NCT02862210

Low-dose lithium for the treatment of behavioral symptoms in Frontotemporal Dementia
Standard Operating Procedures Manual
Version date 31May2021

Introduction

The Alzheimer's Drug Discovery Foundation funded a study titled "Low-dose lithium for the treatment of behavioral symptoms in Frontotemporal Dementia," which examines the efficacy and side effects of low dose lithium treatment for agitation/aggression/repetitive behaviors in 60 patients with FTD in a randomized, double blind, placebo-controlled 12-week trial.

Lithium carbonate or placebo will be started at an oral dose of 150 mg daily, with subsequent dose titration to 300mg/day at the 2-week visit, 450mg/day at the 4-week visit, and 600mg/day (maximum daily dose) at the 6-week visit. This upward dose titration will occur if clinically indicated, tolerated by the patient, and based on real/sham lithium blood level. An absence of response at lower doses without intolerable side effects is defined as clinically indicated. Assessments will take place at study entry (0 weeks), 2, 4, 6, 8, and 12 weeks, and the time-point of protocol exit for dropouts. Lithium levels will be drawn approximately 12-14 hours after the last dose.

Our primary outcome measures will be the Neuropsychiatric Inventory and the Clinical Global Impression scales.

Optimal target serum levels of lithium will be between 0.2 to 0.6 mmol/L due the risk of dropout due to lithium toxicity at higher levels. Clinical response of symptoms and side effects experienced by the patient will be primary in guiding oral lithium dose adjustment, and will override the information obtained from serum lithium levels if such a choice needs to be made.

This study will provide useful data on the efficacy and side effects of low-dose lithium treatment for FTD patients with symptoms of agitation/aggression, and possibly for other behavioral symptoms such as aberrant motor behaviors. The potential utility of lithium would provide an alternative for patients who show no/minimal response to or experience intolerable side effects while on antidepressants and antipsychotics.

During COVID, it was decided that the protocol would be updated to allow for a portion of the study visits to occur remotely. This was largely to reduce risks to participants once the study reopened (I.e. to minimize time traveling to a hospital), but also, we hoped this would make the study less burdensome to patients and study partners moving forward.

Management of Trial (ADDF, IRB, DSMB)

Coordinator Role

The research team at CUMC is responsible for the proper conduct of project and data management. The research coordinator will be responsible for communications essential to the trial, such as those with the grant awarder (the Alzheimer's Drug Discovery Foundation, ADDF), the Data and Safety Monitoring Board (DSMB), the Institutional Review Board (IRB), and the research pharmacy.

Alzheimer's Drug Discovery Foundation (ADDF). This trial is funded through a grant awarded by the ADDF. An interim progress report to the ADDF will be generated by the lead site staff every 6 months, with reports due each year on **April 30st** and **October 30th**. A final progress report will be submitted upon completion of the grant award. Resources to prepare the report are here: https://www.alzdiscovery.org/research-and-grants/resources.

The following information will be included in reports to the ADDF:

- IRB approved changes to the protocol
- Subject recruitment, screening, and enrollment numbers
- Reports of all serious adverse events
- Summary of guidance from the DSMB

The research coordinator is responsible for writing the scientific portion of the report (and reviewing with Dr. Huey). The financial coordinator (currently Michelle Yu) will prepare the financial portion and will send both parts to the grant office. Reports should be prepared ~1 month before they are due and sent to Michelle no later than 2 weeks before they are due for final approval.

After the progress report has been submitted, the ADDF will reach out to schedule a teleconference with Dr. Huey and the research coordinator to discuss the materials of the report.

Recruitment

Sources

1. Direct referral (from DPO clinician or outside clinician)
2. Identified via DPO tracker (log of patients seen by DPO doctors)
3. Identified via Ted's clinic schedule
4. Self-referred (via advertisement)

Procedure (broadly)

1. Confirm diagnosis
2. Confirm eligibility (see details below under "Prescreen")
3. Confirm interest

If DPO patient:

1. Review chart for eligibility
    a. Neurologist clinical notes, MRI/PET scan record, neuropsychological testing
    b. Generally we trust an internal diagnosis, but it is good to confirm and particularly to look for indications of agitation or repetitive behaviors
2. Contact treating physician to ask for referral (or discuss with Ted if his patient)
    a. In email, include patient name / MRN, brief description of study, summary of information relevant to patient eligibility.
3. If referred, reach out to the patient's contact to describe study, determine interest, and confirm eligibility

If outside referral:

1. Discuss by phone to assess potential eligibility
    a. Possible diagnosis of FTD, appropriate symptoms, access to study site
2. If potentially eligible, request record of outside neurological records for review
    a. Neurologist clinical notes, MRI/PET scan record, neuropsychological testing
3. Upon review of records, if insufficient information to determine eligibility, refer them to make a clinical appointment with Ted, after which you can reassess eligibility

For both:

4. If eligible, send study flyer & consent form for review. Plan second call to review information, answer questions, and schedule baseline visit. This can be multiple communications if necessary, but spreading the communication over too long a period runs the risk that they will forget key details. It is good practice to regularly review key components of the study and participation.
    1. Points of emphasis:
        1. The study is voluntary and participation can be ended at any time
        2. It is a placebo-controlled study, so there is a 50% chance of receiving placebo, but at the end of the trial participants on placebo may be started on lithium off-label if clinically indicated

3. Study duration (12 weeks), visit commitment (1-3 hours every 2 weeks, first and last in-person, the rest over zoom)

5. It may also be appropriate to describe observational study options (ALLFTD / NAPS) to the potential participant. This can be coordinated in advance with Masood / NAPS team and will impact scheduling details. In this case, send flyers for these studies as well & refer for conversation with primary study coordinator.
6. All chart reviews and patient communications should be documented in the Research Screening Log excel file or in Ripple
    a. Chart reviews are regularly entered into the DPO review tab for outside DPO doctors and into the DPO Visits Ted Eligibility excel (managed by Masood) for Ted's patients.
    b. Any patients potentially eligible for lithium should be transferred to the Lithium Screen tab, where notes on eligibility review can be added. It should be specified on this tab whether the patient was subsequently contacted (and transferred to the phone screen tab) or was determined ineligible
    c. Once telephone contact for recruitment has been approved, patients should be entered into the phone screen tab, where contact information and recruitment notes will be regularly updated.

Prescreening

To comply with Health Insurance Portability and Accountability Act (HIPAA) regulations, we applied for a partial waiver of HIPAA and were granted a partial waiver for telephone screens and a full waiver for the purpose of accessing an existing database or records to identify potential research subjects (Forms: "Request for HIPAA Waiver Authorization and/or Waiver of Consent)". These waivers were granted with initial IRB approval of the protocol.

1. For the prescreening process, review patient charts for:
    a. Age
        i. (40-85)
    b. Active medical conditions
        i. (include: bvFTD, svPPA, nfvPPA with behavioral symptoms of agitation, aggression, disinhibition, repetitive behaviors, aberrant motor movements, etc)
        ii. (exclude: Parkinson's disease, Lewy body disease, multiple sclerosis, CNS infection, HD, amyotrophic lateral sclerosis, other major neurological disorder, clinical stroke with residual neurological deficits e.g. small infarcts, lacunes, periventricular disease (if these cerebrovascular diseases are found from MRI in absence of stroke it will not lead to exclusion), medical contraindication to lithium treatment or prior history of

intolerability to lithium treatment such as resting tremor causing functional impairment, untreated thyroid disease or any abnormal thyroid function, unstable cardiac disease, schizophrenia, other psychosis or bipolar 1 disorder, current or last 6 month alcohol or substance abuse, major depression or suicidality, acute, severe, unstable medical illness (e.g. active or metastases cancer will be excluded, but past history of successfully treated cancer will not lead to exclusion).

c. Current medications
    i. (exclude: therapeutic or higher doses of diuretics, i.e. hydrochlorothiazide greater than 25mg daily, furosemide greater than 10mg daily, no higher than 1 mg/day of lorazepam for anxiety/insomnia)
d. Recent Lab results
    i. (exclude: abnormal TSH, T3, or T4, creatinine level greater than 1.5mg/100ml or a glomerular filtration rate less than 44ml/min/$1.73m^2$, blood pressure > 170/100 mmHg, heart rate < 50 bpm)
e. Recent physician evaluation/follow-up notes
    i. (include: if physician mentions agitation, aggression, or having behavioral disturbances, MMSE 5-30 out of 30, Neuropsych Inventory (NPI) agitation/aggression subscale score or disinhibition subscale score or aberrant motor subscale score ≥ 4 indicating moderate to severe symptoms, or total NPI score ≥ 4)

Screening/Baseline Visit

Since making the protocol hybrid-remote, we have combined the screening and baseline visits into a single in-person visit to increase efficiency and minimize the number of visits to the clinic. This visit will be completed in-person. For a brief checklist to refer to when running the visit, see "Visit Checklists" at the end of this manual.

