects within the anticipated recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?*

Response:

Recruitment will occur from the PI's and Dr. Daniel Sirica's movement disorder clinic patients. The PI and Dr. Sirica care for approximately 500 PD patients of which approximately 70% will be eligible. PD patients are anticipated to be highly interested in participating in this study since there currently are no disease-modifying therapies available for PD. Indeed, 18 PD patients have already voiced

interest in joining the study after being briefly informed of the study's rationale and procedures.

## 8.0 Inclusion and Exclusion Criteria*

*8.1 Describe the criteria that define who will be **included** in your final study sample.*

*NOTE: This may be done in bullet point fashion.*

Response:

Eligibility Criteria:

1. Diagnosed with PD according to the UK Brain Bank Criteria within the past four years with Hoehn & Yahr stage 1 or 2.[66]
2. 45-80yo.
3. Stable PD medications for previous 30 days and no current need for changes in the opinion of the PI.
4. No formed visual hallucinations or delusions for previous year.
5. Screening MoCA ≥ 20.
6. Never taken prescription or over-the-counter lithium.
7. Stable doses of antidepressants, antihypertensives, diuretics and non-steroidal anti-inflammatory medications (NSAIDs) for previous 60 days and no current need to adjust such medications.
8. No history of cardiac arrhythmias besides atrial fibrillation that is rate controlled.
9. No unstable cardiac, medical, neurologic or psychiatric condition in the opinion of the PI.
10. No current use of illicit drugs or current alcohol abuse in the opinion of the PI.
11. Normal thyroid stimulating hormone (TSH) level at screening visit.
12. Estimated renal glomerular filtration rate ≥50 at screening visit.
13. No history of receiving or planning to receive nilotinib or a glucagon-like peptide-1 agonist medication such as exenatide.
14. No use of tobacco, THC or CBD products for the previous year.
15. No history of brain surgery or possible need for brain surgery including deep brain stimulation (DBS) for at least 1-year in the opinion of the PI.
16. Women with child bearing potential will need a negative pregnancy test and not be nursing an infant at screening. Women with child bearing potential will need to report using barrier method or hormonal contraception.
17. Not enrolled in another clinical trial.
18. Willing and able to sign informed consent and follow study procedures.

*8.2 Describe the criteria that define who will be **excluded** from your final study sample.*

*NOTE: This may be done in bullet point fashion.*

Response:

See 8.1.

*8.3 Indicate specifically whether you will include any of the following special populations in your study using the checkboxes below.*

***NOTE: Members of special populations may not be targeted for enrollment in your study unless you indicate this in your inclusion criteria.***

Response:

☐ Adults unable to consent

☐ Individuals who are not yet adults (infants, children, teenagers)

☐ Pregnant women

☐ Prisoners

*8.4 Indicate whether you will include non-English speaking individuals in your study.* ***Provide justification if you will exclude non-English speaking individuals.***

*In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may* ***not*** *be routinely excluded from research as a matter of convenience.*

*In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English. Some examples include pilot studies, small unfunded studies with validated instruments not available in other languages, studies with numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.*

Response:

Non-english speaking patients will not be enrolled as this is a pilot, proof of concept study and many of the PD questionnaires have not been translated out of English.

## 9.0 Vulnerable Populations*

*If the research involves special populations that are considered vulnerable,* ***describe the safeguards included to protect their rights and welfare.***

*NOTE: You should refer to the appropriate checklists, referenced below, to ensure you have provided adequate detail regarding safeguards and protections. You do not, however, need to provide these checklists to the IRB.*

*9.1 For research that involves* ***pregnant women,*** *safeguards include:*
*NOTE CHECKLIST: Pregnant Women (HRP-412)*

Response:

☒ **N/A**: This research does not involve pregnant women.

*9.2 For research that involves **neonates of uncertain viability or non-viable neonates,** safeguards include:*
*NOTE CHECKLISTS: Non-Viable Neonates (HRP-413), or Neonates of Uncertain Viability (HRP-414)*

Response:

☒ **N/A:** This research does not involve non-viable neonates or neonates of uncertain viability.

*9.3 For research that involves **prisoners**, safeguards include:*
*NOTE CHECKLIST: Prisoners (HRP-415)*

Response:

☒ **N/A:** This research does not involve prisoners.

*9.4 For research that involves **persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children")**, safeguards include:*
*NOTE CHECKLIST: Children (HRP-416)*

Response:

☒ **N/A:** This research does not involve persons who have not attained the legal age for consent to treatments or procedures ("children").

*9.5 For research that involves **cognitively impaired adults**, safeguards include:*
*NOTE CHECKLIST: Cognitively Impaired Adults (HRP-417)*

Response:

HRP-417 has been completed as is attached to this submission package.

☒ **N/A:** This research does not involve cognitively impaired adults.

*9.6 Consider if other specifically targeted populations such as students, employees of a specific firm, or educationally or economically disadvantaged persons are vulnerable. **Provide information regarding their safeguards and protections, including safeguards to eliminate coercion or undue influence.***

Response:

## 10.0 Eligibility Screening*

*10.1 Describe **screening procedures** for determining subjects' eligibility. Screening refers to determining if prospective participants meet inclusion and exclusion criteria.*

📎 *Include all relevant screening documents with your submission (e.g. screening protocol, script, questionnaire).*

Response: Screening will occur after the subject signs the consent form by completing the Screening Form. Eligibility can only be confirmed after screening bloodwork results are available.

☐ **N/A:** There is no screening as part of this protocol.

## 11.0 Recruitment Methods

☐ **N/A:** This is a records review only, and subjects will not be recruited. NOTE: If you select this option, please make sure that all records review procedures and inclusion/exclusion screening are adequately described in other sections.

