



Operations Manual Version 3

Version	Date	Section Revised	Type/Reason for revision
1	02 Nov 2017	N/A	Initial Operations Manual
2	20 Nov 2017	Section 6 – assessments	Clarify LP, cognitive assessments must be done in medications “ON” state
3	16 Jan 2018	Section 6 – assessments	Update Montreal Cognitive Assessment (MOCA) directions

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Section 1 -General Information

INTRODUCTION

This operations manual describes procedures related to the NILO-PD Study. The purpose of the operations manual is to facilitate consistency in protocol implementation and data collection across the sites. The operations manual supplements the study protocol by detailing the study's organization, operational data definitions, recruitment, screening, enrollment, randomization, intervention procedures and follow-up procedures, data collection methods, data flow, source documentation and electronic Case Report Forms (eCRFs), and quality control procedures. Procedures in the operations manual should be followed with the same degree of vigor as those documented in the protocol.

All site personnel participating in the conduct of this study should have ready access to the operations manual and be familiar with its contents. The current version and archived versions are posted to **eClinical Portal in the NILO-PD Operations folder**.

The operations manual will be updated throughout the conduct of the study, if applicable, to reflect any changes to the protocol, consent, eCRFs, and/or study procedures. As sections/chapters are revised, the operations manual version information and date on the cover page and Table of Contents will be updated; the Summary of Changes table on the page 2 will list the sections that have changed and will include a general summary of those changes. The entire operations manual version date will be updated when there are changes to any section. When the revisions are final, the revised version will be posted to the eClinical Portal and communicated to the site personnel and clinical site monitor(s) that the operations manual has been updated and available on the portal.

The Site Investigator or designee is responsible for on-site document control of the operations manual and for reviewing and filing updates in the investigator site file (ISF) in a timely manner. If paper copies of the operations manual are maintained in a binder, the Site Coordinator stores the updated materials in the binder. Outdated materials will be removed from the binder and filed in a separate location clearly marked as "obsolete."

MANUALS AND PLANS FOR REFERENCE

The following manuals, plans, and guides will be provided separately for reference. All have been provided by the vendors and are also available on the eClinical portal. A copy of these documents must be placed in the investigator site file (ISF).

- ACM – Laboratory
 - Laboratory Services Manual
 - Additional Blood Collection Guidelines
- Indiana University – Laboratory
 - Biologics Manual
 - Additional Blood Collection Guidelines
- ERT (ECG) Manual and Quick Guides
 - Study Manual Cardiac Safety for the NILO-PD Trial
 - My Study Portal Quick Guide
 - Also located on ERT home page in Reference Materials section
 - Eli PC Quick Guide
 - Also located on ERT home page in Reference Materials section

STUDY CONTACTS

<u>Reason to Call</u>	<u>Whom to Call</u>
Protocol Questions; Investigational Product Supply Issues; Day-to-day Study Operations; Immediately Reportable Events; Notifications; questions regarding regulatory documents	Melissa Kostrzebski Project Manager Phone : 585-273-4239 Fax : 585-461-3554 Email: Melissa.Kostrzebski@chet.rochester.edu
Urgent medical concerns	Jamie Adams, MD Clinical Monitor Phone: 585-276-7305 Email: jamie.adams@chet.rochester.edu
CRF questions; Data queries	Ett Muneath Information Analyst Phone: 585-276-7446 Fax: 585-461-3554 Email: Phounsavath.Muneath@chet.rochester.edu
Assistance with accessing eClinical (user name/password), navigation or electronic enrollment issues within the system Website support for FAQs, information about eClinical training, training manual and contacts.	eClinical System Support Phone: 585-275-3893 (Monday-Friday 8:30 a.m. – 9:00 p.m. ET) Website: http://support.ctcc.rochester.edu/
Subcontract/payment issues	Alexandra Manetas Financial Administrator Phone: 312-503-9709 Email: a.manetas@northwestern.edu
ACM Global Labs Safety Labs	Ashley Willsey Project Manager Phone: 866-405-0400 Email: awillsey@acmgloballab.com
Indiana University Biomarkers/PK samples	Claire Wegel Project Manager Phone: 317-278-6158 Email: cwegel@iu.edu
eResearch Technology (ERT) EKG	Matt Hopkins Project Manager Phone: 215-282-5319 Email: mhopkins@ert.com

GENERAL STUDY PERSONNEL INFORMATION

Site Investigator: Only one Site Investigator (listed in section 1 of Form FDA 1572) may conduct the study at each site. The Site Investigator (SI) is responsible for selection, enrollment and follow-up of all subjects at the site; the SI evaluates all subjects at all visits, including screening visit (unless otherwise specified in the protocol).

Site Personnel: One Site Coordinator (SC) should be named as the study's primary coordinator and main contact at each site. The SC must have documented skills and training to perform the responsibilities required by the study. Other staff members may assist and contribute to the completion of study assessments and data entry. Responsibilities commonly delegated to staff members other than the SC are:

- Data Entry – must have eClinical training confirmation
- Specimen collection – must be trained in biorepository collection
- Shipping – must have documented IATA training
- C-SSRS – must have C-SSRS certification
- MDS-UPDRS – must have MDS-UPDRS certificate

All certificates and training must be kept in the ISF.

CTCC assigned staff codes: Site staff including the Site Investigator, sub-investigators, Site Coordinator(s) and other site staff who will be assisting the investigator and who make a direct and significant contribution to the data are required a CTCC assigned staff code. Additionally, these same site staff names and staff codes must be listed on the Delegation Log. The Site Investigator, back-up investigator(s) and Site Coordinator and back-up coordinator are required to be listed on Form FDA 1572 (instructions provided below).

- The site must notify the CTCC Project Manager (PM) in advance of a site's intention to change Site Investigator or the primary Site Coordinator. Requests for PI and/or SC changes must be approved by the NILO-PD Steering Committee.
- **Investigators and Sub-Investigators must be PSG credentialed.** Any new investigators must be pre-approved by the PSG Credentials Committee and go through the credentialing process.
- Any new staff that has not yet been assigned a CTCC staff code must complete the *New/Change Staff Form* (posted on eClinical portal) and email it to the CTCC Project Manager (PM).
- Page 2 of the *New/Change Staff Form* should also be completed and emailed to the CTCC when a staff member leaves the department, institution or is no longer working on NILO-PD. The last working day on the study must be provided.

Study Contact List: A NILO-PD Contact List is posted to the eClinical Portal Administrative folder for reference. Notify the PM promptly if there are any changes in address, email, fax, telephone numbers, or staffing. The CTCC staff change form will be posted on the eClinical portal; please forward completed form to the NILO-PD project manager when staffing changes occur.

CTCC and Vendor Closings: holiday calendar and office closings will be posted on the eClinical portal and will be updated on an annual basis. If you have an emergency on a day CTCC is closed, call 585-275-7311 and you will be provided with a contact for the study. Please distribute this information to the appropriate staff in your office.

BOX Accounts: instructions for obtaining and using BOX accounts will be posted on the eClinical portal. Please contact the NILO-PD PM if new staff need access to the BOX account.

REGULATORY DOCUMENTS

Complete as follows; all documents should be typed in applicable section- do not handwrite information. However, a **handwritten signature** and **current date** must be provided where requested.

An individual's name on each of the following documents should match. Full name (should match physician medical license). Nicknames should not be interchanged with full name on staff documentation. If a prior name (e.g., maiden name) is referenced and is not consistent with other regulatory documents, a note to file should be present explaining that person is one in the same.

Delegation log: All site personnel who participate in any capacity of the study need to be listed on the NILO-PD Delegation Log provided by the CTCC.

- Site Investigator is responsible for ensuring all study staff listed on the log are trained to complete the study tasks for which they are delegated and that documentation of training is filed in regulatory binder.
- Consistency in completing key assessments with the same study personnel over the duration of the study is essential. This is particularly important with regard to the completion of assessments where consistency of raters is desirable (see Operations Manual Section 6). It is highly recommended to train multiple staff to perform multiple study assessments, however, **ensure same rater completes the same assessments for the same subjects throughout their participation.**

FDA FORM 1572: All section should be completed. If a section is not applicable, "None" should be stated.

Section 1: should include location where Investigator can be reached by mail or in person.

Investigator name should be written as it reads on medical license.

Section 2: Check appropriate box for qualification (Most likely CV)

Section 3: All addresses where the investigation will be conducted and to where the test articles will be shipped. May be multiple locations.

Section 4: All addresses for clinical laboratories or testing facilities directly contributing to or supporting the clinical study.

Section 5: Address of IRB responsible for study review and approval.

Section 6: All staff that will assist the investigator and make a direct and significant contribution to the data.

Section 7: Full Protocol title and study number (if appropriate)

Section 8: Check Phase #

For all study staff listed in section 6 of Form FDA 1572 the following documents should be collected:

Confidentiality Statement: All staff on Form FDA1572 (If prior to signed contract)

Medical License: All staff performing study assessments requiring an license (MD and DO only unless)

CV: All staff on 1572. Must include current affiliation with addresses matching the address listed on the 1572.

- Investigator CV should include site addresses of all locations listed in sections 1 and 3 of the 1572. Note: Affiliation to all locations is necessary for Investigator as he is committing to have direct supervision of all study activities, which includes locations that all study activities occur.
- Staff in section 6 should include at least one site address location from section 3. Name should match other documents (Medical License, Delegation Log, Conflict of Interest, Training)

Conflict of Interest: All staff on Form FDA 1572. Name and role should match all other documentation.

eCLINICAL

eClinical is the web-based electronic data entry system that will be utilized for this study.

***NOTE: A MAC computer cannot be used to access eClinical**

The only compatible internet browser is Internet Explorer (I/E). Other internet browsers such as Google, Google Chrome, FireFox and Safari are not compatible with EDC.

In the event of system technical difficulties with the enrollment process, the eClinical Help Desk should be contacted. Note for study specific issues the Information Analyst (see above) should be contacted.

Windows NT authenticated accounts will be created and maintained by the CTCC for each of the sites participating in the study once appropriate training has been completed by assigned site staff.

The EDC system is available **24/7**, with the following exceptions:

- during routine maintenance every Sunday from 8 am to 12 pm (noon) Eastern Time
- during daily restart at 12 am (midnight) Eastern Time

Note: If your site has any system upgrades it may cause compatibility issues such as being unable to see the folders in the eClinical portal. Refer to the instructions on <http://support.ctcc.rochester.edu> FAQ section for instructions on eClinical portal. If you still have difficulty please contact the CTCC Help Desk.

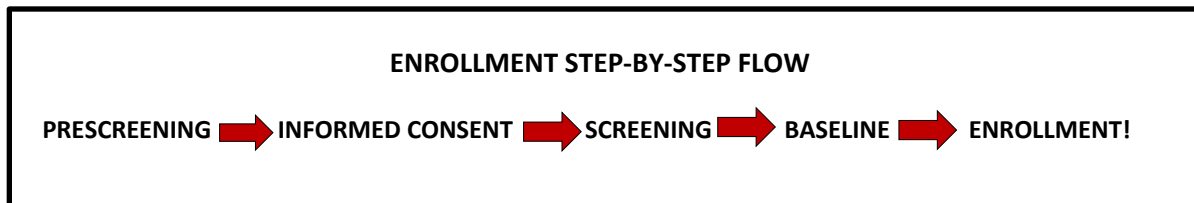
Section 2 -Protocol

Section 3 – Enrollment

GENERAL INFORMATION

Recruitment and retention activities will be tracked from prescreening review of potential candidates through enrollment and completion of study participation.

- A participant is enrolled in the study when randomized at the Baseline Visit
- Participants who are withdrawn or drop out of the study will not be replaced
- Sites will be notified when 75 participants have been enrolled and enrollment is closed



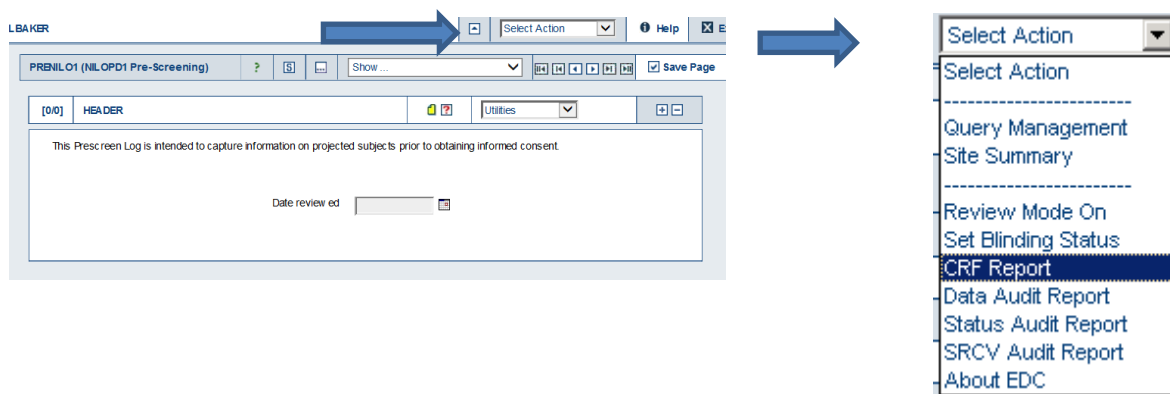
PRESCREENING – SITE MART

Prescreening Procedures

Prospective NILO-PD participants will be tracked on a prescreening log in an eClinical protocol called “Site Mart”. The NILO-PD Prescreening Log will capture the non-identifiable health information that can be shared with the CTCC to help manage enrollment across sites.

Weekly Prescreening Log Completion

- Following patient chart and/or database review, potentially eligible candidates should be added to the eClinical NILO-PD Prescreening Log. The prescreening log should be updated on a weekly basis
- The Monday of the week of the Screening Visit 1 (SC1) visit should be entered into the log
- If there are no updates, enter the current date into the log header to indicate the log is current
- When a patient signs consent to participate, enter the prescreening number from the prescreening log onto the Screening/Demographics eCRF to link the consented participant to the prescreening data.
- To print the prescreening log for the ISF, use the eClinical CRF Report function shown below.



SCREENING VISIT

Informed Consent Process

- Informed consent form is presented to the participant, reviewed, and all questions asked/answered.
- Written consent is obtained, including date and time of consent.
- The entire process must be clearly documented in source documents.

Note: If subject consented to obtain a CTCC Unique ID number, assign as described below.