Study ID

All participants coming in for a screening/baseline visit will be assigned a Study ID, which will be a number from 1001-1999. Even if the participant does not remain in the study, they will retain this study ID and it will not be reassigned.

Consent Procedures

A study physician listed on the site's IRB protocol will obtain voluntary informed consent from patients who retain the capacity consent. Typically, patients with Folstein MMSE greater than 20 out of 30 retain this capacity.

The consent form describes the nature of the procedures and time requirements, potential risks, confidentiality of information, and the rights of research subjects, including their right to withdraw from the research at any time without loss of benefits to which they are otherwise entitled. It is made explicit that this protocol involves a randomized controlled trial in which the patient will be randomly assigned to lithium or placebo for a 12-week period.

Patients' capacity to consent or to assign a surrogate of consent is assessed, as described below. Screening/baseline procedures should be completed on the same day, following consent procedures whenever possible. If not, the screening date should correspond as closely with the informed consent date as possible.

After the informed consent forms are signed, the patient and informant will participate in a screening session. The screening includes structured interviews inquiring about the patient's medical and psychiatric history. To minimize anxiety, patients and informants will be informed about the nature of the interviews beforehand. Patients and informants will also be informed that all findings will be kept strictly confidential.

Consent capacity assessment procedures:

An independent evaluator, an MD or clinical psychologist PhD independent of the research study, will be present to conduct an evaluation to determine whether a patient retains the capacity to consent, and if not, whether they retain the capacity to appoint a surrogate. This will be documented in the research chart. This physician should be familiar with the study and study

personnel, but cannot also be a study physician (typically, this is done by clinical fellows in the Neurology department). Generally, the independent physician makes a decision after observing the study coordinator or study physician explain the study basics to the patient and study partner, and may choose to ask the patient some basic questions to determine understanding (i.e.: "can you describe the study to me in your own words? What are the risks of the study? If you no longer wished to participate, what would you do?").

For patients who lack the capacity to consent, as is expected for most patients in this study, the required NYSPI/Columbia IRB-approved surrogate consent procedures will be followed as detailed below. Patients who lack the capacity to consent will be required to have the capacity to appoint a surrogate, after which the patient will need to appoint the surrogate. The independent evaluator will ask further questions to make this determination (i.e.: "is there someone who you would trust to make a decision for you?"). Out of the patients who lack the capacity to consent, those who also lack the capacity to appoint a surrogate or do not wish to appoint a surrogate will not be included in the study. Under no circumstance will a patient objecting to participation be included in the study. NYSPI PCS forms I-IV should be completed, along with a consent procedure note.

If the patient is determined to have the capacity to appoint a surrogate, two witnesses independent of the research study will be present to bear witness to and declare that the patient is acting willingly and free from duress (one of whom may be the independent physician and the other of whom is usually another RA from the lab). If the patient appoints a surrogate to consent, the CUMC coordinator needs to send notice of this decision, using the NYSPI PCS Policy Letter format, to the Mental Health Legal Service located at 41 Madison Avenue, 26th Floor, New York New York 10010. Copies of this notice should be sent to the CUMC IRB, put in the patient chart, and put in the regulatory binder.

<u>Screening/Baseline Evaluation</u>

The visit encompasses completion of the screening-baseline packet to determine eligibility following consent procedures. Once the informed consent process has been completed, all remaining procedures can occur. It is not permitted to collect biological samples (blood) from a patient before informed consent has been obtained.

To decide the order in which measures and procedures will be completed, consider which items are completed by coordinators and which are completed by physicians. An efficient approach to the screening visit could involve a study physician completing the NPI and other interview measures with the patient's informant in one exam room, while the study coordinator completes the MMSE, vitals, blood draws, and EKG with the patient in a separate exam room. Note that the study physician will need to complete a physical exam with the patient as part of the screening

visit. Alternatively, the coordinator may do all procedures sequentially, scheduling in a brief period for the study physician to complete the clinical examination. Visit structures may vary participant to participant. Some participants cannot be left alone, and so coordinators may consider allowing them to stay present during the caretaker interviews, if this is not disruptive to the reporting. Similarly, caretakers may vary in the amount of information they provide during interviews, and this can be taken into account for time estimates. It is good to remain flexible during each visit.

At the conclusion of the screening/baseline visit, study staff should know which inclusion/exclusion criteria are met and which are not, with the exception of those that require lab results to determine. If at this point the patient has not been excluded, the participant should be informed that after all lab results are returned, the research pharmacy will ship the study drug kit directly to the participant's home.

<u>The following assessments will be completed at the screening/baseline visit:</u>

Physician-completed:

- Clinical Evaluation & Physical Examination
- CGI (Global Impression of Severity)
- SCID and CSSR-S
- Lawson IDLs
- Simpson-Angus Scale
- Treatment Emergent Symptoms Scale (baseline measure for comparison)

Coordinator-completed

- Confirmation of diagnoses*
- Medical History & Concomitant Medications*
- MMSE (Folstein Mini Mental Exam)
- MDRS (Mattis Dementia rating Scale)
- FBI (Frontal Behavioral Inventory)**
- Zarit Caregiver Burden Interview**
- NPI (Neuropsychiatric Inventory and Stereotypic and Ritualistic Behaviors)**
- Vital signs
- Blood specimens collected (CBC, BMP, Thyroid panel, BDNF) – 3 tubes total
- EKG

*Note that much of this can be filled out from past medical records

** For COVID safety or convenience, these may be completed by phone/Zoom after the visit, but completing everything during the in-person evaluation is preferred.

The breakdown between study physician and coordinator is what was agreed upon by Dr. Huey and Hannah Silverman, but can be renegotiated as needed depending on who is acting as physician/coordinator.

Sample schedule:

Color-codes
Coordinator
Physician
Coordinator, Physician, Independent Evaluator

Time	**Assessment**
30 mins	Consent & Capacity Assessment
30 mins	Physical Exam, SCID, CSSR, CDR, Lawson, SAS, TESS, CGI
30 mins	MMSE, MDRS with patient
30 mins	EKG, Blood Draw with patient
45-60 mins	NPI, FBI, Zarit with Study Partner

Note that after the blood draw, samples must be dropped off at the respective labs by 3pm.

- The biomarker core lab is located on PH10-104 through the double doors in the opposite direction of the clinical rooms from the Irving reception area. There is a drop-off bin at the entrance of the lab.
- The CALM lab is located on the 15th floor of the Presbyterian Hospital in room 15-401, where there is a drop-off bin when you enter the lab.

If a patient is ineligible at a screening visit but is still interested in participating in the study, it is up to the clinical judgment of a study physician to decide whether or not to re-screen this patient. Some lab results or vital signs may change over time, making a patient eligible for the study. If a patient is re-screened and found eligible, they are no longer considered a screen fail and their status can be updated on the screening log.

<u>Doubtful Subjects for Inclusion/Exclusion</u>

Obtain recent labs and relevant medical records for potential research recruits whenever possible. Ideally, you will have obtained a recruit's medical records and reviewed them with a study physician prior to a screening visit. If there is any doubt that a recruit will be eligible on one or more specific criteria, study staff should do their best to obtain records and get in contact

with a patient's other treating physicians to clarify their status and safety to enter the trial. Review any active or concerning medical conditions with patient's primary care physician (PCP) or specialists such as a cardiologist. You may also want to discuss the consent process with the study partner in advance of the visit to assess whether the patient is likely to be able to consent or assign a surrogate for consent.

Electrocardiogram

EKGs will be taken at screening and week 12 visits. QTc interval > 460 ms at the time of baseline EKG is an exclusion criterion for treatment. All EKGs should be read, signed and dated by a study physician, then filed in the patient's research chart. If a screening visit EKG leads to a question of whether it is safe for a patient to take lithium, study staff should consider contacting, and discussing this concern with, the patient's cardiologist if they have one. EKGs must be completed by a trained coordinator or study physician. If this is not possible, Ismael or Sonia at the CRR may be scheduled to conduct the EKG – this request must be included in the CRR room booking form when the visit is scheduled.