*11.1 Describe when, where, and how potential subjects will be recruited.*

*NOTE: Recruitment refers to how you are identifying potential participants and introducing them to the study. Include specific methods you will use (e.g. searching charts for specific ICD code numbers, Research Participant Groups, posted advertisements, etc.).*

Response:

Potential subjects will be recruited by the PI and Dr. Sirica from their personal clinic patients. Patients will be given a brief verbal overview of the study rationale and procedures. Interested patients will be given a consent form to review at home and contacted within 1 week to answer questions and potentially schedule a screening visit.

*11.2 Describe how you will protect the privacy interests of prospective subjects during the recruitment process.*

*NOTE: Privacy refers to an individual's right to control access to him or herself.*

Response:

The PI will ask potential subjects if and how they wish to be contacted after they have had time to review the consent form. Subjects requesting not to be contacted will not be.

*11.3 Identify any materials that will be used to recruit subjects.*

*NOTE: Examples include scripts for telephone calls, in person announcements / presentations, email invitations.*

*For advertisements, include the final copy of printed advertisements with your submission. When advertisements are taped for broadcast, attach the final audio/video tape. NOTE: You may submit the wording of the advertisement prior to taping to ensure there will be no IRB-required revisions, provided the IRB also reviews and approves the final version.*

Response:

None.

## 12.0 Procedures Involved*

*12.1 Provide a description of **all research procedures or activities** being performed and when they are performed once a subject is screened and determined to be eligible. Provide as much detail as possible.*

*NOTE: This should serve as a blueprint for your study and include enough detail so that another investigator could pick up your protocol and replicate the research. For studies that have multiple or complex visits or procedures, consider the addition of a schedule of events table in in your response.*

Response:
PD patients who have had time to review the consent form and have expressed interest in the study will first undergo a screening visit.

**Screening Visit (Visit 1)– performed up to 21 days before Visit 2**

- The study rationale and procedures will be reviewed and all questions answered. The patient's understanding of the study will be confirmed prior to signing of the consent.
- The Screening Form will be completed. If the subject is eligible for the study, the Montreal Cognitive Assessment (MoCA) will be administered.[7]
- About 2 teaspoons (10ml) of venous blood will be obtained from the antecubital or dorsal hand vein for screening blood work (CBC, CMP, TSH, calcium, ESR, urate, HgA1C) performed by Kaleida Laboratory Services. The tests will include a pregnancy test if the subject is female of child-bearing potential.

**Baseline MRI Visit– performed within 21 days after Visit 1**

- This visit will occur at the University at Buffalo's Clinical and Translational Research Center located at 875 Ellicott Street, Buffalo, NY 14203.
- This brain MRI scan will take about 45-60 minutes of actual scanning to complete.
- There will not be any intravenous injection needed for this scan.
- If the subject is claustrophobic, Dr. Guttuso can prescribe valium to help the subject relax during the scan. If valium is taken, the subject will arrange to have someone else drive them home.

**Baseline Visit (Visit 2)– performed within 21 days after Visit 1**

- Eligible subjects will receive medium-dose lithium aspartate therapy for 24 weeks with the following dose titration: 10mg bid x 1 week, then 15mg bid x 1 week, then 20mg bid x 2 weeks, then 20mg qAM and 25mg qhs thereafter. Patients will be contacted weekly over the first 4-6 weeks to assess for side effects that are likely to be due to lithium, such as sedation, dizziness or confusion. If side effects occur and are bothersome to the patient, the dose will be decreased incrementally to a minimum of 30mg/day.
- Subjects will receive 24 weeks of study lithium aspartate capsules as well as dosing instructions and study team emergency contact cards. The contact cards will include a list of medications that can interact with lithium that should not be started or changed during the 24-week study. The subject's PMD will be informed of the subject's enrollment if the subject consented to this on the consent form.
- A review of subjects' symptoms and concomitant medications will be recorded.
- The PI will complete the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Movement Disorder Society-Unified Parkinson's

Disease Rating Scale (MDS-UPDRS), Part III (Motor Examination) with subjects in the "on" state.[1]

- Subjects will complete the following questionnaires: Parkinson's Anxiety Scale,[2] Geriatric Depression Scale-15,[3] Fatigue Severity Scale,[4] Insomnia Severity Index[5] and Parkinson's Disease Questionnaire-8.[6]
- About 8 teaspoons (40ml) of venous blood will be obtained from the antecubital or dorsal hand vein to assess for the following therapeutic targets: PBMC Nurr1 and SOD1 mRNA levels by PCR; PBMC phosphorylated (p) and total (t) levels of pS9 and t-GSK-3β, pThr308, pS473 and t-Akt and plasma interleukin-6 (IL-6) levels. Serum lithium levels will also be assayed the UB Chemistry Instrument Center utilizing an inductively coupled plasma mass spectrometer (ICPMS).

**Week 12 phone call- performed about 12 weeks after Visit 2**

- Subjects will be called by a study team member to answer questions, assess for adverse events, assess for changes in concomitant medications, confirm study drug is being taken appropriately and confirm the date and time of the next study site visit.

**Week 24 Visit- performed about 24 weeks after Visit 2**

- Subjects' adverse events and concomitant medications will be assessed.
- The PI will complete the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Part III (Motor Examination) in the "on" state.[1]
- The MoCA version 2 will be assessed.
- Subjects will complete the following questionnaires: Parkinson's Anxiety Scale,[2] Geriatric Depression Scale-15,[3] Fatigue Severity Scale,[4] Insomnia Severity Index[5] and Parkinson's Disease Questionnaire-8.[6]
- About 2 teaspoons (10ml) of venous blood will be obtained from the antecubital or dorsal hand vein for CBC, CMP, TSH, calcium, ESR, urate, HgA1C and serum lithium performed by Kaleida Laboratory Services.
- About 8 teaspoons (40ml) of venous blood will be obtained from the antecubital or dorsal hand vein to assess for the following therapeutic targets: PBMC Nurr1 and SOD1 mRNA levels by PCR; PBMC phosphorylated (p) and total (t) levels of pS9 and t-GSK-3β, pThr308, pS473 and t-Akt and plasma interleukin-6 (IL-6) levels. Serum lithium levels will also be assayed the UB Chemistry Instrument Center utilizing an inductively coupled plasma mass spectrometer (ICPMS).