***See “Instructions for CTCC Unique ID Number Assignment” below**

Note: If the subject has consented to the optional DNA testing, complete the “Consent for DNA Sample Collection and Retention”.

Key Reminder: Review consent to ensure all optional sections are complete, signature applied, and date and time have been recorded accurately.

- Assign 4-digit Participant Identification number (ID)
 - A series of IDs will be provided to each site by the CTCC.
 - Each potentially eligible person who has signed a consent form will be assigned an ID from this list.
 - Record the ID on all source documents, safety labs, EKG and in all study vendor databases.
 - If subject is rescreened, the ID will remain the same.
 - If a participant is considered a screen failure, the specific ID assigned to this participant should not be reissued to another participant.
 - Once a subject is randomized, an enrollment ID is assigned to the subject. The enrollment ID, which corresponds to the drug kit number, is described further in this section.

Note: Participant ID Number is called ‘Patient ID’ in the eClinical system.

- Within 2 business days of Screening Visit 1, enter all data in eClinical.
 - Enter/Save the Inclusion/Exclusion (INC/EXC) page. The investigator must esign the page to confirm eligibility. This will start the pre-enrollment review process at the CTCC. Data will be reviewed and ultimately, the Clinical Monitor will approve a participant for enrollment.
 - Two items must be complete prior to entering the INC/EXC page
 1. All assessments must be entered

2. “SC1 Con Meds Complete” status field must be “clicked” and signed by the Coordinator

SCREENING/DEMOGRAPHICS FORM

- Data will be captured about all potential subjects who have signed consent, including those who are pre-screened, for possible enrollment into NILO-PD.
- Reflects site predictions about the number and timing of future enrollments
- Used to determine such things as projected timelines, the need for additional supplies, and the frequency with which the site should be monitored, and difficulties sites may be having identifying potential subjects.
- Information provided is also used to describe recruitment efforts in reports to the sponsor and IRB annual reports.
- Information about number of subjects screened vs. number randomized and reason for screen failures are reported in the primary manuscript as well as the final technical report submitted to FDA by the sponsor.

NOTE: The web-based Screening/Demographics Form must be updated regularly to document status of potentially eligible subjects. For example, when the subject signs a consent form complete the form. If a subject decides to decline participation in the study prior to randomization the form must be updated in the web-based system.

SCREEN FAILURES

In the case of a screen failure (a subject who provided an informed consent but was not enrolled, for whatever reason, e.g., declined, excluded), the following minimum set of pages must be completed:

- Screening Demographics
- Any additional assessments that may have been completed should also be entered into the system.
- Visit Status
- Investigator Signature
- Remember to update the web-based Screening/Demographics Form in the event of a screen fail (e.g., “signed consent” and “Declined” or was “Excluded”).

BASELINE VISIT

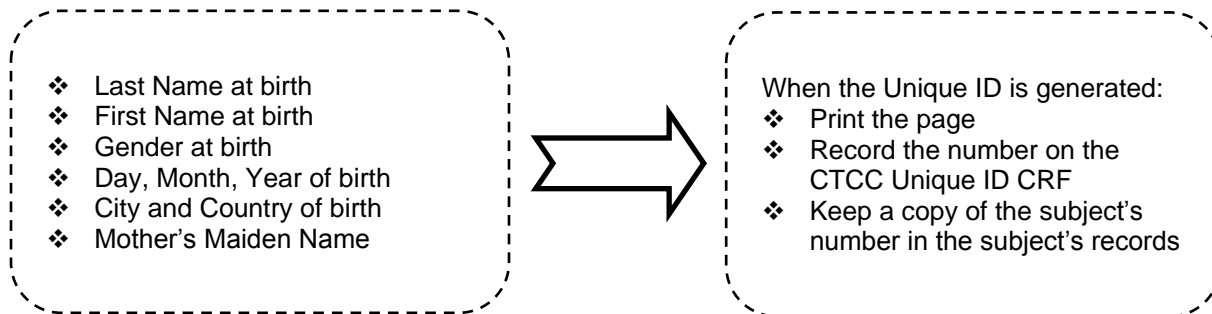
- Subject eligibility criteria will be re-affirmed.
- Complete RANDOM page in eClinical.
 - *See “Complete RANDOM Page in eClinical to Complete the Electronic Enrollment Process in eClinical EDC System” below**
 - 5-digit Randomization Authorization Code (Enroll ID) will be generated when RANDOM page is saved. This is NOT the Participant ID number

Once randomization is complete, proceed with remaining Baseline Activities.

*Refer to corresponding Step number below for additional details.

INSTRUCTIONS FOR CTCC UNIQUE ID ASSIGNMENT

If the subject has consented to acquiring a CTCC Unique ID number, the following 9 data elements about the subject will need to be entered into a secure website <https://www.ctcc.rochester.edu/uniqueid> to generate the Unique ID number:



If at any point the subject forgets his or her CTCC Unique ID number, you or the subject can go back to the website and enter the 9 data elements again. These 9 data elements must be identical to those entered before (i.e., if no middle initial was used the first time data was entered, there should be no middle initial used when re-entering the data) to obtain the same unique ID number. The computer program will create the same fingerprint and return the same unique ID number each time the subject's data elements are entered.

If the subject has consented to acquiring a CTCC Unique ID number and a number has been generated during participation in a previous study, the number previously generated may be used to avoid duplication of ID numbers assigned to one subject. The site may file a copy of the original printout or document in the visit progress note that the number was generated during a previous study.

If a subject declines consenting to create a CTCC Unique ID at the time of screening, the subject may still enroll. The subject may provide consent at a later date to obtain a CTCC Unique ID number.


CREATING A SUBJECT IN ECLINICAL

Subjects will be created via the web-based electronic data entry system eDC (eClinical). eClinical allows 24/7 access to the module - see Operations Manual Section 1 for important eClinical user tips.

Site staff with user access will be directed to a page where they will enter their assigned **User ID** and **Password** in order to access the system. Once these have been validated, there will be options for entering a new subject into the system.

In the event of system difficulties with the enrollment process, the eClinical Help Desk should be contacted (585-275-3893). NOTE: International callers should call (00 +1) 585-275-3893. Hours of operation are Monday - Friday from 8:30 a.m. – 9:00 p.m. ET. Leave a message during these hours and after hours, someone will return your call.

Sample eClinical Login Page:



Welcome!
Home - Sign In

EXPeRT Clinical

Sign In

Login

Password

Sign In


Forgot Password?

<http://support.ctcc.rochester.edu>
265 Crittenden Blvd. CU 420694
Rochester, NY 14642
1-888-406-6704 / 585-275-3893
Normal Hours of Operation:
Monday - Friday
8:00 am - 9:00 pm ET

Sample EDC New Patient Page:

NOTE: 'Participant Number' is called 'Patient ID' by the system.

eData Entry - Microsoft Internet Explorer provided by CTCC



All Protocols | PHENDUS | 001

User ID: KHODGEMA

Select Action

Help

Exit

Filter Panel

None

Navigation Panel

All Protocols

PHENDUS

001

017

101

111

112

123

222

234

333

987

1001

9876

Add patient into the center: 001

Patient ID:

Initials:

Baseline Visit Date: (MMDDYYYY)

Country:

Save Changes

Cancel

Powered By
Research Technology, Inc.

Done

start

Inbox - Mi...

CTCC Vers...

PHD-Sin3-...

eResearch...

eData Entr...

Desktop

Internet

2:51 PM

Patient ID = Participant ID	The 4-digit subject number assigned to the person who signed consent. This number is assigned consecutively from the block of numbers provided from the CTCC.
Initials	Enter participant initials: First, Middle, Last. If a middle initial is not available, please enter a dash (-) example: A-B.
Baseline Visit Date	Leave this field <u>blank</u> . This will be auto-populated once the subject is enrolled (Random page is completed).
Country	Leave this field <u>blank</u> . We are not collecting country at the present time.

COMPLETE RANDOM PAGE TO COMPLETE ELECTRONIC ENROLLMENT

When all appropriate Screening and Baseline Visit activities have been completed and the NILO-PD Clinical Monitor has determined the participant is eligible for the study, the participant may be officially enrolled/randomized via the electronic data capture (EDC) enrollment system.

The web-based EDC enrollment system will confirm that requirements for eligibility have been met and will assign a random Enrollment ID Number. **The assigned Enrollment ID number corresponds to the number on the drug kit that the participant is to be given.**

- * **Enrollment ID numbers will be recorded on the *Drug Dispensing Log* and will identify the drug kit supplied to the subject.**
- * **Under no circumstances is drug to be dispensed without logging the enrollment into the web-based electronic data entry system**

What Information Must Be Available to Complete the RANDOM Page and Enroll a Subject?

Eligibility confirmation from the NILO-PD Clinical Monitor.

Required data to be entered

- Staff Code (investigator/coordinator reporting enrollment)
- Enrollment Date (date of Baseline Visit)
- Subject Initials
- Subject's Date of Birth
- Subject's Gender
- Date Consent Form was Signed

Sample EDC Enrollment (Random) Page:

Enrollment will require the site to verify that the subject meets study inclusion/exclusion criteria, Clinical Monitor enrollment approval and confirmation the participant has not already been randomized. Once the site coordinator clicks the last check box on the RANDOM page (as shown above), the system will run a check to confirm eligibility criteria has been met and subject has not been previously randomized.

If applicable, an Enrollment ID Number of the next available drug kit will be supplied. Enrollment ID Numbers are not distributed sequentially, but in a randomized order, so treatment assignments are doubly randomized. The actual treatment assignment will not be revealed to the site.

All site personnel and CTCC staff will remain blinded to treatment. The CTCC will have an unblinded statistician who will have access to the treatment codes should they be needed for safety reasons. These individuals **will not** communicate about study-related matters to any other staff involved with the study.

Enrollment Verification: A CRF Report listing the subject's visit window schedule should be printed from the eClinical system after completing the RANDOM page (enrollment). The coordinator should file the report in the participant's study binder.

Once the RANDOM page is completed, a system generated email will be sent to the site and study team to confirm that subject has enrolled.

The EDC system uses the date of enrollment (Baseline Visit date) to calculate the subject's follow-up visit window schedule (dates which the subject should be seen by the study staff for a given visit to be considered on time or "within window"). A full Visit Window Schedule report that includes enrollment dates during the anticipated enrollment period is posted to the ePortal Administrative folder.

SUBJECT IDENTIFICATION CODE LIST

- A confidential record of all subjects enrolled into the study.
- Contains individuals' names and addresses.
- Maintained only at the site and should remain in a safe, secure location. **DO NOT DISTRIBUTE A COPY TO SPONSOR OR THE CTCC.**
- The original must be retained at the site and may not be destroyed until notified by sponsor or the CTCC that the document is no longer needed.
- A blank copy of this form may be obtained from the ePortal "Source Document Worksheets" folder.

Section 4 -Study Drug

DRUG PACKAGING

Study drug will be packaged in participant-ready kits by the Clinical Materials Services Unit (CMSU), University of Rochester Medical Center. The kits will be labeled with a 5-digit unique enrollment ID number that is matched to the participant enrollment ID. Each participant kit will contain 4 bottles of study drug. Individual kits will be labeled with 5-digit enrollment ID number and Kit ID#.

STUDY DRUG SHIPMENT TO SITES

Initial Shipment- A site will be activated when all start-up requirements have been met (IRB approval, contract execution, training, regulatory documents). CTCC project management will notify CMSU when a site is activated and study drug can be released to the site.

- The initial shipment will contain 3 participant specific baseline (BL) kits. Individual participant resupply **will not** be required for Cohort 1.
- Study Drug will be shipped 2 day via FedEx from the CMSU to allow for tracking of shipments.
- Shipping temperature excursions outside 15° to 30 °C (59° to 86°F) may result in the Study Drug being placed into quarantine in the CMSU system.

Any study drug supply issues that you may encounter should be addressed directly with the CMSU (contact information below). For drug issues pertaining to the protocol or site-specific issues, please contact the CTCC NILO-PD Project Manager.

Pat Bolger, R.Ph., MBA
Manager, Clinical Supply Operations
Clinical Materials Services Unit (CMSU)
University of Rochester Medical Center
77 Ridgeland Road
Rochester, NY 14623
Tel: 585-758-0508
E-mail: Patrick.bolger@cmsu.rochester.edu

STUDY DRUG RESUPPLY/RE-STOCK

Cohort 1- the BL shipment will provide adequate study drug to complete 6 months of treatment

- After a Cohort 1 randomization CMSU will ship a replacement kit within 2 business days of being notified of a randomization. This will allow sites to maintain one kit for each arm available for any randomization taking place at a site.
- **3 study drug kits must be on site when a participant is randomized**

Cohort 2 - Participant resupplies will be automatically triggered by the CTCC's monthly resupply report.

Emergency Resupply - In the event that an urgent resupply is needed, the Project Manager must be notified, so the participant or site-specific issue can be documented as a study notification. To contain costs, inventory of drug must be monitored carefully at the site to ensure an adequate supply is available.

STUDY DRUG RECEIPT

- CMSU will place the Packing List/Acknowledgement of Receipt form in the "Invoice Enclosed" sleeve attached to the shipping carton (Appendix 2: Packing List/ Invoice/Acknowledgement of Receipt (AOR)).
- Study Drug receipt must be acknowledged by the site **within 48 hours of receipt** by uploading a signed and dated AOR to a NILO BOX account. The AOR should be uploaded to the site-specific AOR file.
- File the original, signed AOR in the site regulatory binder.
- Maintain Drug Inventory Log for all kits received. Log can be found on the ePortal in the "Source Document Worksheet" folder.
- Ensure the drug is properly secured and stored per handling instructions in Appendix 1

STUDY DRUG STORAGE

Reference: Protocol **Section 7.4** and handling instructions in Appendix 1

All study drug must be kept in a secure, safe area where temperature is controlled and monitored under recommended storage conditions as stated on the labeling (at 25°C (77°F) with access limited to persons directly involved in the study.

- A temperature log must be maintained for the storage area that captures a minimum of one temperature recording daily.
- Brief excursions from the required temperature for 48-72 hours may be permissible. Report any temperature excursion to CTCC Project Manager to confirm.