Biological Sample Collection

Biological sample processing is done by both the Center for Advanced Laboratory Medicine (CALM) lab and the Biomarkers Core Laboratory.

<u>Tubes used for biological sample collection:</u>

- Blood for CBC must be collected in lavender top glass tubes
  (Lavender EDTA tube; Catalog BD 367841)

- Blood for Basic Metabolic Panel (BMP), Thyroid panel, and serum lithium level must be collected in gold tubes with gel
  (Gold serum tube; Catalog BD 367986)

- Blood for BDNF must be collected in red top tube without gel
  (BD Vacutainer Plus plastic serum tube with silicone coating; Catalog BD 367820)

<u>Fisher Scientific - Ordering</u>

Blood tubes are ordered by phone via Fisher Scientific using the registered **Columbia account number 162597-018**. It is necessary to order through this account for Columbia discounts. Be sure to regularly check tube expiration dates.

- Columbia Contact, Jeff Stein: 973-265-3311; jeff.stein@thermofisher.com (*preferred contact method)*
- Generic contact number: 1-800-766-7000

Assays by visit:

Screening/Baseline:

- CBC (Lavender tube)
- Basic Metabolic Panel (BMP), T3, T4, TSH (gold tube)
- BDNF (red tube)

Week 6:

- CBC (Lavender tube)
- Basic Metabolic Panel (BMP), T3, T4, TSH, Serum Lithium (gold tube)

Week 8:

- Serum Lithium (gold tube)

Week 12:

- CBC (1 Lavender tube)
- Basic Metabolic Panel (BMP), T3, T4, TSH, Serum Lithium (1 gold tube)
- BDNF (1 red tube)

Note that if it is clinically indicated for the participant to come into the clinic for Week 2, 4, or 10, additional blood may be drawn depending on clinician recommendation.

Processing Biological Samples:

(DONE BY LAB, NOT BY RA)

- For CALM lab processing (Lavender/Gold): tubes should be labeled with subject number and submitted with a CALM requisition form.
- For the CUMC Biomarkers Lab (Red): tubes should be labeled with date, CRC project number (2016-039) and subject number and submitted with a Biomarkers specimen delivery form. Note that the COVID screen referenced on this form is the same as the screening form completed for use of the Irving Institute rooms.

- **CBC** 1 Lavender top tube

1. Invert tube 8 times.

2. Allow to sit at room temperature.

- BMP, Thyroid Tests & Lithium Levels: 1 Gold top tube with Gel

1. Invert tube 5 times.
2. Allow to clot for 30 minutes at room temperature
3. Spin for 10 minutes at 3500rpm

- BDNF: 1 10mL Dark red top tube w/ silicone coating REF: 367820

1. Allow to clot for 30 minutes at room temperature
2. Spin the sample in a refrigerated centrifuge for 15 minutes
3. Pipette samples into tubes
4. These samples should then be labeled in sharpie and immediately placed in a -80°C freezer

Obtaining results

After each visit, download the results of blood testing, which should become available within 24 hours

1. On Internet Explorer, navigate to sac-cu.org and log in
2. Click on "Samples" for the Lithium in FTD study and download a "detailed spreadsheet" of the most recent "batch"
3. Copy the results that correspond to the correct subject/visit into the "Lithium Reference Ranges" Excel document in dopamine>Lithium>CALM. Convert the results from "text" to "number" in Excel. Results which are out of range will automatically highlight red.
4. Print this for Ted's signature and date.

ExamOne Mobile Phlebotomy

To facilitate remote visits while maintaining safety monitoring, we have established a partnership with ExamOne, a mobile phlebotomy unit run by Quest Diagnostics. We will use their services during the Week 6 and Week 8 visits, which will be otherwise conducted virtually. This means that the coordinator will need to prepare two blood collection kits for each participant enrolled prior to their screening/baseline visit as well as use the ExamOne portal to schedule at-home blood draws prior to the week 6 and week 8 visits.

Blood Collection Kits

Kits for the two at-home blood draws should be prepared in advance and given to the participant at the end of the screening-baseline visit. Kits are ordered from Fisher Scientific, catalog number

22 130 420 (see "Biological Sample Collection" for ordering instructions) and come with materials necessary for specimen packaging. This includes the following:

- Freezer therapak gel pack.
- Biohazard and Biological Substance Category B stickers.
- Tube sheath and specimen transport bag.
- Silver padded insulated envelope.

In addition to the materials that come with the kits, the following should be added:

- Documents in dopamine > Lithium in FTD > ExamOne > Kit Materials
    - Biological Sample Collection Instructions
    - Vital Signs Form
    - Pre-populated CALM requisition form
- Blood tube(s) labeled with subject ID.
- Prepared, addressed FedEx label (see below).

Once the necessary materials are enclosed, the kits should be closed and the top surface of the kit should be labeled with:

1. A prepared FedEx label (see below)
2. The Category B and Biohazard stickers included in the kit
3. An additional label (e.g. a taped post-it) with
    a. Kit # (e.g. *"Kit #1"* or *"Kit #2"*)
    b. The anticipated week of kit use (e.g. "*for use week of 5/30/2021*").
    c. On Kit #1, also write "Use this kit first!" to aid the mobile phlebotomist in distinguishing the correct kit.

Preparation of FedEx Labels

1. Navigate to fedex.com
2. Log in: Username= Taubadm, Password= Happy2bhere
3. Under the "shipping" tab select "create a shipment" and fill in the information
    a. From: The name should be that of the research coordinator followed by "Lithium in FTD". The rest of the address should be that of the study participant. Phone number should be listed as the office phone of the RA.
    b. To:
    Columbia University Medical Center
    Erin Poptanich - CALM
    630 W 168th Street
    P&S Building, 15-401
    New York, NY 10032
    (212) 305-4837

c. Package & Shipment Details:
    i. Ship date: OK to leave as date label was prepared
    ii. Pricing option: FedEx Standard Rate
    iii. Weight: 5 lbs
    iv. Declared value: $20
    v. Service type: Standard overnight
    vi. Package type: Your Packaging
    vii. Dimensions: 13x10x3
d. Billing Details:
    i. Bill transp. To Acct-507-507;
    ii. Reference: “Huey-Lithium-PG007021"; leave the rest blank
e. Leave all other fields blank

4. Print this label and adhere to outside of the collection kit with packaging tape.

Scheduling Remote Blood Draws

Each coordinator will be given a unique login after filling out information in dopamine > Lithium in FTD > ExamOne > “Portal User Set Up” and emailing this to Kimberly. To schedule at-home blood draws, first the participant will need to be entered as a new “case.” Then, for each blood draw, a new order will be created.

To add a participant to the system:

1. Log in
2. Navigate to “Create Case”
3. Study: “Dr. Huey’s Lithium in FTD trial at Columbia”
4. Policy: “Health individual”
5. Policy #: subject ID
6. Policy amount: 0
7. Quote back: leave blank
8. Applicant/Address/Contact: put in participant information. Only information with an asterisk is needed, with the exception of contact phone number, which is required

To create an order:

1. Click the correct case (participant) on the home page
2. On the upper right side of the page, click “Create Order”
3. Select “paramedical services”
4. Select our account. Services have been pre-assigned-- leave as is.
5. Notes: Specify that all communication will go through the study partner & provide his or her name. Include the week or date when you would like the draw to occur.

6. Do not attach any files
7. Click “submit and schedule” to schedule the draw yourself after consulting the participant for his or her availability, or “schedule” to have the company schedule the appointment directly. (*Note:* In my experience so far, the latter is more efficient, as the appointment availability is not up to date when I attempt to schedule myself.)
8. If scheduling directly:
    a. Click “personal location” to have the draw scheduled to the participant’s home.
    b. Available times will be shown for each open date. Draws must be scheduled more than two days in advance. Draws should be scheduled for mornings Mondays through Thursdays.
    c. Click the stethoscope
9. The mobile phlebotomist will confirm the visit with the participant 24 hours in advance. Even if they do not receive a response, they will still go to the scheduled appointment.