**Week 24 MRI Visit– performed within 10 days of the Week 24 Visit**

- This visit will occur at the University at Buffalo's Clinical and Translational Research Center located at 875 Ellicott Street, Buffalo, NY 14203.
- This brain MRI scan will take about 45-60 minutes of actual scanning to complete.
- There will not be any intravenous injection needed for this scan.
- If the subject is claustrophobic, Dr. Guttuso can prescribe valium to help the subject relax during the scan. If valium is taken, the subject will arrange to have someone else drive them home.

After the Week 24 visit, the study will be completed and subjects will be instructed to stop all study lithium drug. Lithium therapy does not need to be weaned.

*12.2 Describe what data will be collected.*

*NOTE: For studies with multiple data collection points or long-term follow up, consider the addition of a schedule or table in your response.*

Response:

**Overview of study activities:**

| | Screening Visit | Baseline Visit | Week 24 Visit |
|---|---|---|---|
| Medical History | X | | |
| MDS-UPDRS | | X | X |
| Questionnaires | | X | X |
| MoCA | X | | X |
| Adverse events and concomitant medications | X | X | X |
| Blood Test | X | X | X |
| MRI scan | | X | X |

MRI scans will be stored using an eXtensible Neuroimaging Archive Toolkit (XNAT) system. XNAT integrates with the MRI scanner via a DICOM Storage Class Provider (SCP) receiver, where the scanner can send DICOMs directly to XNAT. XNAT's DICOM SCP receiver operates on port 8106 behind a firewall allowing only the pre-approved whitelisted IP addresses of the CBI scanners to upload DICOMs. The XNAT system is hosted on a Linux server on Amazon Web Services (AWS), which provides encrypted filesystems in alignment with FedRAMP and NIST 800-53 risk management programs. Users will be given access to XNAT via individual accounts to access the system's web interface over encrypted HTTPS. Access will only be provided to study team members and CBI staff. The web interface is behind a firewall allowing access only from within the UB network. All data transfers, including DICOM transfer initiated by the scanners and web interface access, will be routed through an encrypted VPN tunnel established and administrated by UBIT. The XNAT system will never host any directly identifying information, such as subject names; only subject codes will be used on the scanner to prevent identifying information from being transferred to XNAT. DICOM files will be stored indefinitely on the server's file system, with daily snapshots retained for 14 days.

*12.3 List any instruments or measurement tools used to collect data (e.g. questionnaire, interview guide, validated instrument, data collection form).*

*Include copies of these documents with your submission.*

- Response: The screening form, concomitant medication form, subject ID form, subject visit form, UK Blood Bank PD diagnosis form, MDS-UPDRS, Parkinson's Anxiety Scale,[2] Geriatric Depression Scale-15,[3] Fatigue Severity Scale,[4] Insomnia Severity Index[5] and Parkinson's Disease Questionnaire-8 have been included in this submission package.[6]

*12.4 Describe any source records that will be used to collect data about subjects (e.g. school records, electronic medical records).*

Response: None.

*12.5 Indicate whether or not **individual** subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings will be shared with subjects or others (e.g., the subject's primary care physician) and if so, describe how these will be shared.*

Response: Individual subject results will be mailed or emailed to subjects after study completion.

*12.6 Indicate whether or not **study** results will be shared with subjects or others, and if so, describe how these will be shared.*

Response: Study results will be shared with subjects by forwarded each a copy of the published manuscript.

## 13.0 Study Timelines*

*13.1 Describe the anticipated duration needed to enroll all study subjects.*

Response: 7 months.

*13.2 Describe the duration of an individual subject's participation in the study. Include length of study visits, and overall study follow-up time.*

Response: Each subject will participate for 25-27 weeks. Each visit will take 60-90 minutes.

*13.3 Describe the estimated duration for the investigators to complete this study (i.e. all data is collected and all analyses have been completed).*

Response: 12 months.

## 14.0 Setting

*14.1 Describe all facilities/sites where you will be conducting research procedures. Include a description of the security and privacy of the facilities (e.g. locked facility, limited access, privacy barriers). Facility, department, and type of room are relevant. Do not abbreviate facility names.*

*NOTE: Examples of acceptable response may be: "A classroom setting in the Department of Psychology equipped with a computer with relevant survey administration software," "The angiogram suite at Buffalo General Medical Center, a fully accredited tertiary care institution within New York State with badge access," or, "Community Center meeting hall."*

Response: All subject clinical visits will occur at UBMD Neurology at 5851 Main Street, Williamsville, NY 14221. This is a clinic where neurology patients are routinely treated. The facility is staffed during business hours and otherwise locked. The MRI visits will occur at the University at Buffalo's Clinical and Translational Research Center located at 875 Ellicott Street, Room 7020, Buffalo, NY 14203

*14.2 For research conducted outside of UB and its affiliates, describe:*

- *Site-specific regulations or customs affecting the research*
- *Local scientific and ethical review structure*

*NOTE: This question is referring to UB affiliated research taking place outside UB, i.e. research conducted in the community, school-based research, international research, etc. It is not referring to multi-site research. UB affiliated institutions include Kaleida Health, ECMC, and Roswell Park Cancer Institute.*

Response:

☒ **N/A:** This study is not conducted outside of UB or its affiliates.