ADMINISTRATION OF STUDY DRUG

Reference: Protocol **Section 7.8.1**

- Study drug must be taken on an empty stomach
- Participants should avoid eating food for at least 2 hours before the dose is taken and avoid eating for at least 1 hour after the dose is taken
- Study drug should be taken at a regularly scheduled time (except when scheduled for specific study visits)
- If a participant is late by 12 hours in taking their daily dose, it is considered a missed dose and should be instructed to take their next dose at their regularly scheduled time.
- Participants should not take two doses at the same time to make up for a missed dose.

STUDY DRUG ACCOUNTABILITY/DESTRUCTION

Reference: Protocol **Section 7.5**

- The site Investigator, Study Coordinator, or Pharmacist must maintain accurate records (including dates) of all supplies received and returned using the Drug Dispensing and Accountability Logs.
 - All study drug supplies issued to participants must be documented on the Study Drug Dispensing Log
 - Participants will return all unused study drug, including empty bottles to the site.
 - Study drug used by, and returned by each participant must be recorded on the Study Drug Accountability Log
 - Reconciliation of study drug must be clearly documented on Drug Accountability log.
 - Drug destruction will occur on site per institutional policy (SOP must be maintained in investigator site file and at the CTCC). Approval for destruction must be approved by the CTCC PM or monitor by completing the following steps:
 1. Accountability log must be complete and confirmed to be accurately captured in the database by CTCC project manager or monitor
 2. Drug destruction log (located on eClinical portal in “Source Document Worksheet Folder”) must be completed and reviewed by CTCC PM or monitor prior to on-site destruction. NOTE: drug accountability must be completed and documented by 2 site staff members prior to CTCC approval to destroy study drug.
- Unused and returned study drug must be kept on site for review during monitoring visits OR until drug destruction is approved by a CTCC PM or monitor.
- Only if local environmental regulations prohibit the destruction of study drug at the site level will the CMSU accept a return of unused study drug from the site. Contact the CTCC for further instruction.
- The Site Investigator is responsible for keeping current and accurate records of study drug received, dispensed and its disposition.
- All study drug documentation must be maintained and stored in the site regulatory file.

STUDY DRUG DOSE ADJUSTMENTS

Reference: **Sections 7.9.1 and 7.9.2** for specific instructions regarding intolerability or safety reasons

- **Dose Reductions for intolerability**
 - Can occur at any time during the study
 - **MUST** be called into the CTCC Project Manager
 - In the case of intolerability at two capsules daily dosage reduction to one capsule daily should be attempted prior to discontinuing study drug.
 - Instructions for dosage reduction may be given either over the phone after review of any adverse events, or at an in-person visit
- **Dose Reductions/Suspension for safety reasons**
 - Can occur at any time during the study

- Safety variables outlined in protocol section 7.9.2 table 2 will trigger a dose reduction/suspension

Please follow instructions in protocol **Sections 9.11 (Cohort 1) and 9.25 (Cohort 2)** for participants who discontinue the study drug or safety and tolerability reasons (premature withdrawal visit).

STUDY DRUG RE-CHALLENGE

Reference: **Section 7.10** for specific instructions regarding re-challenges

Participants may be re-challenged once, for intolerability, during the study titration phase at the discretion of the Site Investigator.

All attempts at re-titration of study drug must be called into the CTCC Project Manager.

Rules for Dose Re-Challenge for Intolerability

- Provided the intolerability issues have resolved, participants may resume titration to two capsules daily dosage at the discretion of the Site Investigator.
 - Participants unable to tolerate the dose increase will be reduced to one capsule daily and enter the maintenance phase of the study.
 - Participants unable to tolerate one capsule daily will be taken off the study drug and will follow procedures outlined for study termination for intolerability (See Section 9.11- Premature Withdrawal).
 - **No re-challenges will be allowed after Safety Visit 02 (SV02), Day 60.**
- **Rules For Dose Re- Challenge for Safety Reasons**
 - Dosage suspension for safety reasons can occur at any time during the study. Re-challenge will be allowed when abnormalities have resolved fully.
 - Please, refer to protocol section 7.9.2, Table 2
 - **Rules For Dose Re-Challenge In Cases Not Related To Safety Or Tolerability**
 - If study drug is temporarily suspended for occurrences other than study drug related safety or tolerability issues, study drug may be resumed by the Site Investigator.
 - If drug suspension is less than 7 days, the participant can restart study drug at prior dosing level.
 - Drug suspensions lasting more than 7 days require re-titration. **Please refer to section 7.10.3 for specific instructions.**

PERMANENT DISCONTINUATION OF STUDY DRUG

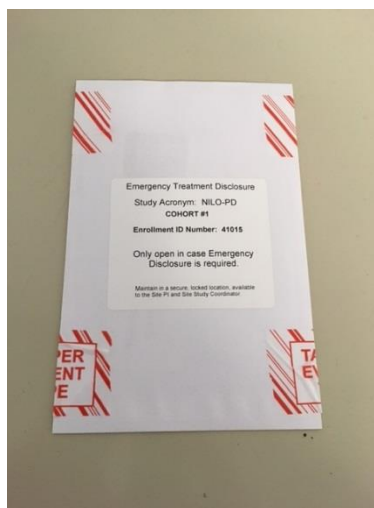
Reference: protocol **Sections 9.10, 9.11, 9.23 and 13**

The CTCC must be informed within 24 hours of all participants who Prematurely Withdrawal from study for any reason.

- Participants will not be allowed to remain in the study if study drug is permanently discontinued.
- If a participant needs to discontinue study drug for safety reasons, the site should complete a Premature Withdrawal visit (**section 9.10 cohort 1 or 9.23 cohort 2**) either while still taking the study drug or as soon as possible after drug discontinuation.
 - The participant will be encouraged to return to the study site for the 30 and 60 day safety follow-up visits (for Cohort 1 = Visit 05 and Visit 06; for Cohort 2 = Visit 07 and Visit 08).
- AEs will be followed for 30 days after a Participant's last dose of study drug.
- In case the study drug has been discontinued for safety laboratory values or ECG abnormalities reasons, ECG and abnormal laboratories values must be repeated in 2 weeks and at 30 days.
- In instances where the participant refuses or cannot to return for a PW visit, it is acceptable to attempt to obtain data by telephone and arrange for return of study drug.
- It is important to collect the final date and time of day the last dose of study drug.

EMERGENCY DISCLOSURE OF TREATMENT ASSIGNMENT

- CMSU will prepare printed emergency treatment disclosures for each participant. The Site Investigator or Site Pharmacist (if applicable) will be provided with a sealed code envelope for each Enrollment ID (Randomized Kit Number) for all kits received from the CMSU.
- Distribution of Emergency Treatment Disclosures to Sites:
 - Individual treatment disclosures will be included with each shipment of baseline kits.
 - Each kit specific treatment disclosure will be enclosed in an envelope (see photo below) that will include the following:
 1. An outside label listing the Participant Randomization Number that coincides with the scratch-off panels contained within
 2. A study specific approved Emergency Treatment Disclosure Instruction Sheet
 3. Blank study specific Treatment Assignment Disclosure Form
 4. Empty business envelope labeled with the address for the CMSU (attention: Pat Bolger) and space to record Participant Randomization Number



- The printed emergency treatment disclosure will provide the participant specific treatment assignment (Placebo or Nilotinib) under a laminated, black, opaque scratch-off panel. The following statements will be printed on the face of the scratch-off panel:

Drug Information Inside
In Case of Emergency
Scratch off the Surface of Blinded Area

- A study-specific Emergency Unblinding Instruction Sheet was created by the CMSU (see Appendix 3). It contains the following information:
 - Procedure to follow for storage of unblinding materials
 - Procedure to follow for unblinding
 - Procedure to follow once disclosure of treatment assignment has occurred
 - Instructions for return of unblinding materials upon conclusion of the study
- A study-specific Emergency Disclosure Report Form was created by the CMSU (see Appendix 4).
 - The form provides a place for site personnel to enter the following information:
 1. Participant ID Number
 2. Site Number
 3. Investigator Name
 4. Date of Disclosure
 5. Reason for Disclosure
 6. Person Responsible for Disclosure
 7. List any other staff members that were made aware of the disclosure
 8. Confirmation that the Clinical Trials Coordination Center was made aware of the disclosure.
 - The form instructs site personnel to make a copy of the completed form and place the copy and the used emergency unblinding scratch-off panel in one of the enclosed empty business envelopes. Instructions for final disposition of the original form is also outlined.
- All sealed treatment disclosure envelopes will be collected at the closeout monitoring visit and returned to CMSU.
- Sealed treatment disclosure envelopes should only be opened in emergency situations for participant safety.
- **Site Investigator should consult with the Clinical Monitor or another member of the study team prior to opening the sealed code envelope and “breaking the blind”.**
- If a sealed treatment disclosure envelope has been opened, the reason must be fully documented detailing the purpose, date and personnel involved in the source document and entered on the case report form. The participant will be withdrawn from the study.
- Send the disclosure envelope and contents to an unblinded designee at CMSU with 48 hours of disclosure
- Drug assignment should not be disclosed to anyone on the study team

Section 5 - Electronic Case Report Forms

eCLINICAL eCRF GUIDELINE

- NILO-PD study data will be recorded via the electronic data capture (EDC) tool within the CTCC eClinical suite of applications.
- A complete set of guidelines for the eClinical system including EDC basics and the query management process is detailed in the *eClinical eCRF Guideline*.
- Please refer to the guideline for expanded topic discussions as well as step-by-step procedures. The guide is located in the ePortal Training folder.

ACCESS TO EDC AND PORTAL

Welcome!
Home - Sign In

CTCC
Clinical Trials Coordination Center

EXPeRT Clinical

Sign In

Login

Password

Sign In

Forgot Password?

Login = User ID

<http://support.ctcc.rochester.edu>
265 Crittenden Blvd. CU 420694
Rochester, NY 14642
1-888-406-6704 / 585-275-3893
Normal Hours of Operation:
Monday - Friday
8:00 am - 9:00 pm ET

- After successful completion of all training requirements, protocol (study) personnel will be assigned a permanent User ID and temporary password.
- After logging in for the first time you will be prompted to change your password
- Access to the study protocol is based upon the user role.
 - **Investigator/Coordinator/Co-coordinator:** permitted to enter and update data, provide resolutions to queries and apply electronic signatures
 - **Data Entry staff:** limited to data entry only; query resolution not permitted with this role
 - **Regulatory Managers:** limited to read only
- Users are responsible for maintaining the security of their access to the applications. The eRT application requires each user to change their password every 60 days.

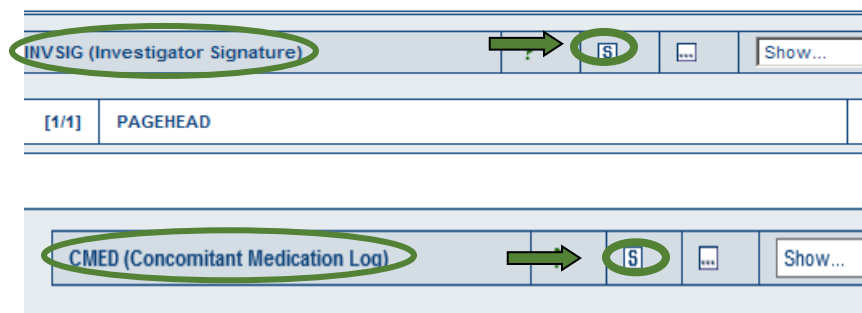
NOTE: The EDC application will automatically time out after [30] minutes of inactivity. Data must be saved as each eCRF page is entered. You will be prompted to save the page if you attempt to move to the next page without saving data. However, if the system times out, unsaved data is lost.

- 1) The system is not compatible with a Macintosh, PC required.
- 2) Your browser may not be compatible. If you are not using Internet Explorer (i.e. you are using Firefox, Safari, Opera, etc.) you may not be able to see your study in the system.

Please contact the **eClinical Support Line** at **585-275-3893** to try to troubleshoot

ELECTRONIC SIGNATURES

- The definition of an electronic signature is “a computer data compilation of any symbol or series of symbols executed, adopted or authorized by an individual’s handwritten signature.”
 - The FDA and Clinical Trials Coordination Center consider electronic signatures to be the equivalent of handwritten signatures.
- An electronic signature (eSignature) is required by the Site Investigator on the following eCRFs:
 - Inclusion/Exclusion (Screening Visit Only)
 - Investigator Signature Form (All Visits)
- An eSignature is required by the Site Coordinator on the concomitant medication log, at the SC1 visit, to indicate that entry of all medications has been entered prior to enrollment.
- To apply an electronic signature, click on the “S” box.



- The following screen comes up. Click on the appropriate box based on your role.

Current Page Statuses

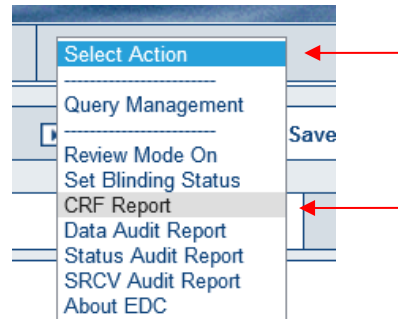
<input checked="" type="checkbox"/>	SC1 conmeds complete	←
<input type="checkbox"/>	Reviewed	
<input type="checkbox"/>	Source Verified	
<input type="checkbox"/>	Coordinator Signature	
<input type="checkbox"/>	Investigator Signature	←
<input type="checkbox"/>	Assessment not Performed	

Please remember that an applied signature will be removed if any change is subsequently made to the page, and therefore, the signature will need to be

NOTE: Prior to the first study visit, print off a blank set of the source document worksheets from the ePortal “Source Document Worksheets” folder and keep the blank set in your study binder as back-up. Should you experience any issues with accessing the internet to enter data or download CRF worksheets, you will have a blank set to copy and use as needed.

Sites have the ability to print the Visit Window schedule from the RANDOM page.

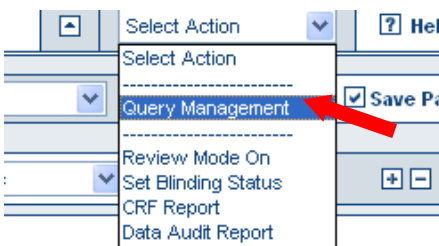
- Open the RANDOM page Click Select Action
- Click CRF Report
- A new window will open with a 2-page PDF document
- Print document



GENERAL DIRECTIONS FOR eCRF COMPLETION

Data should be entered within 2 business days of a completed visit.