To view orders:

1. Once an order has been created, you can view it in the “Order Center” tab.
2. “ Paramedical Examination Order” will show the order status and number
3. “Office details” will show the contact information for the office out of which assigned the phlebotomist is based. If you need to reschedule the visit, use this contact information (and you may also contact Kimberly).
4. “Order Services” will show the date/time of the scheduled order
5. “Freight #” will show the fedex tracking number once the order has been shipped
6. “Status messages” will describe any participant contact

Randomization

Randomization is initiated once it is determined that a patient satisfies all of the inclusion and none of the exclusion criteria. This means that a study drug order form should not be submitted to the pharmacy until all screening visit lab results have been reviewed by a study physician.

Within the study drug order form, the IRB# field should be filled as 7310. For the drug name, strength, dosage form, and Quantity fields, both should be filled as 1 Lithium 150 mg/placebo kit. The Study Week/Visit/Phase field should be filled as Week 0.

Randomization is not officially completed until the medication has been shipped to and received by the participant. If a study drug order form has been submitted and a drug ID has been generated but the patient will not be officially randomized, the randomization order can be canceled by completing the bottom portion of the study drug order form and re-submitting it to the NYSPI pharmacy. If the randomization order is canceled, the drug ID will be made available to the next patient. Once a patient has been officially randomized at baseline, their drug ID cannot be used for any other patient under any circumstances.

Randomization Procedures:

When a new patient enrolls in the study, research coordinator (R.C.) will send a study drug order form via email to the NYSPI pharmacy.

-Drug IDs will be assigned by the pharmacy

CUMC Drug ID#: LF101-LF199 (last two digits of drug ID are one lower than the last two digits of the subject ID, e.g. subject ID #1017 and drug ID #LF116)

Each time a new patient is randomized, the pharmacy must email the updated randomization tables to the unblinded physician, Dr. Roose. The pharmacist should be reminded of this instruction when the randomization form is sent.

The pharmacy should be instructed to mail the kit directly to the research participant. They should not include the unblinding envelope in the kit. The coordinator/physician should review dosing instructions with the caregiver at the time of the visit (starting dose = 1 pill daily in the evening, use the same bottle between for the full two week interval). The coordinator should notify the caregiver once the study drug has shipped and should ask the caregiver to contact them when it arrives. Once the kit has been received, the coordinator should review these instructions with the caregiver by phone, and the dosing should begin that day. At this time, the Week 2 virtual visit may be scheduled to occur approximately 2 weeks after the participant begins the study medication.

Sample email to pharmacy upon randomization:

"Please find attached a new study drug order.

Please mail the study drug kit to directly to the participant at the listed address. Please do not include an unblinding envelope. The cost of this can be billed to our study protocol, NYSPI #7310, Lithium in FTD.

Week 2 Visit

Typically, this will be a virtual visit with no at-home blood draw. If there are clinical concerns (e.g. significant side effects), this can be converted into an in-person visit, which is true for all visits that typically occur virtually.

The visit should be scheduled in advance, and a calendar invitation (with a zoom link and schedule) should be sent to both the study physician and the caregiver.

At the visit, the oral dose may be adjusted from 150 mg/day up to 300 mg/day. This will be based on assessments and evaluation of the following:

- Clinical response
- Side effects

<u>The following assessments will be completed at the week 2 visit:</u>

- Concomitant Medications
- NPI
- Stereotypic and ritualistic behaviors
- CGI Behavior (CGI-S, CGI-C)
- CGI Global (CGI-S, CGI-C)
- TESS
- Medication compliance (the study partner will be asked to count on camera the number of pills remaining in the bottle they used for the first two weeks to ensure correct dosing. 14 pills should remain in the bottle if the medication has been taken for 14 days).

The week 2 visit is estimated to take 60 minutes on average.

Color-codes
Coordinator
Physician

Time	Assessment
20 minutes	Vitals, TESS, Concomitant Meds, CGI, with Patient and Caregiver.
10 minutes	Medication compliance review
30 minutes	NPI with Caregiver

At the end of the visit, caregivers should be given new dosing instructions (if the dose has increased, this would be 2 pills/day, one in the morning and one at night) and instructed to switch to a new pill bottle until the next visit (the bottle caps can be labeled with sharpie for ease). The week 4 visit should be scheduled and calendar invitations sent out.

Week 4 Visit

At week 4, the oral dose maybe adjusted from 300 mg/day up to 450 mg/day. This will be based on based on assessments and evaluation of the following:

- Clinical response
- Side effects

<u>The following assessments will be completed at the week 4 visit:</u>

- Concomitant Medications
- Clinical Dementia Rating (CDR)
- CGI Behavior (CGI-S, CGI-C)
- CGI Global (CGI-S, CGI-C)
- NPI
- Stereotypic and ritualistic behaviors
- TESS
- SAS
- Lawson ADL
- Zarit Caregiver Burden Interview.
- Medication compliance (the study partner will be asked to count on camera the number of pills remaining in the bottle they used for the first two weeks to ensure correct dosing. 0 pills should remain in the bottle if the medication has been taken for 14 days at 300mg/day).

The week 4 visit is estimated to take 70 minutes on average.

Color-codes
Coordinator
Physician

Time	Assessment
20 minutes	Vitals, TESS, Concomitant Meds, Simpson-Angus, CDR, CGI, Lawton with Patient and Caregiver. Lithium Prescription
10 minutes	Medication compliance review
40 minutes	NPI, Zarit with Caregiver

Week 6 Visit

At week 6, blood for serum lithium level will be drawn and the oral dose subsequently adjusted from 450 mg/day up to 600 mg/day if needed. This will be based on the following assessments and evaluations:

- Clinical response
- Side effects
- Blinded lithium level obtained from the unblinded physician

<u>The following assessments will be completed at the week 6 visit:</u>

- Concomitant Medications
- CGI Behavior (CGI-S, CGI-C)
- CGI Global (CGI-S, CGI-C)
- NPI
- Stereotypic and ritualistic behaviors
- TESS
- Medication compliance (the study partner will be asked to count on camera the number of pills remaining in the bottle they used for the first two weeks to ensure correct dosing. 14 pills should remain in the 2nd bottle if the medication has been taken for 14 days at 450mg/day).

Completed by ExamOne:

- Vital signs
- Serum lithium level
- Safety labs

The week 6 visit is estimated to take 1.5-2 hours on average.

Color-codes
Coordinator
Physician

Time	Assessment
10 minutes	TESS, Concomitant Meds, CGI, with Patient and Caregiver.
30 minutes	NPI with Caregiver
10 minutes	Medication compliance review

Vital signs and blood draw will be scheduled separately and completed by the Exam One mobile phlebotomy team, who will ship samples directly to the CALM lab for processing.

Week 8 Visit

At week 8, blood for serum lithium level will be drawn and the oral dose subsequently adjusted up to 600 mg/day if needed based on the following assessments and evaluations:

- clinical response
- side effects
- Blinded lithium level from the unblinded physician.

<u>The following assessments will be completed at the week 8 visit:</u>

- Concomitant Medications
- CDR
- CGI Behavior (CGI-S, CGI-C)
- CGI Global (CGI-S, CGI-C)
- NPI
- Stereotypic and ritualistic behaviors
- TESS
- SAS
- LADL
- Zarit Caregiver Burden Interview.
- Medication compliance (the study partner will be asked to count on camera the number of pills remaining in the bottle they used for the first two weeks to ensure correct dosing. 0 pills should remain in the 2nd bottle if the medication has been taken for 14 days at 600mg/day).

Completed by ExamOne:

- Vital signs
- serum lithium level

The week 8 visit is estimated to take 50 to 60 minutes on average.

Color-codes
Coordinator
Physician

Time	Assessment
20 minutes	TESS, Concomitant Meds, Simpson-Angus, CDR, CGI, Lawton with Patient and Caregiver. Lithium Prescription
40 minutes	NPI, Zarit with Caregiver
10 minutes	Medication Compliance Review

Vital signs and blood draw will be scheduled separately and completed by the Exam One mobile phlebotomy team, who will ship samples directly to the CALM lab for processing.

Week 10 Visit

Medication will not be increased above 600mg/day at this visit. However, if medication adjustments are still needed, an additional blood draw for a serum lithium level may be scheduled with Exam One, with an additional blood draw kit shipped to the participant in advance, OR the participant may be scheduled to complete the visit in clinic.