## 15.0 Community-Based Participatory Research

*15.1 Describe involvement of the community in the design and conduct of the research.*

*NOTE: Community-Based Participatory Research (CBPR) is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. CBPR begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.*

Response:

☒ **N/A:** This study does not utilize CBPR.

*15.2 Describe the composition and involvement of a community advisory board.*

Response:

☒ **N/A:** This study does not have a community advisory board.

## 16.0 Resources and Qualifications

*16.1 Describe the qualifications (e.g., education, training, experience, expertise, or certifications) of the Principal Investigator **and** staff to perform the*

*research. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research.*

*NOTE: If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify a person by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that the person meets the qualifications described to fulfill their roles.*

Response: The PI, Thomas Guttuso, Jr., MD is a Professor of Neurology at UB and a Movement Disorder specialist with 22 years of caring for PD patients. Dr. Guttuso has served as PI on 9, hypothesis-driven clinical trials and site-PI on 3, industry-sponsored clinical trials. Daniel Sirica, MD is an Assistant Professor of Neurology at UB and a Movement Disorder specialist with 3 years of caring for PD patients. The study coordinator has over 10 years of experience in this role on clinical trials.

***Describe other resources available to conduct the research.***

*16.2 Describe the time and effort that the Principal Investigator and research staff will devote to conducting and completing the research.*

*NOTE: Examples include the percentage of Full Time Equivalents (FTE), hours per week. The question will elicit whether there are appropriate resources to conduct the research.*

Response: The PI will devote 0.2FTE and the coordinator 0.2FTE towards this project.

*16.3 Describe the availability of medical or psychological resources that subjects might need as a result of anticipated consequences of the human research, if applicable.*

*NOTE: One example includes: on-call availability of a counselor or psychologist for a study that screens subjects for depression.*

Response: N/A

*16.4 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.*

Response: The PI will directly communicate with all study staff to review study procedures and define each member's duties. The PI will monitor all staff throughout the study to ensure that study procedures are being followed appropriately.

## 17.0 Other Approvals

*17.1 Describe any approvals that will be obtained prior to commencing the research (e.g., school, external site, funding agency, laboratory, radiation safety, or biosafety).*

Response:

☐ **N/A:** This study does not require any other approvals.

## 18.0 Provisions to Protect the Privacy Interests of Subjects

*18.1 Describe how you will protect subjects' privacy interests during the course of this research.*

*NOTE: Privacy refers to an individual's right to control access to him or herself. Privacy applies to the person. Confidentiality refers to how data collected about individuals for the research will be protected by the researcher from release. Confidentiality applies to the data.*

*Examples of appropriate responses include: "participant only meets with a study coordinator in a classroom setting where no one can overhear", or "the participant is reminded that they are free to refuse to answer any questions that they do not feel comfortable answering."*

Response: Study subjects will meet with either the PI or coordinator in a clinic room with the door shut for privacy.

*18.2 Indicate how the research team is permitted to access any sources of information about the subjects.*

*NOTE: Examples of appropriate responses include: school permission for review of records, consent of the subject, HIPAA waiver. This question **does apply** to records reviews.*

Response: Consent of the subject.

## 19.0 Data Management and Analysis*

*19.1 Describe the data analysis plan, including any statistical procedures. This section applies to both quantitative and qualitative analysis.*

Response: Given the proof-of-concept nature of the proposed study there is not a single primary outcome but rather treatment groups will be compared with regards to multiple outcomes in a primary fashion. While there are tests of several outcomes being carried forth, which will inflate the experiment-wise error rate to be greater than the specified nominal level of 0.05, it is reasonable to expect these tests to be highly correlated. Hence, given we are in the preliminary phase of our investigation, no adjustments for multiple tests across outcomes will be made. Standard adjustments for multiple testing for a given outcome will still be implemented.

Missing data:

The amount and nature of missing data will be characterized and no method of imputation will be used for missing data. A summary of missing data will be provided according to the number of subjects and the time points where the data are missing. We acknowledge the possibility of informative missingness, that is, the probability of a particular observation being missing may be related to the health of a subject, and therefore analyses will be interpreted with caution.

Descriptive analyses:

Measured outcome variables will be summarized overall and by relevant demographic and baseline variables. Descriptive statistics such as frequencies and relative frequencies will be computed for all categorical variables. Numeric variables will be summarized using simple descriptive statistics such as the mean, standard deviation and range. A variety of graphical techniques will also be used to display data, ex., histograms, boxplots, scatterplots, etc. MRI data will be processed and analyzed by the Buffalo Neuroimaging Analysis Center (BNAC) under the direction of Robert Zivadinov, MD.

Statistical analyses:

All statistical analyses of outcomes at each time point will be performed using identical methodologies. The statistical assessment of each considered outcome will be based on a standard analysis of variance (ANOVA) model. In this case, each outcome will be fit as a function of randomized group assignment, baseline cognition, and the interaction between group assignment and baseline cognition. Rather than utilizing the null distribution associated with the classic tests for treatment differences within the ANOVA framework which is dependent on the validity of distributional assumptions, an exact permutation testing approach will be utilized. The randomization mechanism at work is a crucial component in this study in that it will be used to create the randomization distribution by which statistical significance will be determined. Reported p-values will be obtained from the permutation distributions of the test statistics based on 10,000 Monte Carlo simulations. All possible pairwise comparisons will be made between the three treatment groups in conjunction with a Bonferroni adjustment for multiple comparisons performed at a 0.05 family-wise error rate. All statistical tests will be two-sided. In addition, since the comparability of treatment groups may be questioned due to chance imbalance in confounding variables, covariates will be added to the above models as a series of secondary analyses. The interaction of patient covariates and randomized assignment will be examined so to assist in the identification of patient subgroups of interest. All adverse events will be recorded during the study period and then tabulated at the end of the study along with the results of the physical exams. All available data from subjects who fail to complete this study will be included in the safety summaries. The probability of an adverse event will be estimated for each treatment group along with the 95% exact confidence interval based on the method of Clopper and Pearson. All analyses will be carried out using SAS version 9.4 (or higher) statistical software (Cary, NC).