Range and edit checks run concurrently with data entry. Sites should develop a practice of immediately checking the Query Management Module to review and resolve any queries that may have been generated from these checks. The protocol Information Analyst (IA) will also routinely run consistency checks which review the data for consistency within a page and across multiple pages and/or multiple events.



The Query Management module is accessed by clicking on the down arrow next to Select Action, which appears on the top right side of every eCRF.

NOTE: Sites are responsible for logging into the system to review and resolve additional queries that may have been generated or applied manually. It is expected that sites will log in at least weekly but it is recommended to log in to check this more frequently.

The EDC system audit trail tracks all the required elements:

- Initial entry of data: by whom and when;
- Updates to data: by whom, when, the old and new values, and why the change was made to the data.

TOPIC	INSTRUCTIONS
Abbreviations	Sites are discouraged from abbreviating, but abbreviation is acceptable when the meaning is unambiguous.
Misspellings	Misspellings by site staff are corrected in the database by CTCC staff as long as there is no ambiguity in the meaning. If the meaning is unclear, the site is queried for clarification.
Numeric Data	All numbers will be auto justified and do not require any leading zero fills. If a response requires a decimal point, the decimal point must be entered into one of the answer boxes. (Note, the decimal point may be pre-printed on the source document worksheet.)
Dates	Dates are recorded in the MMDDYYYY format. If exact date is not known, you will be prompted to identify which part of the date is estimated.
Time	Time is recorded in the hours:minutes (HH:MM) format using military time. For example: 13:31 (1:31 pm). The EDC application requires entry of the colon.
Data Entry Errors	Errors due to incorrect data entry ('keypunch error') are corrected by the site in the database and assigned 'data entry error' as reason for change.
Corrections or Updates to Saved Data	If a change is made to an eCRF after it is saved in the database, the correction will require the Site Coordinator or Site Investigator to indicate the reason for change within the audit dialog box. An eSignature will need to be reapplied to pages that originally required one.
Missing Data	Unexpected blanks are queried.
Missing Assessments *	If part of an assessment is not performed, an explanatory note should be added to the Comment section of the Visit Status page. If the entire assessment is missed, the page status should be marked with Assessment not Performed and the Visit Status page Comment section should document why the assessment was missed or not done.
Missed Visits	If a visit is not performed, it should be noted on the Visit Status page. No other eCRFs from the visit should be entered. If the final visit is missed, the site must complete the <i>Conclusion of Study Participation form</i> and <i>all logs</i> .
Out Of Window Visits	If a visit is performed outside of the target visit window, it should be noted on the Visit Status Page Comment section. The comment should include a brief description of why the visit was conducted out of window.
Premature Withdrawal	If a subject wishes to discontinue study drug the subject will follow the visit schedule for the PW visit to be completed per the schedule of activities.
Unscheduled Visits	If the unplanned visit falls outside of the window for the next regular follow-up visit, the visit is considered an Unscheduled Visit. Refer to the schedule of activities to determine which eCRFs should be completed for an unscheduled in-person or phone visit.
Evaluation Dates	Visit date refers to the actual date of the visit. The date should be consistent on all eCRFs for the visit if the visit occurred on the same

TOPIC	INSTRUCTIONS
	day. If for any reason a visit stretches across several days, this should be documented in the Comment section on the Visit Status page.

*** Status field for missed assessments**

Current Page Statuses

☐ SC1 conmeds complete
☐ Reviewed
☐ Source Verified
☐ Coordinator Signature
☐ Investigator Signature
☐ Assessment not Performed

DIRECTIONS FOR SPECIFIC NILO-PD eCRF PAGES

Dose Management Log

- This log is to be used to record initial dosage and changes throughout the study, per protocol.
 - Total Dosage = total current dosage
 - Dose Frequency= daily dosing or no dosing
 - Start Date of Dosage = date that current dosage was started
 - Stop Date of Dosage = date that current dosage was stopped
- Reason Dose Changed = expected when a stop date is entered and explains the reason for the stop date
- Do not complete *Reason Dosage Changed* column unless dosage has changed or subject has completed study drug dosing.
- Dose change of reduction, temporary suspension or permanent study drug discontinuation requires a response of relatedness to (1) Safety, (2) Tolerability or (3) Not related to study drug
- Each change must be recorded on a separate row.
- Click on “+” to add a row.

Total Daily Dosage (mg/day)	Dose Frequency 0 = no dosing 1 = qd dosing	Start Date (MM/DD/YYYY)	Stop Date (MM/DD/YYYY)	Reason Dose Changed A=Dose initiation (per protocol titration) B=End of Dosing Period 1=dose reduction * 2=rechallenge * 3=temporary suspension * 4=permanent study drug discontinuation* *must notify the CTCC	If reason dose changed is 1, 3 or 4 record response from the list provided on page 2

CONCOMITANT MEDICATION LOG

- One medication per eCRF screen page

[1/2] CONMED (Concomitant Medication Log)		Utilities		Navigation	
<div style="text-align: right;">Row #</div> <div style="text-align: center;">1</div>					
<div>SINEMET 25/100</div>		<div>MEDICATION (List generic name, if possible)</div> <div>09152011</div>		<div>Start Date (MMDDYYYY)</div> <div>1</div>	
<div>1</div> <div>TAB</div>		<div>Dose</div> <div>UNITS (e.g., mg, cc, ml, puffs)</div>		<div>Start Date estimated?</div> <div>1 = Actual (ACT)</div> <div>2 = Day Est. (DAY)</div> <div>3 = Mon/Day Est (MD)</div>	
<div>BID</div>		<div>FREQUENCY (e.g., qd, BID, qid, etc)</div>		<div>Stop Date (MMDDYYYY)</div> <div>Stop Date estimated</div> <div>1 = Actual (ACT)</div> <div>2 = Day Est. (DAY)</div> <div>3 = Mon/Day Est (MD)</div>	
<div>3</div>		<div>Route</div> <div>1 = IV</div> <div>2 = IM</div> <div>3 = PO</div> <div>4 = SC</div> <div>5 = PR</div> <div>6 = Sublingual</div> <div>7 = Inhaled</div> <div>8 = Topical</div> <div>9 = Other</div>		<div>Exclusionary Med</div> <div>WHO RECNO</div> <div>WHO SEQNO1</div> <div>WHO SEQNO2</div>	
<div>1</div>		<div>Ongoing (0=No, 1=Yes)</div>		<div>WHO DRUG NAME</div>	
<div>PARKINSONS</div>		<div>Indication</div>		<div>WHO DRUG NAME</div>	
<div>1</div>		<div>PD Med ? (0=No, 1=Yes)</div>		<div>WHO DRUG NAME</div>	
<div>0</div>		<div>Corresponding AE? (0=No, 1=Yes)</div>		<div>WHO DRUG NAME</div>	
<div>100</div>		<div>For combination PD medications only, enter the dose of Levodopa only</div>		<div>WHO DRUG NAME</div>	

- Relatedness to an Adverse Event

[0/0] CMEDAE (Related AEs)		Utilities		Navigation	
<div style="text-align: right;">Row #</div> <div style="text-align: center;">AE#</div> <div style="text-align: center;">Adverse Event</div> <div style="text-align: center;">Start Date</div> <div style="text-align: center;">Verbatim</div>					
<div></div>					
<div></div>					

- To add next medication click the plus (+) sign

[2/3] CONMED (Concomitant Medication Log)

Utilities

2 Row #

TYLENOL

350

MG

PRN

3

MEDICATION
(List generic name, if possible)

Dose

UNITS
(e.g., mg, cc, ml, puffs)

FREQUENCY
(e.g., qd, BID, qid, etc)

Route
1 = IV
2 = IM
3 = PO
4 = SC
5 = PR
6 = Sublingual
7 = Inhaled
8 = Topical
9 = Other

09222013

3

Start Date (MMDDYYYY)

Start Date estimated?
1 = Actual (ACT)
2 = Day Est. (DAY)
3 = Mon/Day Est (MD)

Stop Date (MMDDYYYY)

Stop Date estimated
1 = Actual (ACT)
2 = Day Est. (DAY)
3 = Mon/Day Est (MD)

Exclusionary Med

000200

01

005

WHO RECNO

WHO SEQNO1

WHO SEQNO2

1

HEADACHE

0

0

Ongoing (0=No, 1=Yes)

Indication

PD Med ? (0=No, 1=Yes)

Corresponding AE? (0=No, 1=Yes)

For combination PD medications only, enter the dose of Levodopa only

WHO DRUG NAME

TYLENOL

ADVERSE EVENT LOG

- The AE log will be reviewed by the Independent Medical Monitor (IMM) for any Serious Adverse Event (SAE)
 - Seriousness
 - Life Threatening
 - Causality
 - Expectedness

- One adverse event per eCRF screen

AE (Adverse Event Log) [1/2] AE (Adverse Event Log)

AE# 1 Adverse Event TACHYCARDIA

08112017 Start Date
1 Start Date Estimated?
Stop Date
Stop Date Estimated?
3 Severity
1 SAE
0 Related to LP
3 Relationship to Study Drug
3 Action taken with study drug
Premature Withdrawal due to AE
Outcome
AE Follow-up

Verbatim Term TACHYCARDIA
Low Level Term tachycardia
Preferred Term Code 10043071
Preferred Term Name tachycardia
High Level Term Rate and rhythm disorders NEC
High Level Group Term Cardiac arrhythmias
System Organ Class 1 Card
MedDRA Version 20.1

SAEIMM (IMM Assessment of SAE) [1/3]

AE# 1 IMM Sequence 1

SERIOUSNESS ASSESSMENT:
☒ 1 - Yes ☐ 0 - No

FATAL/LIFE THREATENING:
☒ 1 - Yes (7 day FDA reporting requirement) ☐ 0 - No (15 day FDA reporting requirement)

CAUSALITY ASSESSMENT:
☐ 1 - unrelated ☐ 2 - unlikely ☒ 3 - possible ☐ 4 - probable ☐ 5 - definite

EXPECTEDNESS ASSESSMENT:
☒ 1 - Expected ☐ 2 - Not Expected

Comments
Subject experienced rapid pulse within an hour of study dru

- To add additional adverse event click the plus (+) sign

AE (Adverse Event Log) [2/2] AE (Adverse Event Log)

AE# 2 Adverse Event PROFUSE SWEATING

08112017 Start Date
1 Start Date Estimated?
08112017 Stop Date
1 Stop Date Estimated?
2 Severity
0 SAE
0 Related to LP
3 Relationship to Study Drug
3 Action taken with study drug
Premature Withdrawal due to AE
Outcome
0 AE Follow-up

Verbatim Term PROFUSE SWEATING
Low Level Term
Preferred Term Code
Preferred Term Name
High Level Term
High Level Group Term
System Organ Class 1
MedDRA Version

STUDY DRUG DISPENSING LOG

- Dispense visits per protocol are BL and V03
- Drop down allows other visits

The screenshot displays the 'STUDY DRUG DISPENSING LOG' interface. At the top, there's a header bar with '[3/3] DRUGDIS (Study Drug Dispensing Log)' and a 'Utilities' dropdown. Below this is a table with columns: Visit #, Kit #, # Capsules Dispensed, Bottle B ID (B1 B2), Total # Capsules Dispensed from Bottle B, and Comments. A dropdown menu is open for the Visit # column, showing a list of codes and descriptions: BL, PW, SV1, SV2, SV3, SV4, V01, V02, V03, V04, V05, and V06. The background table has rows with some data entered, including a row with 'BL' in the Visit # column and '1' in the Total # Capsules Dispensed column.

STUDY DRUG ACCOUNTABILITY (RETURN) LOG

- Return visits per protocol are V03 and V04
- Drop down allows other visits

The screenshot displays the 'STUDY DRUG ACCOUNTABILITY (RETURN) LOG' interface. At the top, there's a header bar with '[3/3] DRUGRET (Study Drug Accountability Log)' and a 'Utilities' dropdown. Below this is a table with columns: Visit #, Kit #, Total # Bottle A Capsules reported Lost by Subject, Total # Bottle A Capsules Retained for Destruction by Staff, Bottle B ID (B1, B2), Total # Bottle B Capsules counted by Staff, Total # Bottle B Capsules reported Lost by Subject, and Total Bott Cap Reti for by s. A dropdown menu is open for the Visit # column, showing a list of codes and descriptions: BL, PW, SV1, SV2, SV3, SV4, V01, V02, V03, V04, V05, and V06. The background table has rows with some data entered, including a row with 'V03' in the Visit # column and '1' in the Total # Bottle A Capsules reported Lost by Subject column.

MDS UPDRS Part III: ON and OFF

- Note: there are 2 separate forms
 - NUPDRS30 (OFF)
 - BL, V03, V04, V05, V06, PW
 - NUPDRS3 (ON)
 - V01, V02, V03, V04, V05, V06

Entry Status Legend		
		<input type="checkbox"/> No Pages Entered
		<input checked="" type="checkbox"/> Some Pages Entered
Page ID	Description	
INEX	Inclusion / Exclusion	
VITAL	Vital Signs	
GENPHYEX	General Physical Exam	
EKG	Electrocardiogram	
PDMEDUSE	Use of PD Medication	
STDYDRG	Use of Study Drug	
NUPDRS30	MDS UPDRS Part III (Off State)	
NUPDRS1	MDS UPDRS Part I	
NUPDRS1P	MDS UPDRS Part I: Patient Questionnaire	
NUPDRS2P	MDS UPDRS Part II: Patient Questionnaire	
NUPDRS3	MDS UPDRS Part III (On State)	
NUPDRS4	MDS UPDRS Part IV	
MODSEADL	Modified Schwab & England ADL	
CGIP	Clinical Global Impression Scale (Part)	
CGII	Clinical Global Impression Scale (INV)	
BIOLAB	Biomarkers Laboratory Procedures	
MDRS	Mattis Dementia Rating Scale	
PDQ39	PD Quality of Life Questionnaire (PDQ39)	
EQ5D	EQ-5D Instrument	
PDSLEEP	Parkinson's Disease Sleep Scale Summary	
PDEXQBL	Parkinson Disease Expectancy Ques SC1/BL	
CAFFEIN	PD RFQ-U Caffeine	
SMOKTOB	PD RFQ-U Smoking and Tobacco	
INVSIG	Investigator Signature	
VISSTAT	Visit Status	

Section 6 – Assessments

NILO-PD ASSESSMENT REQUIREMENTS

Cognitive assessments and Lumbar Puncture should be completed in the medications “ON” state; based on the participant/Site Investigator defined BEST ON and/or approximately hour after dose of symptomatic therapy.