<u>The following assessments will be completed at the week 10 visit:</u>

- Concomitant Medications
- CGI Behavior (CGI-S, CGI-C)
- CGI Global (CGI-S, CGI-C)
- NPI
- Stereotypic and ritualistic behaviors
- TESS
- Medication compliance (the study partner will be asked to count on camera the number of pills remaining in the bottle they used for the first two weeks to ensure correct dosing. 14 pills should remain in the 2nd bottle if the medication has been taken for 14 days at 450mg/day).

Completed by ExamOne (IF NECESSARY):

- Vital signs
- Serum lithium level
- Safety labs

The week 10 visit is estimated to take 50-60 minutes on average.

Color-codes
Coordinator
Physician

Time	Assessment
10 minutes	TESS, Concomitant Meds, CGI, with Patient and Caregiver.
30 minutes	NPI with Caregiver
10 minutes	Medication compliance review

Vital signs and blood draw will be scheduled separately and completed by the Exam One mobile phlebotomy team, who will ship samples directly to the CALM lab for processing.

Week 12 Visit

At CUMC, unblinding by the study physician will occur after all week 12 measures and procedures have been completed.

The following assessments will be completed at the week 12 visit:

- Concomitant Medications
- CDR
- CGI Behavior (CGI-S, CGI-C)
- CGI Global (CGI-S, CGI-C)
- NPI
- Stereotypic and ritualistic behaviors
- TESS
- Zarit Caregiver Burden Interview
- Vital signs
- blood specimens collected
- ECG
- protocol exit form
- Medication compliance: kit collection. An additional 4 bottles (128 pills) should have been used since the week 8 visit if the bottle if the medication has been taken for 28 days at 600mg/day).

Blinding: Lithium/sham levels procedures

While study staff is to remain blinded to drug assignment (lithium/placebo) during the 12 week trial, patients will have lithium blood levels taken at weeks (2, 4,) 6, 8, and 12 for safety monitoring and dosage adjustment. We will follow the procedures successfully used for blinded lithium levels in controlled trials in mood disorders. A physician independent of the study will receive lithium levels. This unblinded physician will provide the actual lithium level to the study physician for patients randomized to lithium, and make up a comparable sham level for patients on placebo. This sham level will vary from low to high levels and will be largely based on the number of pills taken by the patient. Target serum lithium level is 0.4 - 0.6 mmol/L. Based on the blood level received and clinical response and tolerability, the study physician will adjust the number of pills at study visits.

Masood will act as the unblinded RA. At each study visit where lithium levels are drawn (weeks 2,4,6,8,12) the study coordinator will give the serum lithium/sham lithium level form to the unblinded RA with the following information already filled in: current daily dose of lithium/placebo, how administered, number of hours between last oral dose and blood draw, date blood drawn. The unblinded RA will receive lab results for patients active in the protocol, including their real lithium level results, via the CALM website. The unblinded RA will email both the partially completed serum lithium/sham lithium level form, and that patient's lab results to the unblinded physician (Dr. Roose). The unblinded physician will complete the form by writing either a real lithium level or a sham lithium level and then signing and dating the form. At this time, the unblinded physician will also enter the real lithium/sham lithium level into the updated randomization spreadsheet provided to them by the NYSPI pharmacy. The unblinded physician will email the completed form to the unblended RA, who will forward it to the study coordinator

Upon receipt of the completed serum lithium/sham lithium levels form, the study coordinator will contact the study physician and report: the sham/real lithium level, current daily dose, and study interval. Based on this information, as well as observed tolerability and side effects, the study physician will choose to change the patient's dosage or continue with current dosage. The study coordinator will then call the patient's caregiver to inform them of the dosing change or lack thereof. The study coordinator will log all of this information on the lithium/sham level log located in the front of the patient's research chart.

If there are unusual circumstances pertaining to dosage, such as a patient having skipped a dose the day before the blood draw, provide as much relevant information as needed to the unblinded physician so they may generate the most realistic sham level.

Study coordinators and physicians should instruct caregivers to avoid administering study medication to a patient the same morning of a blood draw. We are targeting trough serum lithium levels for consistent measurement. If lithium is administered the same morning as a blood draw, the serum lithium level is likely to be artificially high and exceed our target therapeutic levels for this protocol. Caregivers can be instructed to give the lithium dose after the study visit.

Breaking the Blind and Open Treatment

Once all week 12 measures are completed, the study physician will break the blind with the participant and the study partner. The unblinding information is contained in an envelope provided by the research pharmacy, which must be requested and collected prior to the week 12 visit.

The study physician will review outcome measures and results based on the first 10 weeks of the study, which will be compiled in Excel by the study coordinator before the visit (using the template "Exit Summary" excel document in dopamine>Lithium in FTD>Exit Summaries). The physician will then discuss the possibility of whether to continue the dose of lithium, if the participant was an active responder, or whether to begin a low dose of lithium if the participant was on placebo. If the study physician is not the primary physician for the participant, this decision must be discussed with the referring physician, to whom the study physician may make a recommendation. When referring to outside physicians, it is important to thoroughly inform them of the plan for lithium treatment and the target therapeutic levels for this population. The study coordinator is expected to remain blinded even after the participant completes the trial.

Adverse Events and Protocol Deviations

Adverse events and serious adverse events will be carefully monitored, recorded, and reported in this study. An adverse event (AE) is an unexpected medical occurrence or worsening of symptoms, which does not necessarily have a causal relationship with study treatment. Study physicians should monitor gait disturbances or tremor of at least moderate intensity as well as falls in particular for this study. A serious adverse event (SAE) is a medically serious event, any event requiring hospitalization, and death.

Each patient that has an AE or SAE reported will have an AE log filed in their research chart. Both AE and SAE are to be recorded on the AE log version date 07/18/2016. AE logs are to-data forms for this study. Hardcopy AE forms are rewritten each time new information about the event is

made available, with all revisions kept in paper research charts. However, the database AE form will only contain information reflecting the final resolved event or last recorded information once the patient has left the protocol. Information regarding the treatment provided, outcome, and presumed relationship to study drug will be updated as new information becomes available. Site PIs will sign the bottom of the AE logs for their own site once the patient has exited the protocol.

Serious adverse events (SAE) are also logged on the AE form for data purposes in this study. SAEs will be reported to the IRB following the procedures on PRISM. All documentation of SAE reports and correspondence should be filed in the study regulatory binder.

If unavoidable deviations from the study protocol occur, they will be recorded on a protocol deviation form filed in the patient's research chart. A copy of each deviation form will also be filed in the site's regulatory binder.

Caregiver Communications

Study coordinators will call or email caregivers to confirm their appointments one day before the scheduled date. When calling to confirm an appointment, take the opportunity to remind caregivers to bring study medication bottles to the clinic (if relevant), confirm that they have been administering the correct dosage to the patient, and remind them not to administer the dose the morning of the visit, if a blood draw is scheduled.

Refer to the "Lithium Email Scripts" file for specific communication recommendations.

Research charts

Study site coordinators are responsible for assembling and updating each patient's research chart (or binder). Coordinators will also periodically conduct chart review while a patient is active in the protocol.

It is recommended that the forms in the front of a research chart be ordered as follows: lithium/sham level log, contact frequency form, protocol exceptions (if needed).

It is recommended that the sections of a research chart be ordered as follows: consent, screening, week 0, week 2, week 4, week 6, week 8, week 10, week 12.

Study IDs are assigned as follows:

- IDs will start with 1001 and will continue to 1999 (IDs are unlikely to continue past 1100). IDs will be generated chronologically by the study team at the site.

Drug IDs are assigned as follows:

- Drug IDs will start with LF101 and will continue to LF199 (IDs are unlikely to continue past LF160). IDs will be generated chronologically by the study team at the site.

Database management

Study coordinators will enter data collected in this study. Each study coordinator who will be entering data will have their own account login through the Columbia Neurology REDCap database (https://niapp003.neuro.columbia.edu/redcap). Data entry should be completed either directly, during visits, or as soon as possible after data collection at study visits.

To be added to the REDCap database, contact the department administrator.

Certificate of Confidentiality

Participants are protected by a certificate of confidentiality, which ensures that we cannot turn over their personal medical information even if subpoenaed by a court order. An extension must be applied for whenever a certificate expires. Applications can be accessed here: https://public.era.nih.gov/commonsplus/public/coc/request/init.era.

Prior to submitting an application, the correct institutional official for the study must be identified.