*19.2 If applicable, provide a power analysis.*

*NOTE: This may not apply to certain types of studies, including chart/records reviews, survey studies, or observational studies. This question is asked to elicit*

*whether the investigator has an adequate sample size to achieve the study objectives and justify a conclusion.*

Response: N/A

*19.3 Describe any procedures that will be used for quality control of collected data.*

Response: N/A

## 20.0 Confidentiality*

## A. Confidentiality of Study Data

*Describe the local procedures for maintenance of confidentiality of **study data and any records that will be reviewed for data collection**.*

*20.1 A. Where and how will all data and records be stored? Include information about: password protection, encryption, physical controls, authorization of access, and separation of identifiers and data, as applicable. Include physical (e.g. paper) **and** electronic files.*

Response: A study binder will be assembled for each subject that will contain all of the non-biomarker data collected. However, the forms linking subjects' personal identifiable information to their study ID numbers will be kept in a separate folder. This folder and all study binders will be stored in a locked room in a locked cabinet at the study site. These data as well as biomarker data will be entered into an excel file on the coordinator's password protected computer located in this same locked room. The excel file will only contain subject ID numbers and no personal identifiable information.

*20.2 A. How long will the data be stored?*

Response: Indefinitely.

*20.3 A. Who will have access to the data?*

Response: The study coordinator and PI.

*20.4 A. Who is responsible for receipt or transmission of the data?*

Response: The study PI.

*20.5 A. How will the data be transported?*

Response: Electronically.

## B. Confidentiality of Study Specimens

*Describe the local procedures for maintenance of confidentiality of **study specimens**.*

☐ **N/A:** No specimens will be collected or analyzed in this research. *(Skip to Section 19.0)*

*20.6 B. Where and how will all specimens be stored? Include information about: physical controls, authorization of access, and labeling of specimens, as applicable.*

Response: Subjects' blood samples will be labeled with their ID#, DOB, date and time of collection. Some samples will be stored in a locked freezer at the study site until the time of analysis. Some samples will be immediately transported to the laboratory of Luciana Frick, PhD, 5th floor CTRC. MRI scans will be labeled with subject ID#, DOB, date and time of collection.

*20.7 B. How long will the specimens be stored?*

Response: Indefinitely

*20.8 B. Who will have access to the specimens?*

Response: The study coordinator and PI, Luciana Frick, and the technician at UB's Chemistry Instrument Center (Room 330, Natural Sciences Complex, UB North Campus).

*20.9 B. Who is responsible for receipt or transmission of the specimens?*

Response: The PI.

*20.10 B. How will the specimens be transported?*

Response: By local courier to Luciana Frick's laboratory and UB's Instrument Center.

## 21.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

***NOTE: Minimal risk studies may be required to monitor subject safety if the research procedures include procedures that present unique risks to subjects that require monitoring. Some examples include: exercising to exertion, or instruments that elicit suicidality or substance abuse behavior. In such cases, N/A is not an acceptable response.***

*21.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.*

- Adverse Events (AEs) will be assessed at baseline (BL), at the week 24 study and by phone at week 12. Appropriate management can be implemented, as needed, such as adjustments of other PD medications, referral to PCP or withdrawal from the study. Subjects will also be provided with the study teams' business phone and emergency phone contacts.
- Subjects who develop a TSH >7.5mIU/L, a serum calcium >10.1mg/dL, an estimated glomerular filtration rate (EGFR) <50ml/min or a >35% decrease in EGFR from BL will be referred to their PCP for further evaluation and treatment. The study PI will also contact the subject's PCP to discuss the most appropriate management, which could include initiating thyroid replacement therapy or withdrawing the subject from the study.

*21.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.*

Response: Subjects' adverse events and blood work (detailed above).

*21.3 Describe any safety endpoints.*

Response: Number of adverse events possibly related to lithium therapy and number of subjects who withdraw due to adverse events possibly related to lithium therapy.

*21.4 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).*

Response: Described under 21.1.

*21.5 Describe the frequency of safety data collection.*

Response: Described under 21.1.

*21.6 Describe who will review the safety data.*

Response: The PI and study coordinator.

*21.7 Describe the frequency or periodicity of review of cumulative safety data.*

Response: Subjects' safety blood tests will be reviewed by the PI within 3 business days of results being available. The PI will review subjects' clinical adverse events in real time.

*21.8 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.*

Response: None.

*21.9 Describe any conditions that trigger an immediate suspension of the research.*

Response:

Data and Safety Monitoring Plan:

- Subjects will be asked about adverse events at each study site visit and each phone contact. Subjects will also be instructed to contact the study team immediately if they require medical attention at any time during the study. The study team will then contact the medical facility to obtain the information needed for this study. All subjects will sign a medical release form at the time of enrollment.

- For non-serious subject adverse events:
  Subjects will be directly asked by one of the study team members about any adverse events during every study site visit and phone contact. All adverse events (AE's) will be recorded on the AE report form. Non-serious adverse events will be categorized as follows:
  - **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".

- For serious subject adverse events (SAE):
  An adverse event will be considered "serious" (SAE) if the adverse event resulted in subject death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, or a persistent or significant incapacity or substantial disruption of

the ability to conduct normal life functions. This is the definition of SAE according to the FDA's Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies. When a study team member becomes aware of a possible subject SAE, the study team member will contact the PI by phone the same day.