The table below indicates with an “X” which staff members are expected to perform assessments as well as requirements for certified training. The gray box under Coordinator indicates this assessment is not to be completed by the Coordinator.

Note: Where an assessment can be conducted by either the investigator or coordinator, each participant should have the same individual conduct the assessment at every visit in order to maintain consistency. Not maintaining a consistent assessor will be a minor protocol deviation. All other study assessments not listed here may be undertaken by appropriately trained study personnel. See Section 1 of Operations Manual for information on the completion of assessments by Sub-Investigators or Back-up Coordinators. It is preferred that a visit be rescheduled than have a different rater. Contact the NILO-PD Project Manager with questions.

Assessments should be completed in the order listed in section 9.0 of the NILO-PD protocol closely as possible to ensure that the neurological tests are performed at approximately the same time (mornings) on each testing day.

See Appendix 5 for complete list of assessments and requirements for administration.

***Certified training required**

MOVEMENT DISORDER SOCIETY UNIFIED PARKINSON’S DISEASE RATING SCALE

Section		Completed by	Special instructions
I Non Motor experiences of daily living	IA Complex behaviors	Investigator	none
	IB Patient questionnaire	Subject/care partner	May be reviewed for completeness but should be independent of investigator
II Motor experiences of daily living		Subject/care partner	Reviewed by investigator for completeness/clarity
III Motor examination		Investigator	Rated in the “OFF” and “ON”
IV Motor complications		Investigator	Integrates subject information with Investigator’s judgment/observation

Certified training is required for all Investigators completing the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) assessments. Primary Coordinators may complete the review of Part 1B and Part IV, without certified training. **Please be sure to follow the instructions as provided on the MDS-UPDRS Source Document Worksheets.**

The MDS-UPDRS will be assessed per protocol schedule of activities. The MDS-UPDRS has four parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living), Part III (motor examination) and Part IV (motor complications). The complete MDS-UPDRS Parts I-IV should be completed in the ON state. For Cohort 1 participants, Part III must also be completed in the OFF state (approximately 12 hours post dose).

Part I has two components: **IA** concerns a number of behaviors that are assessed by the investigator with all pertinent information from study participants and caregivers, and **IB** is completed by the participant with or without the aid of the caregiver, but independently of the investigator. These sections should be reviewed by the Investigator or Coordinator to ensure that all questions are answered clearly, and to help explain any perceived ambiguities.

This portion of the scale assesses the non-motor impact of Parkinson's disease (PD) on participants' experiences of daily living. There are 13 questions. Part 1A is administered by the Investigator or Coordinator (six questions) and focuses on complex behaviors. Part 1B is a component of the self-administered Participant Questionnaire that covers seven questions on non-motor experiences of daily living.

Part 1A:

In administering Part 1A, the examiner should use the following guidelines:

1. Mark at the top of the form the primary data source as participant, caregiver, or participant and caregiver in equal proportion.
2. The response to each item should refer to a period encompassing the prior week including the day on which the information is collected.
3. All items must have an integer rating (no half points, no missing scores). In the event that an item does not apply or cannot be rated (e.g., amputee who cannot walk), the item is marked UR for Unable to Rate.
4. The answers should reflect the usual level of function and words such as "usually", "generally", "most of the time" can be used with participants.
5. Each question has a text for you to read (Instructions to participants/caregiver). After that statement, you can elaborate and probe based on the target symptoms outlined in the Instructions to examiner. You should **NOT READ the RATING OPTIONS** to the participant, because these are written in medical terminology. From the interview and probing, you will use your medical judgment to arrive at the best response.
6. Participants may have co-morbidities and other medical conditions that can affect their function. You and the participant must rate the problem as it exists and do not attempt to separate elements due to Parkinson's disease from other conditions.

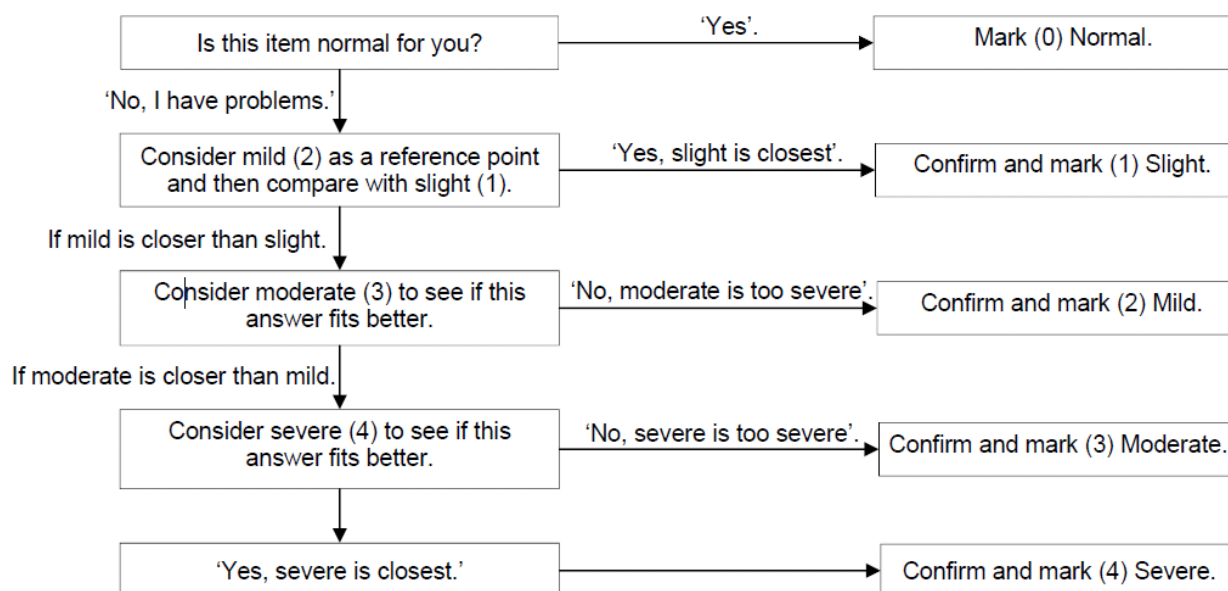
EXAMPLE OF NAVIGATING THROUGH THE RESPONSE OPTIONS FOR PART 1A

Suggested strategies for obtaining the most accurate answer:

After reading the instructions to the participant, you will need to probe the entire domain under discussion to determine normal vs. problematic: If your questions do not identify any problem in this domain, record 0 and move on to the next question.

If your questions identify a problem in this domain, you should work next with a reference anchor at the mid-range (option 2 or Mild) to find out if the participant functions at this level, better or worse. You will not be reading the choices of responses to the participant as the responses use clinical terminology. You will be asking enough probing questions to determine the response that should be coded.

Work up and down the options with the participant to identify the most accurate response, giving a final check by excluding the options above and below the selected response.



Part II is designed to be a self-administered questionnaire like Part IB, should be reviewed by the investigator to ensure completeness and clarity.

Part III has instructions for the Investigator to give or demonstrate to the participant; this part is completed by the Investigator.

This portion of the scale assesses the motor signs of PD. In administering Part III of the MDS-UPDRS the examiner should comply with the following guidelines:

- At the top of the form, mark whether the participant is on medication for treating the symptoms of Parkinson's disease and, if on levodopa, the time since the last dose.
- If the participant is receiving medication for treating the symptoms of Parkinson's Disease, mark the participant's clinical state using the following definitions:

ON: based on the participant/ Site Investigator defined BEST ON and/or approximately hour after dose of symptomatic therapy

OFF: approximately 12 hours after last dose of symptomatic therapy

NOTE: Part III should be completed in the ON and OFF state

The investigator should “rate what you see”. Admittedly, concurrent medical problems such as stroke, paralysis, arthritis, contracture, and orthopedic problems such as hip or knee replacement and scoliosis may interfere with individual items in the motor examination. In situations where it is absolutely impossible to test (e.g., amputations, plegia, limb in a cast), use the notation “UR” for Unable to Rate. Otherwise, rate the performance of each task as the participant performs in the context of co-morbidities.

All items must have an integer rating (no half points, no missing ratings).

Specific instructions are provided for the testing of each item. These should be followed in all instances. The investigator demonstrates while describing tasks the participant is to perform and rates function immediately thereafter. For Global Spontaneous Movement and Rest Tremor items (3.14 and 3.17), these items have been placed purposefully at the end of the scale because clinical information pertinent to the score will be obtained throughout the entire examination.

At the end of the rating, indicate if dyskinesia (chorea or dystonia) was present at the time of the examination, and if so, whether these movements interfered with the motor examination.

Part IV has instructions for the Investigator and also instructions to be read to the participant. This part integrates participant-derived information with the Investigator’s clinical observations and judgments and is completed by the Investigator.

In this section, the examiner uses historical and objective information to assess two motor complications, dyskinesias and motor fluctuations that include OFF-state dystonia. Use all information from participant, caregiver, and the examination to answer the six questions that summarize function over the past week including today. As in the other sections, rate using only integers (no half points allowed) and leave no missing ratings. If the item cannot be rated, place UR for Unable to Rate. You will need to choose some answers based on percentages, and therefore you will need to establish how many hours generally are awake hours and use this figure as the denominator for “OFF” time and Dyskinesias. For “OFF dystonia”, the total “OFF” time will be the denominator.

Operational definitions for examiner’s use:

Dyskinesias: Involuntary random movements. Words that participants often recognize for dyskinesias include “irregular jerking”, “wiggling”, “twitching”. It is essential to stress to the participant the difference between dyskinesias and tremor, a common error when participants are assessing dyskinesias.

Dystonia: contorted posture, often with a twisting component: Words that participants often recognize for dystonia include “spasms”, “cramps”, “posture”.

Motor fluctuation: Variable response to medication: Words that participants often recognize for motor fluctuation include “wearing out”, “wearing off”, “roller-coaster effect”, “on-off”, “uneven medication effects”.

OFF: Typical functional state when participants have a poor response in spite of taking medication or the typical functional response when participants are on NO treatment for parkinsonism. Words that participants often recognize include “low time”, “bad time”, “shaking time”, “slow time”, “time when my medications don’t work.” PD medication should be held 12 hours prior to completing the MDS-UPDRS part III OFF assessment.

ON: Typical functional state when participants are receiving medication and have a good response: Words that participants often recognize include “good time”, “walking time”, “time when my medications work.”

MODIFIED SCHWAB AND ENGLAND

The Investigator, participant and care partner should rate the participant’s independence. Note: Increments of 5% may be used.

PDQ-39 QUALITY OF LIFE QUESTIONNAIRE

The PDQ-39 is a self-administered questionnaire. The PDQ-39 will be assessed at per the schedule of activities.

The 39 items address eight domains of health that participants consider to be adversely affected by the disease. This scale includes:

- Mobility (e.g. fear of falling when walking)
- Activities of daily living (e.g. difficulty cutting food)
- Emotional well-being (e.g. feelings of isolation)
- Stigma (e.g. social embarrassment)
- Social support
- Cognition
- Communication
- Bodily discomfort

The PDQ-39 is scored on a scale of 0 to 100, where lower scores indicate a better perceived health status. Higher scores are consistently associated with the more severe symptoms of the disease such as tremor and stiffness. The results are presented as eight discrete domain scores as well as a summary score.

Instructions: The participant should complete the PDQ-39 prior to the administration of any motor exams or assessments to minimize participant bias. The participant should be given a copy of the PDQ-39. Review the instructions, which are: “Due to having Parkinson’s disease, how often have you experienced the following, during the last month.” The coordinator should highlight the portion of the instruction regarding **Parkinson’s disease** and the time frame of the **last month**. Refer to the key on the scale: 0 = Never, 1 = Occasionally (now and then), 2 = Sometimes (a few times per week), 3 = Often (greater than once per day), 4 = Always or cannot do at all.

Review the participant responses prior to the participant leaving the site to assure accuracy and completeness.

HOEHN AND YAHR

The Hoehn & Yahr scale is an Investigator assessment of the participant's stage of Parkinson's disease. The scale allocates stages from 0 to 5 to indicate the relative level of disability.

NOTE: H&Y must be >2 and <4 for participant to be eligible for Cohort 1.

Stage 0 = Asymptomatic

Stage 1 = Unilateral involvement only

Stage 2 = Bilateral involvement without impairment of balance

Stage 3 = Mild to moderate involvement; some postural instability but physically independent; needs assistance to recover from pull test.

Stage 4 = Severe disability; still able to walk or stand unassisted

Stage 5 = Wheelchair bound or bedridden unless aided

Assessment conducting at screening visit and every in-person visit thereafter. This assessment should be conducted in the ON state.

MONTREAL COGNITIVE ASSESSMENT

The Montreal Cognitive Assessment (MoCA) is a brief assessment of cognition in adults. This assessment is used to evaluate mild cognitive impairment through memory recall, visuospatial abilities and language tasks.

If the subject has 12 years of education or fewer, a point is added to his/her total score. Note that this number of years does not refer to a particular education level, for example, it does not refer to individuals that have or have not completed high school. The number of years of education must actually be counted starting after kindergarten (kindergarten must not be included in the count). Please note that the maximum score is 30, therefore, if a subject scores 30/30, a point is not added if he/she has 12 years of education or less.

If at Screening the MoCA score makes a subject ineligible and the Investigator determines that repeating the MoCA assessment at a later time (within the Screening visit window) might result in a different score, (s)he is allowed to rescreen the MoCA assessment.

Administration and Scoring:

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

1. Alternating Trail Making:

Administration: The examiner instructs the participant: "Please draw a line, going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)]."

Scoring: Allocate one point if the participant successfully draws the following pattern:
1 -A- 2- B- 3- C- 4- D- 5- E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

2. Visuoconstructional Skills (Cylinder):

Administration: The examiner gives the following instructions, pointing to the cylinder:
“Copy this drawing as accurately as you can, in the space below”.

Scoring: One point is allocated for a correctly executed drawing.

- Drawing must be three-dimensional
- All lines/ovals are drawn
- No line is added
- The horizontal lines are relatively parallel
- The objects at the end must be oval rather than circles
- The horizontal lines must touch the top/bottom of the ovals

A point is not assigned if any of the above-criteria are not met.

3. Visuoconstructional Skills (Clock):

Administration: Indicate the right third of the space and give the following instructions:
“Draw a clock. Put in all the numbers and set the time to 10 after 9 (ten past nine)”.