Alternate Scenarios

1. Medical interruption: If a patient is medically unstable and unable to come in for study visits or taking study medication, the study physician may opt to place the patient on medical interruption rather than considering them a dropout from the study. A one-month medical interruption period is permitted in this study. If the patient is able to resume the study during this period of time, they should complete the next study visit that they would have completed on a normal schedule. If a patient cannot resume the study after one month, they should be brought in for an early termination visit if possible.

2. Early study medication termination: If a patient discontinues study medication prior to the week 12 visit, they should complete all week 12 measures and termination forms at their next visit.

3. When a patient is at risk of dropping out: When a patient is at risk of dropping out, study staff should assess the concern and take action accordingly. If a patient is at high risk for dropping out, all week 12 measures and procedures should be completed immediately to serve as an early termination visit in case the patient does not return for another visit. The duration of the study protocol can be accelerated by shortening visit intervals from 2 weeks to 1 week if the patient is past week 6. If the risk of dropout is due to a patient's increased agitation or difficulty sleeping, a study physician can prescribe lorazepam, up to 1 mg daily, as a rescue medication during the protocol.

4. Early study termination: Early study termination visits will include all measures and procedures that would be completed at a week 12 visit, including all biological samples. This visit will be entered in the database as a week 12/early termination, and for each form entered, the data enterer will be prompted to record which study interval they are closest to based on the number of weeks since randomization (e.g. weeks 2, 4, 6, 8, or 10).

5. If a patient cannot swallow the pills: If a patient is having difficulty swallowing the study medication capsules, a study physician can let the caregiver know that the lithium/placebo capsule can be opened and dissolved in applesauce or milk products such as yogurt. The NYSPI pharmacy has approved this procedure with these foods. Do not instruct caregivers to use any other foods without discussing with the lead site. The contents of the active and inactive capsules cannot be distinguished from each other when opened. Caregivers should be instructed to empty as much of the contents of the capsules into a small amount of food (1 tablespoon) and then stir the contents in before administering it to the patient. If this deviation from the protocol does occur, it will be filed as a protocol deviation for that patient.

Visit Checklists

These are item-by-item instructions for reference immediately before/during/after visits. Please refer to earlier sections of the manual for more details.

Screening / Baseline

Pre-visit:

- ❑ Complete instructions under "Scheduling Visits" section of manual
- ❑ Enter subject ID, date, and coordinator/physician initials on page 37 of the "Screening-Baseline INPERSON Packet" (dopamine>Lithium in FTD>Visit Instruments>In Person) & print double-sided. Also print visit schedule.
- ❑ Separate into the consent forms, clinician forms (which can be placed in a blue folder), and coordinator forms (kept however you like)
- ❑ Add paper MMSE, MDRS, and MDRS cards, response sheets (for FBI & Zarit), and copy of consent to coordinator materials
- ❑ Prepare & label blood tubes (1 red, 1 gold, 1 purple), petty cash + receipt booklet ($20/visit hr payment + $40 transportation payment if applicable)
- ❑ Add print names to consent forms where appropriate and mark signature lines with colored post-its (different color for each signer). Note that a study physician must be the "person obtaining consent". It is useful to clip the participant consent not staple so you can easily make photocopies once signed (one for the participant, one for Irving).
- ❑ Fill in as much demographic information as you can based on past research / clinical chart. If you are unsure of the accuracy of something, use pencil and confirm at visit.

During visit:

- ❑ Conduct consent. Arrange for the independent assessor of capacity to be present either during or immediately following the presentation of consent information. Give them all necessary forms.
- ❑ After capacity assessment is complete and consent is signed, have the study physician come down to answer any questions, add signatures to consent forms, and complete clinical forms. During this time you may photocopy the signed patient consent.
- ❑ Complete missing items on demographics/medication forms
- ❑ Complete MMSE and MDRS with patient. Study partner should sit in waiting room or affirm that they will not aid the participant if they stay in the room.
- ❑ Complete blood draw in the phlebotomy room (Sonia will perform this). Collect the purple and gold tubes in a biohazard bag (provided by Sonia) along with the CALM requisition form. Collect the red tube in a biohazard bag with the Biomarkers Core Laboratory requisition form
    - Drop the Biomarkers Sample in the Biomarkers Core Laboratory (PH10-104): walk past the reception area to the opposite side of the hall from the clinical rooms &

through the double doors. On your right several doors in, you will see the entrance to a large lab space with many cubicles. At the entryway, there is a drop-off bin. Please notify anyone there that you are dropping off a sample. This must be done before 3:30pm.
    - Then go to the 15th floor to drop off the CALM sample (drop-off bin in room 15-401 in P&S building, down the blue and white hallway)
- ❑ When you return, obtain the ECG machine from the phlebotomy room and a gown from the closet (in rooms 2&4) or drawer under the exam table (rooms 3&5). Close the door blinds and draw the curtain by the exam bed. Have the participant change into the gown with their top clothes removed and the gown tied with the opening in front. Lie the participant down on the exam bed and then place the leads on the sternum and below the ribs and connect the ECG machine as trained. If you are not trained, Ismael, Sonia, or the study physician may complete the ECG.
- ❑ Once the participant is dressed and the ECG machine is retuned, you may EITHER 1) complete the NPI, FBI, and Zarit with the caregiver or 2) end the visit and schedule a time within 3 days to complete these by phone or zoom. If completing in person, it is helpful to provide the response options (printed in a laminated sheet), and if completing virtually, you may email these to the caregiver in advance.
- ❑ At the end of the visit, pay the study partner ($20/visit hour + $40 for transportation if relevant) and complete/sign a petty cash receipt.
- ❑ Review next steps: 1) confirmation of eligibility after lab results are returned, 2) shipment of study drug and phone call once it arrives (it is good to go over the starting dosing schedule / potential side effects at this time as well), 3) scheduling of week 2 virtual visit 2 weeks after study drug arrives.

Post-visit:

- ❑ Obtain any missing signatures
- ❑ Score cognitive testing & caregiver forms
- ❑ Fill in any incomplete documents (e.g. inclusion/exclusion) to the best of your ability
- ❑ Check CALM website for posting of testing results
    - sac-cu.org on internet explorer-- download “detailed results”
    - Copy the results into the “Safety Labs Template” file in dopamine>Lithium in FTD>Biological Samples, convert the results to numbers in excel (out of range results will highlight in pink), & print
- ❑ Obtain physician signature on lab results & ECG
- ❑ Prepare pharmacy referral form to send to pharmacy once inclusion/exclusion criteria met (get physician signature & scan). See "Randomization” section for sample email.
- ❑ Organize forms in new participant binder or folder
- ❑ Enter data on REDCap- you will need to use both “screening” and “week 0” tabs

- ❑ Complete MHLS form (if surrogate signed consent) & email to IRB, print and put in participant binder / regulatory binder, and mail or fax to the NY office of Legal Services.
- ❑ Complete study drug issue/return log once the participant receives the drug kit. For this log, note that each kit contains 12 medication bottles. Each bottle contains 28 pills and is labeled by week (#1-12). Each pill is 150mg of study drug.
    - Under "Study Drug Bottle ID", put "LF1XX Week(s) X" to denote the bottle you are instructing the participant to use up until the next study visit (in this case it would be LF1XX Week 1).
    - For number of pills dispensed, indicate the number of pills in the bottle(s) you are instructing the participant to use. You will refer to these bottles at the following visit when you fill in information for study drug returned, and will include the pills remaining in the previously specified bottle as "pills returned".
    - For dose recommended, write the daily dose in mg.
    - It is important to instruct the participant to begin a new bottle after each study visit, regardless of whether pills remain in the old bottle. While taking 150-300mg/day, participants will only need one bottle between visits, but when taking 450-600mg/day, they will need two.