An SAE that is determined by the study PI to be, a) unexpected, and b) reasonably possible to have been caused by lithium will be considered a "Reportable Event". The PI will report such events to the University at Buffalo's IRB within 5 business days of the study team's first awareness of the event.

An SAE that is unexpected by virtue of it not being listed in either the FDA approved product package insert, protocol or consent form with regard to occurrence or at an increased frequency, severity or duration than previously published will be considered a "Reportable Event". FDA Guidance from 2012 notes that an event should be reported if:

-A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)

-One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

-An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

- If similar "Reportable" SAEs occur in 4 subjects, the study will be terminated and subjects instructed to stop lithium therapy.
- Safety blood work will also be monitored at each study site visit. Particular attention will be given to TSH and estimated glomerular filtration rate (EGFR) as long-term standard-dose lithium therapy is known to potentially cause hypothyroidism, hyperparathyroidism and renal failure. Subjects found to have a TSH>7.5mIU/L, a serum calcium >10.1mg/dL, an EGFR<50ml/min or a >35% decrease in EGFR from BL will be referred to their PCP for further evaluation and treatment. The study PI will also contact the subject's PCP to discuss the most appropriate management, which could include initiating thyroid replacement therapy or withdrawing the subject from the study. Among the 20 PD patients that the PI has been treating with adjunct low-dose lithium therapy for 0.5-5.2 years, two have developed hypothyroidism. One had a history of hypothyroidism, which worsened after 8 months of low-dose lithium therapy. The other developed new hypothyroidism after 18 months of low-dose lithium therapy. No patients have had any clinically significant changes in serum calcium or EGFR.
- No interim data analysis will be performed as this is a pilot, exploratory trial.
- This study will be registered on clinicaltrials.gov prior to subject enrollment.

## 22.0 Withdrawal of Subjects*

☐ **N/A:** This study is not enrolling subjects. This section does not apply.

*22.1 Describe **anticipated** circumstances under which subjects may be withdrawn from the research without their consent.*

Response: Subjects found to have a TSH>7.5mIU/L, a serum calcium >10.1mg/dL, an EGFR<50ml/min or a >35% decrease in EGFR from BL will be referred to their PCP for further evaluation and treatment. The study PI will also contact the subject's PCP to discuss the most appropriate management, which could include initiating thyroid replacement therapy or withdrawing the subject from the study. Subjects experiencing a "reportable" SAE (defined above) will be withdrawn.

*22.2 Describe any procedures for orderly termination.*

*NOTE: Examples may include return of study drug, exit interview with clinician. Include whether additional follow up is recommended for safety reasons for physical or emotional health.*

Response: Subjects withdrawn from the study will be asked to make a final study visit during which all Week 24 procedures will take place.

*22.3 Describe procedures that will be followed when subjects withdraw from the research, including retention of already collected data, and partial withdrawal from procedures with continued data collection, as applicable.*

Response: Described in 22.2.

## 23.0 Risks to Subjects*

*23.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related to their participation in the research. Consider physical, psychological, social, legal, and economic risks. Include a description of the probability, magnitude, duration, and reversibility of the risks.*

*NOTE: Breach of confidentiality is always a risk for identifiable subject data.*

Response:

Standard dosages of lithium can cause the following side effects: hand tremors when using the hands (not at rest like in PD), increased urination, increased thirst, diarrhea, vomiting, drowsiness and lack of coordination. Use of higher dosages of lithium for several years can cause kidney damage that can be irreversible. Both low and high dosages of lithium can cause a decrease in natural thyroid hormone levels that may necessitate the need for thyroid replacement medication. Both kidney and thyroid functions will be monitored during this study.

RISKS OF STUDY PROCEDURES:

- Blood samples: possible side effects from blood drawing include faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection.
- Questionnaires: filling out the questionnaires or answering the study doctor or study staff's questions could lead subjects to feel uncomfortable or upset. Subjects will be instructed to tell the study doctor or study staff if feeling uncomfortable or upset while filling out a questionnaire or answering questions. Subjects have the right to refuse to answer any questions.
- MRI scan: some people can feel anxious during an MRI scan. Subjects will be instructed to let the MRI staff know if they would like to take a break during the scan. No contrast agent will be injected for the MRI scans.

*23.2 Describe procedures performed to lessen the probability or magnitude of risks, including procedures being performed to monitor subjects for safety.*

Response:

A dose titration schedule will be used to achieve a target dosage of 30-45mg/day of lithium aspartate. Subjects will be instructed to push the dosage to the highest amount that causes no side effects. Based on this study's earlier results, this dosing strategy is anticipated to greatly minimize lithium-induced side effects and maximize patient retention. The informed consent will contain a list of common medications that can interact with lithium and increase lithium serum levels and the potential for side effects. Subjects will be educated about these drug-drug interactions and provided with a list of such medications. Blood draws will occur under sterile conditions to minimize the chance for infection.

*23.3 If applicable, indicate **which procedures** may have risks to the subjects that are currently unforeseeable.*

Response:

UNFORESEEN RISKS:
Since the study drug is investigational in PD when taken alone or in combination with other medications, there may be other risks that are unknown. All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life-threatening. Some things that happen during an allergic reaction that could be a sign or symptom of a life-threatening allergic reaction (anaphylaxis) are:

- a rash
- a fast pulse
- sweating
- a feeling of dread
- swelling around the eyes and mouth
- swelling of the throat
- wheezing
- having a hard time breathing
- a sudden drop in blood pressure (making you feel dizzy or lightheaded)

- inability to breathe without assistance

*23.4 If applicable, indicate which research procedures may have risks to an embryo or fetus should the subject be or become pregnant.*

Response:

Lithium therapy is associated with higher rates of birth defects.