Scoring: One point is allocated for each of the following three criteria:

- Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
- Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
- Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centered within the clock face with their junction close to the clock center.

A point is not assigned for a given element if any of the above-criteria are not met.

4. Naming:

Administration: Beginning on the left, point to each figure and say: “Tell me the name of this animal”.

Scoring: One point each is given for the following responses: (1) donkey (or mule), (2) pig or hog, (3) kangaroo.

5. Memory:

Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions: *“This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn’t matter in what order you say them”.*

Mark a check in the allocated space for each word the participant produces on this first trial. When the participant indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: *“I am going to read the same list for a second time.*

Try to remember and tell me as many words as you can, including words you said the first time.” Put a check in the allocated space for each word the participant recalls after the second trial.

At the end of the second trial, inform the participant that (s)he will be asked to recall these words again by saying, “I will ask you to recall those words again at the end of the test.”

Scoring: No points are given for Trials One and Two. Scoring is based on the delayed recall trial.

6. Attention:

Forward Digit Span: Administration: Give the following instruction: *“I am going to say some numbers and when I am through, repeat them to me exactly as I said them”*. Read the five number sequence at a rate of one digit per second.

Backward Digit Span: Administration: Give the following instruction: *“Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order.”* Read the three number sequence at a rate of one digit per second.

Scoring: Allocate one point for each sequence correctly repeated, (N.B.: the correct response for the backwards trial is 4-7-1).

7. Vigilance:

Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: *“I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand”*.

Scoring: Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A).

8. Serial 7s:

Administration: The examiner gives the following instruction: *“Now, I will ask you to count by subtracting seven from 80, and then, keep subtracting seven from your answer until I tell you to stop.”* Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correct subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 80. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond “72 – 65 – 58 – 51 – 44” where the “72” is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

9. Sentence repetition:

Administration: The examiner gives the following instructions: *“I am going to read you a sentence. Repeat it after me, exactly as I say it [pause]:*

She heard his lawyer was the one to sue after the accident.”

Following the response, say: *“Now I am going to read you another sentence. Repeat it after me, exactly as I say it [pause]:*

The little girls who were given too much candy got stomach aches.”

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "too much") and substitutions/additions (e.g., "... his lawyer sued after ..."; "the girls"), altering plurals, etc.).

10. Verbal fluency:

Administration: The examiner gives the following instruction: *"Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Peter or Paris), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready? [Pause] Now, tell me as many words as you can think of that begin with the letter B.[time for 60 sec]. Stop."*

Scoring: Allocate one point if the participant generates 11 words or more in 60 sec. Record the participant's response in the bottom or side margins.

11. Abstraction:

Administration: The examiner asks the participant to explain what each pair of words has in common, starting with the example: *"Tell me how an orange and a banana are alike"*. If the participant answers in a concrete manner, then say only one additional time: *"Tell me another way in which those items are alike"*. If the participant does not give the appropriate response (fruit), say, "Yes, and they are also both fruit." Do not give any additional instructions or clarification.

After the practice trial, say: *"Now, tell me how an eye and an ear are alike"*. Following the response, administer the second trial, saying: *"Now tell me how a trumpet and a piano are alike"*. Do not give any additional instructions or prompts.

Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:

Eye-Ear = sensory organs, parts of the head, parts of the body;

Trumpet-Piano = musical instruments, you can play them.

The following responses are **not acceptable**:

Eye-Ear =parts of the face.

12. Delayed recall:

Administration: The examiner gives the following instruction: *"I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember."* Make a check mark (___) for each of the words correctly recalled spontaneously without any cues, in the allocated space.

Scoring: Allocate 1 point for each word recalled freely without any cues.

Optional:

Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (✓) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, “Which of the following words do you think it was, BICYCLE, TRAIN, or BOAT?”

Use the following category and/or multiple-choice cues for each word, when appropriate:

TRAIN:	category cue: mode of transportation	multiple choice: bicycle, train, boat
EGG:	category cue: something you eat	multiple choice: sandwich, carrot, egg
HAT:	category cue: article of clothing	multiple choice: hat, glove, scarf
CHAIR:	category cue: piece of furniture	multiple choice: table, chair, lamp
BLUE:	category cue: a color	multiple choice: blue, brown, orange

Scoring: No points are allocated for words recalled with a cue. A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

13. Orientation:

Administration: The examiner gives the following instructions: *“Tell me the date today”*.

If the participant does not give a complete answer, then prompt accordingly by saying: *“Tell me the [year, month, exact date, and day of the week].”* Then say: *“Now, tell me the name of this place, and which city it is in.”*

Scoring: Give one point for each item correctly answered. The participant must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if participant makes an error of one day for the day and date.

TOTAL SCORE: Sum all subscores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal. Scores are entered on the MoCA eCRF.

PRIMARY DIAGNOSIS ASSESSMENT

The Primary Diagnosis form captures, in the Site Investigator’s opinion, a current percentile probability the participant has idiopathic Parkinson disease as well as meets current diagnostic criteria for the study based on available information. Ranges include: 90-100%; 50-89%, 10- 49% and 0-9%. In addition, the Site Investigator selects the most likely primary diagnosis from a listing that includes idiopathic PD, many other neurological disorders, and the option of no neurological disorder nor other neurological disorder, or other neurological disorder.

BECK DEPRESSION INVENTORY

The BDI-II (BDI-II) is a 21-item self-report instrument for measuring the severity of depression in adults and adolescents ages 13 and older. **To be eligible for Cohort 1, the person must score greater than 17 out of the possible 63 points at SC1.**

The BDI-II typically takes 5 to 10 minutes to complete. The following instructions should be read to the respondent: *"This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the one statement in each group that best describes the way you have been feeling during the past two weeks, including today. Blacken the circle beside the statement you have picked. If several statements in the group seem to apply equally well, blacken the highest number. Be sure that you do not choose more than one statement for any group, including Item 16 (Changes in Sleeping Pattern) and Item 18 (Changes in Appetite)."*

It is permissible for the coordinator (not family) to read these items to the subject if the subject is unable to self-administer (e.g., forgot glasses). Please note that all options must be read even if the subject agrees to one of the first options read.

If a subject circles more than one statement, the highest rating should be scored (e.g., if a response of "2" and "3" is indicated, a score of "3" should be recorded for that item). After obtaining the score for each response, record the TOTAL score on the BDI Score Sheet CRF.

PARKINSON'S DISEASE SLEEP SCALE (PDSS)

Self-administered questionnaire rating sleep experience during the past week.

EUROPEAN QUALITY OF LIFE SCALE (EQ-5D)

The EuroQOL Group's EQ-5D is a brief, self-administered questionnaire consisting of 5 questions related to mobility, self care, activities, pain/discomfort and anxiety/depression. Participants should be instructed to complete the scale independently following the directions on the form. The directions state: "Choose one statement in each group below, please indicate which statement best describes your own health state today."

One additional question rates overall health using a thermometer like scale with ratings 0 to 100. The directions on this form state: "To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0. We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health is today."

BLINDEDNESS QUESTIONNAIRE

The Blindedness Questionnaire is completed by both the study participant and the Investigator. This questionnaire assesses the Investigator and study participant's belief as to whether the study participant was taking active drug or placebo.

COLUMBIA SUICIDE RATING SCALE

The Columbia Suicide Severity Rating Scale (C-SSRS) is a systematic administration of a tool designed to track suicidal events across a treatment trial. This assessment brings clarity among trained clinicians in both behavior and intent of suicidality. It is a *prospective version* of the system Dr. Kelly Posner developed for the FDA and it is designed to collect better safety monitoring data and avoid inconclusive results.

The Investigator or Coordinator may complete the C-SSRS. Certified training is required for all assessors and can be obtained at http://www.cssrs.columbia.edu/training_cssrs.html.

Requirements for NILO-PD

- This assessment will be administered per the schedule of activities and in the setting of suicidal ideations (if possible) to ensure that the reporting of suicidality is consistent across study centers. Decisions about continued study participation of participants found to be suicidal will be made collaboratively by the site Investigator, Principal Investigator, and CTCC Clinical Monitor. The site Investigator will make a referral to psychiatrist or other Mental Health Care professional as appropriate.
 - This examination will be administered by a trained Investigator or Coordinator.
 - The same individual will perform the C-SSRS evaluation on the same participant throughout the study.
 - There are two separate C-SSRS assessments; 1) Baseline and 2) Since Last Visit.
 - The C-SSRS 'Baseline' version of the scale is preformed at the screening visit 1 (SC1).
 - The C-SSRS 'Since the Last Visit' version is performed at all other visits indicated on the schedule of activities
 - The C-SSRS (Since Last Visit) will be administered as clinically indicated at Unscheduled visits and in the setting of any suicide attempt.

“Baseline” assessment consists of 4 categories:

- 1) Suicide Ideation
Response expected: Yes or No
- 2) Intensity of Ideation
Response expected: 1-5 (severity scale)
- 3) Suicidal Behavior
Response expected: Yes or No (with total number of attempts)
- 4) Answer for Actual Attempts Only
Response expected: Attempt Date for: Most Recent, Most Lethal or Initial/First then code from 0-5.

“Since Last Visit” assessment consists of 4 categories:

- 1) Suicide Ideation
Response expected: Yes or No
- 2) Intensity of Ideation
Response expected: 1-5 (severity scale)
- 3) Suicidal Behavior
Response expected: Yes or No (with total number of attempts)
- 4) Answer for Actual Attempts Only
Response expected: Attempt Date for: Most Lethal and code from 0-5.

MATTIS DEMENTIA RATING SCALE (DRS-2)

The Mattis Dementia Rating Scale (DRS-2) is an assessment designed to measure and track mental status in adults with cognitive impairment. The DRS-2 usually takes 15 – 30 minutes to administer.

The DRS-2 assesses cognitive functioning on five subscales: Attention (ATT, 8 items); Initiation-Perseveration (I-P, 11 items); Construction (CONST, 6 items); Conceptualization (CONCEPT, 6 items); and Memory (MEM, 5 items).

The DRS-2 Score books are considered source and should remain with the subject's source files.

Please refer to the DRS-2 Professional Manual Section 2 (pages 3 – 12) for more detailed instructions on administering the tasks.

General Considerations

- Examiners should conduct several practice administrations before administering the assessment to a subject.
- Administration should take place in a quiet room with adequate lighting.
- In addition to the DRS-2 materials, the examiner will need a pen or pencil for the participant to use and one for the examiner to use for recording the subject's responses.
- A clipboard to hold the scoring booklet is also helpful to shield the scoring booklet from the subject's view.
- The DRS-2 tasks are presented in a fixed order. Note that not all Attention tasks are presented in sequence because some Attention Tasks also serve as time-filling distracters between presentations of Memory Tasks.
- Within each subscale the most difficult tasks are presented first. Generally if the first one or two tasks in a subscale are performed well, subsequent tasks in the subscale are credited with a correct performance, and the examiner proceeds to the next subscale. This procedure has the advantage of significantly shortening the total testing time for individuals who are relatively intact. This scoring procedure is outlined in detail in the DRS-2 Professional manual section 2 Administration and scoring
- With the exception of the Attention Tasks, all instructions to the participant can be repeated.

It is critical to the reliability and validity of the testing that the instructions be repeated or even amended and elaborated so that the examiner is assured that the participant understands the nature of the task and the intended response.

CLINICAL GLOBAL IMPRESSION SCALE

The CGI is a 3-item observer-rated scale that measures illness severity (CGIS), global improvement or change (CGIC), and therapeutic response. Each component of the CGI is rated separately; the instrument does not yield a global score. The CGIS is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients). CGIC scores range from 1 (very much improved) through to 7 (very much worse). Treatment response ratings should take account of both therapeutic efficacy and treatment-related AEs and range from 0 (marked improvement and no side-effects), and 4 (unchanged or worse and side-effects outweigh the therapeutic effects).

PD STUDY TREATMENT EXPECTANCY QUESTIONNAIRE

Self-administered assessment assessing participant expectations of study drug effect prior to and at the end of treatment. This assessment will be completed at several time points throughout the study, see schedule of activities.

Section 7 – Lab Specimen Management

Please insert ACM Global Laboratories and MJFF Biorepository Manuals

Section 8 – Source Documentation

MAINTAINING ADEQUATE SOURCE DOCUMENTS

Sites are required to maintain appropriate source documentation for clinical trials, in compliance with ICH E6 Section 4.9 their regulatory and institutional requirements for the protection of confidentiality of subjects. Per ICH, Source Documents are the original documents and records including (i.e. hospital records, clinical/office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as negatives, microfilm or magnetic data, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial). (*ICH E6 (R2) 1.52*). Examples of source documents or certified copies in NILO-PD are: electronic health records, laboratory reports and EKG readings produced from the device.

Source Data are defined as all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies) (ICH E6 (R2) 1.51). A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. (ICH E6 (R2) 1.63).

Source Document Worksheets (SDW) will be used as a supplemental aide in the NILO-PD study. CTCC has developed a corresponding SDW for each eCRF. These are found in the “Source Document Worksheets” folder on the eClinical portal. The Site Investigator or Coordinator may write directly on SDWs along with providing supplemental information on the source note templates when applicable. Any written or dictated note must, at minimum, contain information specified on the SDW. As a reminder, Source Documents are used to verify the existence of the subjects (informed consent process) and validate the integrity of trial data. **Each page of each assessment and corresponding source document(s) must be signed and dated by the individual who originated the data.** Monitors will confirm that all assessments are attributable to the originator by checking signatures/initials and dates.

The informed consent process should be carefully recorded by delegated site staff (e.g., participant provided an opportunity to ask questions, provided fully executed signed/dated copy of ICF). Ensure that this activity is clearly in the patient’s file. A template for this process is provided in the ePortal “Source Document Worksheets” folder.

Keep SDWs and all source documents either with your clinical record or in a participant folder. The progress notes/source documentation/medical records should contain information about whatever has happened to the subject during the course of the study, especially if it is not captured on the CRF worksheet or visit notes. Please keep your source documents either with your CRF worksheets or in a subject study folder, available at the time of the site-monitoring visit.