Week 2

Pre-visit:

- ❑ Schedule visit with participant for 2 weeks after they receive the study drug kit. During this call, also confirm dosing schedule (1 pill in evenings) and ask them to use the same bottle during the 2 week period.
- ❑ Create zoom link & send along with date/time of visit & visit schedule to the study partner
- ❑ Send a calendar invitation to the study physician. In the calendar invitation, include:
    - Zoom link
    - Links to clinician forms within REDCap for the correct subject/week
    - List of clinician forms: Treatment emergent symptoms, CGI-Severity, CGI-Change
    - Current subject medication dose, anticipated dose change after visit, & any other relevant information

During visit:

- ❑ Complete medication compliance check: have study partner count pills remaining in the bottle they have been using. Each bottle contains 28 pills, so calculate the number of pills that should be remaining (14 if 2 weeks from kit receipt)
- ❑ On REDCap, complete the following forms with the study partner:
    - Visit registry, concomitant meds, NPI, Stereotypic/Ritualistic behaviors, study drug issue/return log

Post-visit:

- ❑ If no contradictions per study clinician, instruct participant/study partner to increase dose to 300mg/day (one pill mornings, one pill evenings), using a new bottle.
- ❑ Schedule Week 4 visit with participant for 2 weeks after their week 2 visit.
- ❑ Obtain clinician signature on REDCap study drug issue/return log, resolve any missing data from clinician forms

Week 4

Pre-visit:

- ❑ Create zoom link & send along with date/time of visit & visit schedule to the study partner
- ❑ Send a calendar invitation to the study physician. In the calendar invitation, include:
    - Zoom link
    - Links to clinician forms within REDCap for the correct subject/week
    - List of clinician forms: Treatment emergent symptoms, CGI-Severity, CGI-Change, Simpson-Angus, Lawton, CDR
    - Current subject medication dose, anticipated dose change after visit, & any other relevant information

During visit:

- ❑ Complete medication compliance check: have study partner count pills remaining in the bottle they have been using. There should be 0 remaining if 14 days have passed since the previous visit (and they were taking 2 pills daily).
- ❑ On REDCap, complete the following forms with the study partner:
    - Visit registry, concomitant meds, NPI, Stereotypic/Ritualistic behaviors, Zarit Burden Interview, study drug issue/return log

Post-visit:

- ❑ If no contradictions per study clinician, instruct participant/study partner to increase dose to 450mg/day (one pill mornings, two pills evenings), using two new bottles.
- ❑ Schedule Week 6 visit with participant for 2 weeks after their week 2 visit.
- ❑ Obtain clinician signature on REDCap study drug issue/return log resolve any missing data from clinician forms

Week 6

Pre-visit:

- ❑ Schedule an at-home blood draw via ExamOne, to occur as close to the virtual visit as possible. Notify the CALM lab of the anticipated date of this visit so they can expect the shipment. Remind study partner not to give medication dose morning of blood draw.

- ❑ Create zoom link & send along with date/time of visit & visit schedule to the study partner
- ❑ Send a calendar invitation to the study physician. In the calendar invitation, include:
    - Zoom link
    - Links to clinician forms within REDCap for the correct subject/week
    - List of clinician forms: Treatment emergent symptoms, CGI-Severity, CGI-Change
    - Current subject medication dose, anticipated dose change after visit, & any other relevant information

During visit:

- ❑ Complete medication compliance check: have study partner count pills remaining in the bottle they have been using. Each bottle contains 28 pills, so calculate the number of pills that should be remaining based on dose & time since the last visit.
- ❑ On REDCap, complete the following forms with the study partner:
    - Visit registry, concomitant meds, NPI, Stereotypic/Ritualistic behaviors, study drug issue/return log

Post-visit:

- ❑ Following the at-home blood draw, complete a Serum Sham Lithium Level Form (dopamine>Lithium in FTD>Serum-Sham Lithium Levels) and send it to Masood, who will send the form to Dr. Roose along with the REAL serum lithium level (once it is available on CALM). Dr. Roose will then complete the form and send it back to Masood, who will send it to you. Save the signed form in a unique subject folder in dopamine>Lithium in FTD>Serum-Sham Lithium Levels.
- ❑ If no contradictions per study clinician, AND serum lithium/sham level is within the target window, instruct participant/study partner to increase dose to 600mg/day (two pills mornings, two pills evenings), using two new bottles.
- ❑ Obtain clinician signature on REDCap study drug issue/return log, resolve any missing data from clinician forms, fill out serum-sham lithium level REDCap form.
- ❑ Download Safety Lab results from the CALM website. Copy results (which will appear on two separate lines in the detailed spreadsheet) into the “Safety Labs Template” excel in dopamine > Lithium in FTD > Biological Samples. Convert all values to ‘number’ in excel so that cell highlighting rules will function. Out of range values will appear pink. Fill in additional information at the bottom of the page using data from the screening visit as a reference. Save in the “Participant Lab Results” folder. You can then EITHER
    - 1) print this page and obtain a clinician signature in person
    - 2) convert to PDF form and add signature line and comments box, then forward to study clinician for review and signature
    - 3) Send to study clinician and then have them sign in REDCap
- ❑ Schedule Week 8 visit with participant for 2 weeks after their week 2 visit.

Week 8

Pre-visit:

- ❑ Schedule an at-home blood draw via ExamOne, to occur as close to the virtual visit as possible. Notify the CALM lab of the anticipated date of this visit so they can expect the shipment. Remind study partner not to give medication dose morning of blood draw.
- ❑ Create zoom link & send along with date/time of visit & visit schedule to the study partner
- ❑ Send a calendar invitation to the study physician. In the calendar invitation, include:
    - Zoom link
    - Links to clinician forms within REDCap for the correct subject/week
    - List of clinician forms: Treatment emergent symptoms, CGI-Severity, CGI-Change, Simpson-angus, Lawton, CDR
    - Current subject medication dose, anticipated dose change after visit (unless at max dose of 600mg/day), & any other relevant information

During visit:

- ❑ Complete medication compliance check: have study partner count pills remaining in the bottle they have been using. Each bottle contains 28 pills, so calculate the number of pills that should be remaining based on dose & time since the last visit.
- ❑ On REDCap, complete the following forms with the study partner:
    - Visit registry, concomitant meds, NPI, Stereotypic/Ritualistic behaviors, Zarit Burden Interview, study drug issue/return log

Post-visit:

- ❑ Following the at-home blood draw, complete a Serum Sham Lithium Level Form (dopamine>Lithium in FTD>Serum-Sham Lithium Levels) and send it to Masood, who will send the form to Dr. Roose along with the REAL serum lithium level (once it is available on CALM). Dr. Roose will then complete the form and send it back to Masood, who will send it to you. Save the signed form in a unique subject folder in dopamine>Lithium in FTD>Serum-Sham Lithium Levels.
- ❑ If no contradictions per study clinician, AND serum lithium/sham level is within the target window, instruct participant/study partner to stay at OR increase dose to 600mg/day (two pills mornings, two pills evenings), using two new bottles.
- ❑ Obtain clinician signature on REDCap study drug issue/return log, resolve any missing data from clinician forms, fill out serum-sham lithium level REDCap form.
- ❑ Schedule Week 10 visit with participant for 2 weeks after their week 2 visit.
- ❑ If not already done, schedule in-person week 12 visit and submit room request to Irving

Week 10

Note: there is no blood draw associated with this visit unless the medication dose was increased at week 8. If this is the case, follow instructions related to at-home blood draws & serum/sham lithium levels.

Pre-visit:

- ❑ Create zoom link & send along with date/time of visit & visit schedule to the study partner
- ❑ Send a calendar invitation to the study physician. In the calendar invitation, include:
    - Zoom link
    - Links to clinician forms within REDCap for the correct subject/week
    - List of clinician forms: Treatment emergent symptoms, CGI-Severity, CGI-Change
    - Current subject medication dose & any other relevant information

During visit:

- ❑ Complete medication compliance check: have study partner count pills remaining in the bottle they have been using. Each bottle contains 28 pills, so calculate the number of pills that should be remaining based on dose & time since the last visit.
- ❑ On REDCap, complete the following forms with the study partner:
    - Visit registry, concomitant meds, NPI, Stereotypic/Ritualistic behaviors, study drug issue/return log

Post-visit:

- ❑ Instruct participant/study partner to stay at current dose, using two new bottles.
- ❑ Obtain clinician signature on REDCap study drug issue/return log, resolve any missing data from clinician forms.