*23.5 If applicable, describe risks to others who are not subjects.*

Response: N/A

## 24.0 Potential Benefits to Subjects*

*24.1 Describe the potential benefits that individual subjects may experience by taking part in the research. Include the probability, magnitude, and duration of the potential benefits. Indicate if there is no direct benefit.*

*NOTE: Compensation **cannot** be stated as a benefit.*

Response:

Possible benefits may include slowing the rate of PD progression. Results from this study may also benefit other PD patients in the future.

## 25.0 Compensation for Research-Related Injury

☐ **N/A:** The research procedures for this study do not present risk of research related injury (e.g. survey studies, records review studies). This section does not apply.

*25.1* ***If the research procedures carry a risk of research related injury,*** *describe the available compensation to subjects in the event that such injury should occur.*

Response:

Subjects will receive medical treatment if injured or become ill as a result of this study. The PI will explain the treatment options to you and tell you where you can get treatment.

The University at Buffalo makes no commitment to provide free medical care or payment for any unfavorable outcomes that result from your participation in this research. Medical services will be billed at the usual charge and will be the subject's responsibility or that of a third-party payer but subjects will not be precluded from seeking to collect

compensation for injury related to malpractice, fault, or blame on the part of those involved in the research including the University at Buffalo.

By accepting medical care or accepting payment for medical expenses, subjects are not waiving any legal rights.

*25.2 Provide a copy of contract language, if any, relevant to compensation for research related injury.*

*NOTE: If the contract is not yet approved at the time of this submission, submit the current version here. If the contract is later approved with **different language regarding research related injury**, you must modify your response here and submit an amendment to the IRB for review and approval.*

Response: N/A

## 26.0 Economic Burden to Subjects

*26.1 Describe any costs that subjects may be responsible for because of participation in the research.*

*NOTE: Some examples include transportation or parking.*

Response:

Transportation costs.

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

## 27.0 Compensation for Participation

*27.1 Describe the amount and timing of any compensation to subjects, including monetary, course credit, or gift card compensation.*

Response:

Participants will be reimbursed for parking fees incurred for each of the two MRI scans downtown in the CTRC. Participants will submit receipts to the study team and will be reimbursed by check mailed to their homes. Parking fees will be $10/MRI visit maximum or $20 maximum for the entire study.

☐ **N/A:** This study is not enrolling subjects, or is limited to records review procedures only. This section does not apply.

☐ **N/A:** There is no compensation for participation. This section does not apply.

## 28.0 Consent Process

*28.1 Indicate whether you will be obtaining consent.*

*NOTE: This does not refer to consent documentation, but rather whether you will be obtaining permission from subjects to participate in a research study. Consent documentation is addressed in Section 27.0.*

☒ ***Yes*** *(If yes, Provide responses to each question in this Section)*
☐ ***No*** *(If no, Skip to Section 27.0)*

*28.2 Describe where the consent process will take place. Include steps to maximize subjects' privacy.*

Response:

The consent process will occur in a closed-door, examination clinic room at UBMD Neurology.

*28.3 Describe how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study.*

*NOTE: It is always a requirement that a prospective subject is given sufficient time to have their questions answered and consider their participation. See "SOP: Informed Consent Process for Research (HRP-090)" Sections 5.5 and 5.6.*

Response:

Potential subjects will be provided with the consent document at least 48 hours prior to the screening visit to ensure adequate time to read and process the entire document.

*28.4 Describe any process to ensure ongoing consent, defined as a subject's willingness to continue participation for the duration of the research study.*

Response:

Subjects will be asked if they wish to continue in the study at each study visit and phone call.

*28.5 Indicate whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." Pay particular attention to Sections 5.4-5.9. If not, or if there are any exceptions or additional details to what is covered in the SOP, describe:*

- *The role of the individuals listed in the application who are involved in the consent process*
- *The time that will be devoted to the consent discussion*
- *Steps that will be taken to minimize the possibility of coercion or undue influence*
- *Steps that will be taken to ensure the subjects' understanding*

Response:

☒ We have reviewed and will be following "SOP: Informed Consent Process for Research (HRP-090)."

***Non-English Speaking Subjects***

☒ **N/A:** This study will not enroll Non-English speaking subjects. *(Skip to Section 26.8)*

*28.6 Indicate which language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.*

*NOTE: The response to this Section should correspond with your response to Section 6.4 of this protocol.*

Response:

*28.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language, how you will ensure that subjects are provided with a sufficient period of time to consider taking part in the research study, and any process to ensure ongoing consent. Indicate the language that will be used by those obtaining consent.*

*NOTE: Guidance is provided on "SOP: Informed Consent Process for Research (HRP-090)."*

Response:

***Cognitively Impaired Adults***

☐ **N/A**: This study will not enroll cognitively impaired adults. *(Skip to Section 26.9)*

*28.8 Describe the process to determine whether an individual is capable of consent.*

Response: After subjects have had adequate time to review the consent and ask questions about the study, they will be asked to give a brief overview of the study procedures. Only subjects that can accurately describe key aspects of the study will be enrolled.