RECORDING OBSERVATIONS

In compliance with ICH E6 (R2) Section 4.9, the site should maintain adequate and accurate source documents that include all pertinent observations on each participant. Source data should be attributable, legible, contemporaneous, original and accurate (ALCOA):

- **Attributable:** (*ICH E6 (R2) 4.9.3*) Any change or correction should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4(n)).
- **Legible:** (*ICH E6 (R2) 4.9.1*) The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data must be permanent, readable and understandable by anyone who is reviewing it.
- **Contemporaneous:** Data should be recorded at the same time they were produced
- **Original:** the first place the data were first recorded – “source data”. Data does not need to be transcribed onto a source worksheet if it was originally recorded elsewhere.
- **Accurate:** (*ICH E6 (R2) 4.9.2*) Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. Data are correct, truthful, complete, valid and reliable.

The NILO-PD study will be monitored by remote centralized monitoring (RCM). Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the site must make available for direct access all requested trial-related records (*ICH E6 (R2) 4.9.7*).

Participant study charts must be made available to the monitor for review, in person or remotely.

The NILO-PD study will use electronic data capture (EDC). Each of the eCRFs used has a corresponding Source Document Worksheets (SDW) for all of the eCRFs that will be used in this study are located in the ePortal “Source Document Worksheets” folder. Photocopy or print extra worksheets as your needs require.

The Investigator or Coordinator should write directly on the SDWs and supplement with additional information on intake or clinic notes as needed.

Please keep your SDWs and source notes either with your clinical record or in a subject folder.

Sites with Electronic Medical Records (EMR) are required to have hard (printed) certified copies for source verification by the monitor, unless your Institution grants access for monitor review of subject's electronic records.

The following SDWs will be considered source for data entered into EDC:

- Subject Identification Code Lis
- CTCC Unique ID
- Screening/Demographics
- Inclusion/Exclusion
- Medical History (General), if not documented elsewhere
- General Physical Exam
- General Neurological Exam
- PD Features
- Fundoscopy Exam
- Vital Signs
- Electrocardiogram SC1
- Electrocardiogram
- Primary Diagnosis
- Use of PD Medication
- Lumbar Puncture
- Assessments
 - BDI I (Beck Depression Inventory Summary)
 - MOCA (Version 7.3)
 - MDS-UPDRS Part I-IV (Including Hoehn and Yarh) On
 - MDS-UPDRS III Off
 - Modified Schwab & England Activities of Daily Living
 - Clinical Global Impression Scale (Participant)
 - Clinical Global Impression Scale (Investigator)
 - Diagnostic Features (PD)
 - CSSRS – Baseline
 - CSSRS – Since Last Visit
 - Quality of Life Scale (PDQ39)
 - EQ-5D Instrument
 - Mattis Dementia Rating Scale (DRS-2)
 - PDSS
 - PD Treatment Expectancy Questionnaire (SC1/BL)
 - PD Treatment Expectancy Questionnaire (EOS)
 - Blindedness Questionnaire
 - PD RFQ-U Caffeine Questionnaire
 - PD RFQ-U Smoking and Tobacco Questionnaire
- Labs

- Safety Labs
- Safety Labs – Coagulation
- Safety Labs – Lipids
- Pregnancy Form
- Biomarkers Laboratory Procedures
- PK Post-Dose Random
- PK Pre-Dose Trough
- PK Pre-Dose Trough/Post-Dose
- PK Post-Dose
- Dispense Study Drug
- Drug compliance
- Dose Titration
 - Adverse Event Log
 - Concomitant Medical Log
 - Dose Management Log
 - Study Drug Dispensing Log
 - Study Drug Accountability Log
 - Adverse Event Follow- Up Log
 - Confidential Log
 - Confidential Subject Identification Code List
- Visit Status Form
- Investigator Signature Form
- IMM Assessment of Seriousness, Causality and Expectedness

The progress notes/source documentation/medical records should contain information about whatever has happened to the subject during the course of the study, especially if it is not captured on the CRF worksheet or visit notes. Please keep your source documents either with your CRF worksheets or in a subject study folder, available at the time of the site-monitoring visit.

NOTE: All assessments and procedures must be signed and dated on the source/CRF and Clinic notes by the individual performing the documentation and/or assessments required at each event. A sheet for all assessments required at each event is provided for your use as a tool. Visit assessment lists may be obtained from the ePortal “Source Document Worksheets” folder.

Section 9 – Monitoring Plan

SITE VISITS

As per federal guidelines, Remote Centralized Monitoring (RCM) or on-site Monitoring visits will be conducted at NILO-PD study sites.

All key study staff involved in the conduct of this study must sign the Delegation Log. It must be updated whenever new staff is added to or removed from the team. A copy of this log will be submitted to the CTCC prior to study start up, at study completion and when the log has been updated for addition or removal of a study team member. The original delegation log will be provided to the CTCC at study closeout.

Sites will be monitored through a remote centralized monitoring process with focused and targeted on-site monitoring visits. RCM is an ongoing, routine assessment of data which includes review for completeness, accuracy and data entry timeliness. On-site monitoring may occur on an annual basis, however, the timing and frequency may vary from site to site based on data trends and outliers found through RCM.

Documents required for RCM will be provided by the site and uploaded to the NILO BOX.COM account. Please refer to BOX account instructions posted on the eClinical Portal in the “Operations Manual” folder.

In addition to remote monitoring of subject visits, Study Monitors will conduct RCM Quarterly Teleconferences with each site (specific information in section below).

STUDY INITIATION

Sites will be activated when all training, regulatory, and contractual obligations are met. Site staff must be appropriately trained on the NILO-PD protocol, operations, and regulatory requirements. Training will occur in one of the following manners:

1. Remote Investigator Meeting – providing protocol training and review of safety lab, biologics and EKG procedures. If the Site Investigator and/or primary Site Coordinator were trained during this session, a start up phone call will also be required. The purpose of this call is to review the important elements of the protocol and operations and confirm the site has a clear understanding of the protocol, operations and responsibilities. A site trained at the remote

Investigator Meeting will be activated only after the start up call is complete and the Project Manager and/or Study Monitor.

2. In-person Investigator Meeting– training requirements for site activation were presented and reviewed during the in-person meeting. Site staff attending this meeting do not require additional training prior to activation.
3. Staff unable to attend either of the Investigator meetings will be required to view recordings of the Remote Investigator meeting. After viewing the videos, a post-review assessment will be required to confirm comprehension of the protocol and operations. If a Site Investigator or primary Site Coordinator are trained in this fashion, a start up call with a NILO-PD Project Manager or Study Monitor will be required.

REMOTE CENTRALIZED MONITORING

The purpose of centralized monitoring is to remotely review the following site data:

- Timely data entry and query responses;
- Accurate and timely completion of regulatory documents
- Check that data is consistent and complete;
- Detect unusual data distribution;
- Identify the higher risk sites to target additional on-site monitoring;
- Discover trends across sites, such as protocol deviations and adverse events.

Selected, critical data that will be reviewed remotely includes but is not limited to:

- Complete signed/dated informed consent and process;
- Protocol eligibility criteria;
- Assessments related to study endpoints (e.g., Dose management, Concomitant Medications (ConMeds), UPDRS part III);
- Patient safety measures (e.g., ECG; labs; AEs, ConMeds; key questionnaires);
- Key protocol deviations;
- Adverse events/Serious adverse event reporting;
- Investigational Product accountability;
- Study conduct and procedures essential to trial integrity (e.g., MDS UPDRS assessor).

Refer to “Chart for Remote Centralized Monitoring Documents” on the eClinical portal for a list of required documents and documents that maybe requested on demand or during the subjects participation. RCM list of assessments/pages required at each event, highlighting the required scanned documents, is provided for your use as a tool. Refer to the ePortal “Source Document Worksheet” folder “RCM list of pages per visit” document.

RCM QUARTERLY TELECONFERENCE

In addition to remote monitoring of subject visits, Study Monitors will conduct a teleconference with each site approximately on a quarterly basis to review and discuss the following: Subject enrollment status, study staff and facilities, regulatory documents, IRB issues, recruitment/retention of subjects, clinical safety (AEs/SAEs/ConMeds), study drug and use, sample storage, Labs/ECGs and action items.

Study Monitors will complete a Monitoring Report and follow up letter to disseminate findings to the PM and site that includes information from the teleconference and the subject data monitored during the quarter.

ON-SITE MONITORING

On-site monitoring may occur at each site once or twice per year, however, the timing and frequency may vary from site to site based on data trends identified and outliers found through RCM. As previously discussed, these visits may be triggered due to findings during RCM or if specific indicators of risk are met (based on the NILO-PD Quality Risk Management Plan).

The Study Monitor is responsible for resolving data queries identified while monitoring, either during remote review or while on-site. If there are any unresolved issues at the conclusion of a visit, the study monitor will apply manual queries, as necessary. Any issues that are not related to the database will be recorded in the Action Items Log, sent to the site and filed as part of the site MVR.

At these visits, the investigator, coordinator, and any other staff members involved in the study should be available (or easily reachable). During this visit, the following will be reviewed:

- Adequacy of study facilities
- Source documentation verification per the “Chart for Remote Centralized Monitoring Documents” which can be found in the “Source Document Worksheet” folder on the ePortal.
- IP dispensing, accountability and storage
- Daily log of minimum/maximum temperatures reached for freezers and refrigerators
- Ensuring that the study staff has a good understanding of the protocol and proper procedures for CRF completion
- Regulatory binder, protocol, case report form worksheets, adverse event reporting, medical record (source) documentation, and informed consents (to assure that the inclusion/exclusion criteria have been properly met, that data forms are completed correctly, and the documentation adheres to the Good Clinical Practice (GCP) requirements)
- Random eCRFs and all logs of currently enrolled subjects will be reviewed for completeness and accuracy and compared to the source documentation
- Study correspondence, including correspondence between the investigator and site IRB, and between the site staff and the CTCC.

CONTENTS OF THE REGULATORY BINDER

The site must maintain a Regulatory Binder (also referred to as an Investigator’s site file - ISF). This content of the ISF will be reviewed at least quarterly (via remote quarterly teleconference) and at close out.

The ISF should contain the following:

CONTRACTUAL DOCUMENTS

- ☐ Confidentiality Statements (if established prior to site contract sign off)

- ☐ Contracts/Agreements (insert NTF if kept outside of ISF)

KEY SITE DOCUMENTS

- ☐ Form FDA 1572 (to reconcile with CVs, licenses, FDFs and DOA logs)
- ☐ CVs: signed and dated CVs for each person listed on the 1572 – current at study start; update every two years
- ☐ Financial Disclosure Forms/Conflict-of-Interest Statement
- ☐ Investigator's and Sub-Investigator's Medical licenses (as applicable) – current
- ☐ Delegation of Authority (Duties) log – current

TRAINING

- ☐ Certification of human subjects protection (HSPP) – current
- ☐ GCP training certificates – current
- ☐ Protocol specific training, including Investigator Meeting/SIV
- ☐ IATA training
- ☐ eClinical Training Documentation – any person with access to database
- ☐ Targeted re-training (if applicable)

IRB

- ☐ IRB Approval letter(s) for protocol, consent form, assent form, subject materials, amendments
- ☐ IRB Communication
- ☐ Annual (or as deemed by the IRB) renewal letter
- ☐ IRB Approved consent/assent form
- ☐ IRB Membership Inquiry Form
- ☐ IRB Federalwide Assurance (FWA)
- ☐ IRB approval of any approved advertisement or recruitment materials
- ☐ Study closeout letter to IRB
- ☐ Protocol Deviations – potentially important/major need to be reported per as required

AEs/SAEs

- ☐ SAE (Safety) Reports
- ☐ Correspondence regarding SAE and/or MedWatch forms

PROTOCOL, ICF(s) & Investigator's Brochure (IB)

- ☐ Protocol – original
- ☐ Protocol signature form
- ☐ Protocol – amendments (when applicable)
- ☐ Protocol amendment signature form(s)

- ☐ Sample eCRFs (a blank set of every case report form used in the study as PDF files)
– file in operations manual Investigator Brochure(s)
- ☐ Investigator Brochure signature form(s)
- ☐ Package Insert

INVESTIGATIONAL PRODUCT/STUDY DRUG

- ☐ Confidential Subject Identification Code List
- ☐ Study Drug Shipment Logs
- ☐ Study Drug Accountability Logs
- ☐ Blinded randomization letter(s) (if applicable)
- ☐ Investigational Product Site Manual (as PDF file on eClinical Portal)
- ☐ Destruction Policy and/or Certificate of (Drug) Destruction

COMMUNICATIONS

- ☐ Letters, faxes, telephone contacts to CTCC, sponsor and monitors
- ☐ Letters, faxes, telephone contacts from CTCC, sponsor and monitors
- ☐ Monitoring Confirmation and Follow-Up Letters
- ☐ General Correspondence
- ☐ Notifications & Incidents (if applicable for site). Subject-specific incidents and notifications may be kept with the subject's source documents.

SAFETY LABS; BIOMARKER LAB; ECG VENDOR (OTHERS)

- ☐ Safety Lab: Investigator's Lab Manual (as PDF file on eClinical Portal, in addition to being provided by central lab)
- ☐ Safety Lab: Laboratory documentation, laboratory reference ranges, laboratory certification/ accreditation
- ☐ Lab Director CV
- ☐ Lab Director License
- ☐ Biomarker Lab: Investigator's Lab Manual (as PDF file on eClinical Portal, in addition to being provided by central lab)
- ☐ Biomarker Lab: Laboratory documentation, laboratory reference ranges, laboratory certification/ accreditation
- ☐ ECG Portal review rules

MISCELLANEOUS

- ☐ Notes to File
- ☐ Monitoring Visit Log
- ☐ Study Operations Manual (as PDF file) – non essential
- ☐ eClinical User Guide (as PDF file)-non essential
- ☐ Confidential caregivers log (if applicable; non-essential)

- Confidential Legally Authorized Representative Log (if applicable; non-essential)

MONITOR ASSIGNMENTS

A Monitoring Visit Log for both RCM and On-Site will be distributed to each site for the ISF and the study monitor will maintain the log(s). The Monitor Visit Log documents the dates and purpose of the visit(s), names(s) of monitor(s), and signatures(s) of study site personnel. Once the site close out monitoring visit has occurred, the **original on-site Monitoring Visit** Log should be forwarded to the CTCC and the site should retain a copy in their regulatory binder. The monitor will provide a final RCM monitor log for the sites ISF.