Week 12

Pre-visit:

- ❑ Confirm in-person date & directions with participant, confirm room booking with CRR, confirm event on RA/physician calendars. Remind participant to bring in used study drug kit & all remaining pills. Remind study partner not to give medication dose morning of visit.
- ❑ Email NYSPI pharmacy ahead of time to request the Unblinding Envelope; pick this up from the NYSPI pharmacy.
- ❑ Prepare a summary of the participant's trajectory through the trial (dopamine>Lithium in FTD> Exit Summaries > TEMPLATE)
- ❑ Enter subject ID, date, and coordinator/physician initials on page 1 of the "Week 12 INPERSON Packet" (dopamine>Lithium in FTD>Visit Instruments>In Person), print double-sided. Also prepare and print visit schedule.
- ❑ Separate into the Clinician forms which can be placed in a blue folder (INCLUDING the unblinding envelope & exit summary) and coordinator forms

- ❑ Add paper MDRS and MDRS cards, laminated response option sheets (for FBI & Zarit) to coordinator materials
- ❑ Prepare & label blood tubes (1 red, 1 gold, 1 purple) & petty cash + receipt booklet ($20/visit hr payment, including past virtual visits, + $40 transportation payment if applicable)

During visit:

- ❑ Collect study drug kit
- ❑ Complete MDRS with patient. Study partner should sit in waiting room or affirm that they will not aid the participant if they stay in the room.
- ❑ Complete blood draw in the phlebotomy room (Sonia or Ismael will perform this). Collect the purple and gold tubes in a biohazard bag (provided by CRR) along with the CALM requisition form. Collect the red tube in a biohazard bag with the Biomarkers Core Laboratory requisition form
    - Drop the Biomarkers Sample in the Biomarkers Core Laboratory (PH10-104): walk past the reception area to the opposite side of the hall from the clinical rooms & through the double doors. On your right several doors in, you will see the entrance to a large lab space with many cubicles. At the entryway, there is a drop-off bin. This must be done before 3:30pm.
    - Then go to the 15th floor to drop off the CALM sample (drop-off bin in room 15-401 in P&S building, down the blue and white hallway)
- ❑ When you return, obtain the ECG machine from the phlebotomy room and a gown from the closet (in rooms 2&4) or drawer under the exam table (rooms 3&5). Close the door blinds and draw the curtain by the exam bed. Have the participant change into the gown with their top clothes removed and the gown tied with the opening in front. Lie the participant down on the exam bed and then place the leads on the sternum and below the ribs and connect the ECG machine as trained. If you are not trained, Ismael, Sonia, or the study physician may complete the ECG.
- ❑ Once the participant is dressed and the ECG machine is retuned, you may EITHER 1) complete the NPI, FBI, and Zarit with the caregiver (preferred) or 2) move on and schedule a time within 3 days to complete these by phone or zoom. If completing in person, it is helpful to provide the response options (printed in a laminated sheet), and if completing virtually, you may email these to the caregiver in advance.
- ❑ Pay the study partner ($20/visit hour, including from virtual visits + $40 for transportation if relevant) and complete/sign a petty cash receipt.
- ❑ The clinician portion of the visit should be conducted LAST and will include the unblinding & planning for future care. Note that the study RA should remain blinded even after the participant completes the trial, so it is recommended for them to pay and say goodbye to the participant before the clinician visit, to avoid being accidentally unblinded.

Post-visit:

- ❑ Obtain any missing signatures
- ❑ Score cognitive testing & caregiver forms
- ❑ Check CALM website for posting of testing results
    - sac-cu.org on internet explorer-- download “detailed results”
    - Copy the results into the “Safety Labs Template” file in dopamine>Lithium in FTD>Biological Samples, convert the results to numbers in excel (out of range results will highlight in pink), & print
- ❑ Obtain physician signature on lab results & ECG
- ❑ Count remaining pills & confirm with expected count. Once done, drop kit off at the NYSPI pharmacy for destruction.
- ❑ Enter data on REDCap
- ❑ Complete Serum-Sham Lithium level form, as described under Weeks 6/8.

Statistical Procedures and Data Analysis.

Outcome measures and covariates. Primary outcome: agitation/aggression score (domain score on the Neuropsychiatric Inventory (NPI), continuous measure from 0-12, longitudinal); Secondary outcome: response (dichotomous, based on 30% decrease in NPI core score (sum of domains for motor activity and agitation/aggression) plus a CGI-C score of much improved or very much improved, longitudinal); Exploratory outcome motor activity score on the NPI. Covariates/Predictor variables: 1) demographic characteristics (e.g., gender, race, age); 2) baseline measures of the corresponding outcomes. Other Measures:1) tolerability, as measured by emergent side effects (TESS scores and adverse events) over the course of the 12 week trial; 2) brain derived neurotrophic factor (BDNF) serum levels.

Sample size and randomization: The randomization will be carried out by the statistician and implemented by the pharmacist, who are both otherwise independent of the research team. The randomization sequences will be balanced in blocks of random size to prevent clinicians from guessing what the next patient's treatment might be.

Modeling longitudinal data and testing hypotheses. Modeling longitudinal data and testing hypotheses. All tests will be two-sided; α=0.05; intent-to-treat with data included for all patients with ≥1 post-baseline assessment. We will use generalized linear mixed models (GLMMs; SAS PROC GLIMMIX) for longitudinal data to evaluate study aims. Models will include fixed effects for treatment group, time, group x time interaction, and any baseline covariates found to be unbalanced despite randomization. Prior to analysis, we will examine all variables at all time points for outliers and inconsistencies and examine their distributions.[41-43]

Primary hypothesis: *Lithium will significantly reduce agitation/aggression as compared to placebo.*
The following linear mixed effects model will be used: $Yij = \beta 0 + \beta 1 liTRT + \beta 2t + \beta 3t*liTRT + \beta 4Xi + bi + \varepsilon ij$ where *Yij* is the agitation/aggression score for the *i*th subject at *t*week, *t* =0, 2,…,12, *yi0* is agitation/aggression at baseline, *liTRT* is the indicator variable for randomized condition (placebo vs. lithium), an indicator of recruitment site (Columbia University Medical Center and Johns Hopkins School of Medicine), and any baseline covariates exhibiting imbalance after randomization, *bi* is a random intercept to account for repeated measures across time within the patient, and *εij* is a random error term. Significant interaction *t*liTRT* indicates that the changes in agitation/aggression in each treatment group is different over time (which corresponds to rejecting the null hypothesis that $\beta 3 = 0$). The effect of time will be estimated for each group separately and the groups will be compared (using contrast) at the last time point *t=12*.
Secondary hypothesis: *Lithium will have greater proportion of responders compared to placebo.* We will test whether the probability of response by end of active treatment differs significantly in the lithium and placebo groups by a chi-square test. In addition, we will test whether change in the probability of response differs across treatment groups by longitudinal analysis. We will use the generalized linear mixed effects model: $\text{logit}(Yij) = \beta 0 + \beta 1\, liTRT + \beta 2t + \beta\, 3t*liTRT + \beta 4Xi + bi + \varepsilon ij$ where *Yij* is the a binary variable indicating response for the *i*th subject at *t* week, *t* =2, 4,…,12. We will first test significance of the treatment effect by testing the group by time interaction.
Exploratory Hypothesis. *Lithium will significantly reduce repetitive behaviors as compared to placebo.* We will use the same model in the analyses for the primary hypthesis where *Yij* is the motor activity score for the *i*th subject at *t* week, *t* =0, 2,…,12.

Tolerability: We will assess the tolerability of low dose lithium by assessing emergent side effects over the course of the 12-week trial on lithium compared to placebo. We will compute descriptive statistics of tolerability measures in each treatment group and provide both point estimates and their confidence intervals. We will test whether the change in TESS score from baseline to week 12 differs significantly in the lithium and placebo arms by a t-test.

Biomarker Hypothesis. Increases in BDNF serum levels will be associated with decreases in agitation/aggression and repetitive behaviors. The relationship between change in BDNF serum levels (defined as baseline minus endpoint of active treatment) and the changes in agitation/aggression score and motor activity score (defined as baseline minus treatment endpoint) will be tested using correlation analyses.

Power Analysis. Given the proof-of-concept nature of this study as a pilot, effect sizes with 95% confidence intervals rather than statistical significance testing will be the primary results of interest. The overarching aim is to demonstrate feasibility for conducting a larger trial which would then be used to adequately test efficacy.[33] Nevertheless, we provide some guidance regarding the statistical power available for testing differences between treatments. With n=60 patients randomized (30 to lithium, 30 to placebo) we conservatively examine power below assuming attrition will be 20% (i.e. 48 completers) though our past studies have all had attrition <20% and all available longitudinal data will be used for all individuals regardless of whether they complete the 12 weeks. For the primary outcome of agitation/aggression score measured by the NPI, we will have 80% power to detect a medium to large treatment effect size of 0.58-0.83 with the range depending on the within person correlation over time. Additionally, for responder status, we will have >80% power to detect a difference between, for example, a 15% response rate and a 50% response rate at 12 weeks. Differences among other exploratory outcomes and tolerability measures will be detectable with similar power.