***Adults Unable to Consent***

☒ **N/A**: This study will not enroll adults unable to consent.
(*Skip to Section 26.13)*

*When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent (Sections 26.9 and 26.10)* ***and, where possible, assent of the individual should also be solicited*** *(Sections 26.11 and 26.12).*

*28.9 Describe how you will identify a Legally Authorized Representative (LAR). Indicate that you have reviewed the "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" for research in New York State.*

*NOTE: Examples of acceptable response includes: verifying the electronic medical record to determine if an LAR is recorded.*

Response:

☐ We have reviewed and will be following "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

*28.10* ***For research conducted outside of New York State****, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the research. One method of obtaining this information is to have a legal counsel or authority review your protocol along with the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response:

*28.11 Describe the process for* ***assent of the adults****:*

- *Indicate whether assent will be obtained from all, some, or none of the subjects.* ***If some, indicate which adults will be required to assent and which will not.***

Response:

- ***If assent will not be obtained from some or all subjects, provide an explanation of why not.***

Response:

*28.12 Describe whether* ***assent of the adult*** *subjects will be documented and the process to document assent.*

*NOTE: The IRB allows the person obtaining assent to document assent on the consent document using the "Template Consent Document (HRP-502)" Signature Block for Assent of Adults who are Legally Unable to Consent.*

Response:

***Subjects who are not yet Adults (Infants, Children, and Teenagers)***

☒ **N/A**: This study will not enroll subjects who are not yet adults. *(Skip to Section 27.0)*

*28.13 Describe the criteria that will be used to determine **whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research** under the applicable law of the jurisdiction in which the research will be conducted **(e.g., individuals under the age of 18 years)**. For research conducted in NYS, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."*

*NOTE: Examples of acceptable responses include: verification via electronic medical record, driver's license or state-issued ID, screening questionnaire.*

Response:

*28.14**For research conducted outside of New York State**, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."*

Response:

*28.15 Describe whether parental permission will be obtained from:*

Response:

☐ One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

☐ Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

☐ Parent permission will not be obtained. A waiver of parent permission is being requested.

*NOTE: The requirement for parent permission is a protocol-specific determination made by the IRB based on the risk level of the research. For guidance, review the "CHECKLIST: Children (HRP-416)."*

*28.16 Describe whether permission will be obtained from individuals **other than parents**, and if so, who will be allowed to provide permission. Describe your procedure for determining an individual's authority to consent to the child's general medical care.*

Response:

*28.17 Indicate whether assent will be obtained from all, some, or none of the **children**. If assent will be obtained from some children, indicate which children will be required to assent.*

Response:

*28.18 When assent of children is obtained, describe how it will be documented.*

Response:

## 29.0 Waiver or Alteration of Consent Process

***Consent will not be obtained, required information will not be disclosed, or the research involves deception.***

☒ **N/A:** A waiver or alteration of consent is not being requested.

*29.1 If the research involves a waiver or alteration of the consent process, please review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure that you have provided sufficient information for the IRB to make the determination that a waiver or alteration can be granted.*

*NOTE: For records review studies, the first set of criteria on the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" applies.*

Response:

*29.2 If the research involves a waiver of the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:*

Response:

## 30.0 Process to Document Consent

☐ **N/A:** A Waiver of Consent is being requested.
*(Skip to Section 29.0)*

*30.1 Indicate whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not or if there are any exceptions, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.*

*NOTE: If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent. This is sometimes referred to as 'verbal consent.' Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information.*

*If you will document consent in writing, attach a consent document with your submission. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)". If you will obtain consent, but not document consent in writing, attach the script of the information to be provided orally or in writing (i.e. consent script or Information Sheet).*

Response:

☒ We will be following "SOP: Written Documentation of Consent" (HRP-091).

## 31.0 Multi-Site Research (Multisite/Multicenter Only)*

☒ **N/A:** This study is not an investigator-initiated multi-site study. This section does not apply.

*31.1 Indicate the total number of subjects that will be enrolled or records that will be reviewed across all sites.*

Response:

*31.2 If this is a multi-site study **where you are the lead investigator**, describe the processes to ensure communication among sites, such as the following. See "WORKSHEET: Communication and Responsibilities (HRP-830).":*

- *All sites have the most current version of the IRB documents, including the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*

- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately in accordance with applicable federal regulations and local laws.*
- *All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.*

Response:

*31.3 Describe the method for communicating to engaged participating sites (see "WORKSHEET: Communication and Responsibilities (HRP-830)"):*

- *Problems (inclusive of reportable events)*
- *Interim results*
- *Study closure*

Response:

*31.4 If this is a multicenter study **where you are a participating site/investigator**, describe the local procedures for maintenance of confidentiality. (See "WORKSHEET: Communication and Responsibilities (HRP-830).")*

- *Where and how data or specimens will be stored locally?*
- *How long the data or specimens will be stored locally?*
- *Who will have access to the data or specimens locally?*
- *Who is responsible for receipt or transmission of the data or specimens locally?*
- *How data and specimens will be transported locally?*

Response:

*31.5 If this is a multicenter study and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods. Local recruitment methods are described elsewheres in the protocol.*

- *Describe when, where, and how potential subjects will be recruited.*
- *Describe the methods that will be used to identify potential subjects.*
- *Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For*

*advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)*

Response:

## 32.0 Banking Data or Specimens for Future Use*

☐ **N/A:** This study is not banking data or specimens for future use or research outside the scope of the present protocol. This section does not apply.

*32.1 If data or specimens will be banked (stored) for **future use, that is, use or research outside of the scope of the present protocol**, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.*

*NOTE: Your response here must be consistent with your response at the "What happens if I say yes, I want to be in this research?" Section of the Template Consent Document (HRP-502).*

Response:

Blood specimens will be stored in a locked freezer at UBMD Neurology, 5851 Main Street, Williamsville, NY 14221 and in the laboratory of Luciana Frick on the 5th flooe of the CTRC. The specimens will be stored indefinitely. Only the PI and Dr. Frick will have access to the stored specimens. MRI scan data will also be stored indefinitely on the password-protected BNAC computer servers.

*32.2 List the data to be stored or associated with each specimen.*

Response:

Subject ID, DOB, date and time collected.

*32.3 Describe the procedures to release banked data or specimens for future uses, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.*

Response:

Any party besides the PI will need to obtain approval from the PI prior to release of any blood specimens. The request will need to have scientific merit, in the PI's opinion.