Monitor Contact Information (refer to NILO-PD Contact List)

CO-MONITOR VISITS

Depending on anticipated workload at the monitoring visit and at the discretion of the sponsor, representatives of the CTCC and/or the sponsor may accompany the study monitor on site visits. Sites will be notified in advance of the additional visitor(s) to ensure adequate space is available.

CLINICAL SITE CLOSE OUT VISIT

The monitor is responsible for a clinical site close out visit when all subjects have completed the study at that site. At the close out visit, final accountability for all investigational products will be conducted. Monitors will also conduct a review of eCRFs and logs for those subjects not previously monitored. The site's regulatory binder will be reviewed for all regulatory documents and correspondence pertaining to the study. In addition, the following will be discussed with the investigator:

- Investigator's role in closing the study (completion of final study report and notification to IRB/IEC of study completion)
- Follow-up and reporting requirements of new and ongoing adverse events
- Contact information for study or payment inquiries following study closeout
- Plans for receipt of PDF file formatted eCRFs for each subject
- Conflict of Interest/Financial disclosure reporting requirements for any changes occurring within 1 year following completion of the study
- Applicable study publications policy
- Study document record retention and archiving regulatory requirements
- Possibility of/procedure for audits/inspections

ARCHIVING

All essential documents and electronic storage media will be archived appropriately, securely, and will be readily retrievable in accordance with GCP and written protocol procedures for subject confidentiality. The Clinical Site Monitor(s) will review archiving arrangements, confirm adequacy of facilities, ensure all documentation and materials to be archived are complete, and provide clear guidance on timeframe to maintain archived documentation.

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least two years after the last marketing application approval or two years after formal discontinuation of the clinical development of the investigational

product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. Northwestern University must be notified in writing (via communication to the CTCC) if a custodial change occurs.

Section 10- Reports

NILO-PD STUDY REPORTING

Described below are some of the reports generated for the NILO-PD study to help the Steering Committee and study team manage the project and ensure sites are meeting expectations and goals of the study. In addition, some reports are generated to assist sites in keeping track of what may be missing as a result of all the data that needs to be entered.

ENROLLMENT PROJECTIONS REPORT

- Generated from information entered on Question 5 of the Screening/Demographics page, “Projected Enrollment Date”.
- Tracks projected baseline visits at each site that are scheduled within the next 30 days, over 30 days, and indicates if a visit is beyond the projected date indicated in EDC.
 - If projected enrollment dates are confirmed or changed during the screening period, make sure to update that field in EDC.
- Distributed on a bi-weekly basis to site Investigator and Coordinator so that sites are able to see where they rank in enrollment status relative to all other sites.
- Steering Committee, sponsor and monitors also receive this report in order to monitor study progress as well as site recruitment and enrollment performance.

INCIDENT REPORT

- May be generated when a site notifies CTCC of any protocol specified reportable event as outlined in Section 14 of the protocol.
- This report is a summary of the event that occurred and is distributed to the site Investigator and Coordinator.
- Review the report to ensure accuracy and file a copy in the study binder.

NOTIFICATION REPORT

- Generated when a site informs the CTCC of any relevant clinical or data management issues that should be noted.
- A summary of the event that occurred is distributed to the site Investigator and Coordinator.
- Review the information to ensure accuracy and file a copy in the study binder.

PENDING QUERIES REPORT

- Generated when a query is left unresolved 5 days beyond the creation date.
- Distributed to site Coordinator on a weekly basis or more frequently during close out.

MISSING PAGES REPORT

- Generated when an expected page is not entered within 5 days of the Target Visit Date for an individual subject.
- Missing pages start to be reported once a subject is enrolled (RANDOM page is completed and the Visit Window Schedule is generated).

MISSING INVESTIGATOR eSIGNATURES

- For any completed visit that does not have the electronic signature of the Investigator applied to the Signature Form.
- The primary Investigator or designated Sub-investigator who conducted the visit should sign off on the visit.
- In addition the following pages will require electronic Investigator signatures:
 - Inclusion/Exclusion
 - Adverse Event Log (required when subject has completed the study or withdrawn prematurely)
 - Follow Up Adverse Event Log (if applicable- at the end of the study)
- Report is sent only to the primary designated Investigator at each site.

MISSING COORDINATOR eSIGNATURES

- At screening visit 1 only, on the concomitant medication log, a Coordinator esignature will be applied to indicate that all concomitant medications have been entered and are complete.

SITE PERFORMANCE REPORT

- Tracks expected forms received (data entered) and the timeliness of data entry (i.e., within 2 days of the visit).
- Tracks how many queries are generated at each site and how timely the site addresses queries (i.e., timely is a comparison of origination date to the resolution date)
- This report will be used by the study team to ensure timely entry of data, as well as accurate and clean data. Any significant issues will be addressed directly with a site.

Section 11- Newsletters

Insert NILO-PD newsletters

Appendix 1- Section 4: Study Drug Handling Instruction Sheet



NILO-PD Study Drug

Attention: Site Personnel

Please complete the following tasks pertaining to your receipt and handling of study drug for the NILO-PD study.

- ☐ Remember to check the shipping contents, verify against the Packing List/Acknowledgement of Receipt, then sign, date and upload to the “AOR” subfolder in NILO-PD Box.com™ for your site.
- ☐ Notify CMSU immediately of any discrepancies.
- ☐ File the Packing List/Acknowledgement of Receipt in your regulatory binder under, “Study Drug Related”.
- ☐ Ensure drug is properly secured (locked area) and stored at room temperature 25° C (77° F). Excursions permitted between 15 ° to 30 °C (59 ° to 86 °F). Complete Study Drug Dispensing/Return forms when a subject is randomized and any time drug is dispensed or returned.

- ☐ Remember to review your IRB approved NILO-PD participant *Directions for Taking Study Medication* form with subject.
- ☐ Contact CMSU with any questions (585) 350-3838 regarding your study drug shipment.

Appendix 2 – Section 4: Packing List/Acknowledgement of Receipt

CLINICAL MATERIALS SERVICES UNIT

UNIVERSITY OF ROCHESTER MEDICAL CENTER

NILO-PD Study Drug Shipment Packing List/Acknowledgement of Receipt

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase IIa, Parallel Group, Two-Cohort Study to Define the Safety, Tolerability, Clinical and Exploratory Biological Activity of the Chronic Administration of Nilotinib in Participants with Parkinson's Disease (PD)

Storage: Store at room temperature 25° C (77° F). Excursions permitted between 15 ° to 30 °C (59 ° to 86 °F)

To:

Contents:

Cohort 1: Four (4) 120-count bottles numbered A1, A2, B1 and B2 each containing 150mg nilotinib or matching Placebo capsules;

Cohort 2 (300mg option): Four (4) 120-count bottles numbered 01-04 each containing 150mg nilotinib or matching Placebo capsules;

Cohort 2 (150 mg option): Two (2) 120-count bottles numbered 01-02 each containing 150mg nilotinib or matching Placebo capsules.

Blinded Subject-Specific Kits		Additional Enclosures (if applicable)	Quantity
Enrollment ID #	Kit Type	Study Drug Handling Sheet	1
		Expiry Date:	
		PO Number:	

CMSU Ship Date:

Entered By:

ACKNOWLEDGEMENT OF RECEIPT:

Inspect and verify the contents of shipment upon receipt. Complete the sections below and **upload to "AOR" subfolder in the NILO-PD Box.com** for your site **within 48 hours**. Retain this form for your records and place in the study files.

Received By:

Date:

☐ Check if received in good condition. Comment if damaged, incorrect or missing contents.

77 Ridgeland Road | Rochester, New York 14623 | Phone: 585-350-3838 |

www.clinicalmaterial.com

Email: CMSU-Resupply@cmsu.rochester.edu |

Appendix 3 – Section 4: Emergency Unblinding Instruction Sheet

EMERGENCY TREATMENT DISCLOSURES Instructions for Use

(NILO-PD)

This envelope contains emergency treatment disclosures that should only be used per the instructions in the study protocol and/or operations manual.

An individual participant's envelope or label should be opened only in the case of a medical emergency. If such action is required, the Clinical Monitor must be notified first, if circumstances permit, rather than disclosing the randomization.

	Clinical Monitor
Name:	Jamie Adams, MD
E-mail:	jamie.adams@chet.rochester.edu
Cell Phone:	585-330-3257

General Procedure:

1. **To disclose:** Locate the correct envelope that contains the participant ID number for the participant whose treatment must be disclosed. Take a coin and use it to scratch off the dark ink as instructed on the label.
2. **Prior to disclosure:** The Site Investigator should make every attempt to notify ***the NILO-PD Medical Safety Monitor or Project Manager at the University of Rochester's Clinical Trials Coordinating Center*** that the investigational medication assignment requires disclosure. DO NOT disclose the treatment assignment to the person taking the call. Every effort should be made to minimize the number of people that are made aware of the actual treatment assignment. If treatment disclosure does occur, the Project Manager must be informed, ***without revealing the actual treatment assignment***, that the treatment assignment has been disclosed, reason for disclosure, date and personnel involved.
 - a. Complete the enclosed Treatment Disclosure Report form with all requested information. A copy of this form should be placed in a sealed envelope with "Unblinded Treatment Assignment for NILO-PD Subject" written on the outside of the envelope and sent to:

Patrick Bolger, R.Ph., MBA
University of Rochester
Clinical Materials Service Unit (CMSU)
77 Ridgeland Road
Rochester, NY 14623
 - b. A copy should be kept at the site and placed in one of the pre-addressed enclosed envelopes, along with the actual emergency scratch-off label that has been used. Label the outside of the sealed envelope with the **Randomization Number (5-digits)**. Leave the sealed envelope with the unused emergency treatment disclosure envelopes.

3. The treatment disclosure envelopes should be kept intact in a secure and locked location available to the site investigator, coordinator and any other appropriate study staff that may be required to access this information.
4. Clinical Research Associates (CRA), also known as site monitors will routinely request to see these materials to verify their integrity. Monitors should not actually open sealed envelopes as part of their routine monitoring visits, but should confirm that correct procedures have been followed. Monitors should remain blinded to treatment assignment.
5. At the conclusion of the study, please return all unused emergency treatment disclosure envelopes within an individual larger envelope. Address information for returning these materials is:

Patrick Bolger, R.Ph., MBA
University of Rochester
Clinical Materials Service Unit (CMSU)
77 Ridgeland Road
Rochester, NY 14623

Appendix 4 – Section 4: Emergency Disclosure Report Form.

EMERGENCY DISCLOSURE REPORT FORM

(NILO-PD)

The following Participant required emergency treatment disclosure:

4-Digit Subject ID #:	
Site #:	
Site Name:	
Investigator Name:	
Date of Disclosure:	
Reason for Disclosure:	
Person Responsible for the Disclosure:	
List any other site staff that were made aware of the Disclosure:	
Date CTCC was made aware of the Disclosure	

Please return this completed Form to:

Patrick Bolger, R.Ph., MBA
University of Rochester
Clinical Materials Service Unit (CMSU)
77 Ridgeland Road
Rochester, NY 14623

NOTE: Make a copy of the completed form and place the copy within the pre-addressed enclosed envelope with the actual emergency scratch-off label that has been used. Seal the envelope, record the Randomization number (5 digits) on the outside of the envelope, and place it back with the unused emergency treatment disclosure envelopes. Retain the original form with the site study records.

Appendix 5 – Section 6: Administration of Study Assessment Chart

Administration of Study Assessments	
Assessment	Assessor
CTCC Unique ID	I/C
INCLUSION / EXCLUSION	I
SCREENING / DEMOGRAPHICS	I/C
SOCIO-ECONOMICS	I/C
VITAL SIGNS – SC/V03, V04, V05, PW	I/C/O
VITAL SIGNS	I/C/O
MEDICAL HISTORY GENERAL	I/C
GENERAL PHYSICAL EXAM	I
GENERAL NEUROLOGICAL EXAM	I
PD FEATURES	I
FUNDOSCOPY EXAM	I
MDS-UPDRS HOEHN AND YAHR	I
PRIMARY DIAGNOSIS	I
ELECTROCARDIOGRAM – SC1	I/C/O
ELECTROCARDIOGRAM	I/C/O
BDI II (BECK DEPRESSION INVENTORY SUMMARY)	I/C
MOCA	I/C
SAFETY LABS, COAGULATION, LIPIDS, PREGNANCY, PK AND BIOMARKER SAMPLING	I/C/O
USE OF PD MEDICATION	I
LUMBAR PUNCTURE	I
USE OF STUDY DRUG	I/C
USE OF STUDY DRUG (LP)	I/C
MDS-UPDRS PART III (Including Hoehn and Yahr) OFF state	I
**subject/caregiver to complete patient questionnaire section	S
MDS-UPDRS (Including Hoehn and Yahr) ON state	I
MODIFIED SCHWAB & ENGLAND ACTIVITIES OF DAILY LIVING	I
CLINICAL GLOBAL IMPRESSION SCALE (PARTICIPANT)	S
CLINICAL GLOBAL IMPRESSION SCALE (INVESTIGATOR)	I
DIAGNOSTIC FEATURES (PD)	I
MATTIS DEMENTIA RATING SCALE (DRS-20)	I/C
*CSSRS-BASELINE	I/C (with training)
CSSRS-SINCE LAST VISIT	I/C
QUALITY OF LIFE SCALE (PDQ39)	I/C
EQ-5D INSTRUMENT	I/C
INFORMED CONSENT (after BL)	I/C
PDSS	I/C
PD TREATMENT EXPECTANCY QUESTIONNAIRE (SC1/BL)	S
PD TREATMENT EXPECTANCY QUESTIONNAIRE (EOS)	S

BLINDEDNESS QUESTIONNAIRE (PARTICIPANT)	S
BLINDEDNESS QUESTIONNAIRE (INVESTIGATOR/COORDINATOR)	I/C
PD RFQ-U CAFFEINE QUESTIONNAIRE	S
PD RFQ-U SMOKING AND TOBACCO QUESTIONNAIRE	S
INVESTIGATOR SIGNATURE FORM	I
VISIT STATUS	I/C
CONCLUSION OF STUDY PARTICIPATION	I/C
CONCOMITANT MEDICATION LOG	I/C
STUDY DRUG DISPENSING LOG	I/C
DOSE MANAGEMENT LOG	I/C
STUDY DRUG ACCOUNTABILITY LOG	I/C
ADVERSE EVENT LOG	I and C
ADVERSE EVENT FOLLOW UP LOG	I and C
IMM ASSESSMENT	Independent Medical Monitor