The Framingham Heart Study
Neuropsychology Group

Parkinson's Disease Review Diagnostic Manual of Procedures

Version 4/29/2024

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Overview of Parkinson's Disease Review

Parkinson's Disease (PD) review is the process used at FHS to adjudicate diagnoses of Parkinsonism and PD cases. The stages of the process are:

1. Participants for review are identified: A list of participants flagged for possibly having signs of PD or parkinsonism is generated. Flags include participants who meet established flagging criteria on a Neurology examination, including the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the Clinician Judgement of Symptoms (CJS) or by referral from Core staff based on newly reported medications, diagnosis by an outside physician, etc.

2. A Research Assistant writes a summary of what is known about a participant: A PD Review Case Summary (PDRCS) is prepared by a trained research assistant, including relevant medical history, education, and exam results. The summary is compiled using several sources of information, although not every participant has every source available. These sources include the FHS Core exam(s), FHS Neuropsychological testing, FHS Neurology exam(s), FHS brain imaging, external medical records, and an interview with a family member (although the family interview is only done for participants who have donated their brain to the study).

3. A Parkinson's Disease Review meeting is held: The PDRCS is brought to a PD Review meeting, which includes an adjudication panel that must have at least two movement disorder neurologists present as well as a research assistant. The panel evaluates each PDRCS to identify whether there is evidence of PD. If so, the dates for the last normal concerning PD, the year of onset (if known), and the date of diagnosis are recorded. For a case to be adjudicated, the United Kingdom Parkinson's Disease Brain Bank clinical diagnostic criteria or the Boston University Parkinson's Disease Center 1992 criteria must be met. A family history of extrapyramidal disease and relevant medications (e.g., Sinemet, L-dopa, dopamine agonists, etc.) are also recorded if applicable to the case. Also noted at the time of DR are a history of stroke, cognitive impairment, or dementia and reports of brain scans. Cases adjudicated following the addendum in July 2023 include relevant findings from the FHS-BAP Neurology Exam if the participant has undergone neurology testing. If details in the PDRCS are unclear, source information is reviewed. This is recorded on the data collection form if no clear evidence of PD or a different diagnosis is made.

4. Parkinson's Disease Review data is entered into a database: During the PD Review meeting, the PD Review form is keyed directly into a REDCap project. The neurologists in attendance view the data entry to ensure accuracy. The REDCap project also has built-in quality control via branching logic and data quality rules.

Parkinson's Disease Review Form

The Parkinson's Disease Review Form in REDcap serves as the primary data collection tool used during Parkinson's Disease (PD) review meetings. See Appendix A for a copy of the PD form that was in use until 2021 and Appendix B for a copy of the current REDCap form, launched in July 2023, which is electronic. The REDCap project is titled "PD Review v.**2023**". This section outlines the basic principles of completing the PD review with guidelines that each reviewing team should follow by the consensus panel.

- At least two neurologists must be present during the PD Review meeting, or the meeting must be rescheduled. The FHS ID for these individuals is entered into the form.
- Participant ID – in REDCap, the ID is entered with a dash, and all 0 placeholders should be included. For example, For ID 1-2345, the entry in REDCap would be 1-2345.
- Beginning information
    - The ID Type and ID should be entered along with the PD Review Number, which is the number of times the case has been to PD Review (e.g., if the first time at PD review, this should be coded as 1, second time at review should be coded as 2, etc.).
    - The review date and the form version should also be completed.
    - Lastly, the technician ID of the research assistant completing the form should be filled out.

Criteria for Diagnosis

This section is filled out with any symptoms of Parkinsonism/PD, regardless of whether the case is considered a PD case. The information for this section comes from the PDRCS, which includes information from medical records, FHS exam cycle records, and Neurology/Neuropsych testing. These categorical variables are coded as Not Present, Present, Maybe, or Unknown. The numbering of the symptoms is arbitrary and not part of any formal criteria or scoring system.

- **1: Bradykinesia (Describe)**: Defined as slowness of initiation of voluntary movement with a progressive reduction in speed and amplitude of repetitive actions.

  When answering "Present" to bradykinesia, there is a section to describe the symptoms. This can include the symptom's extent, laterality, and severity.

- **2: Rigidity**: Increased resistance to passive movement of a muscle group. Among other types of rigidity, it refers to the presence of cogwheel rigidity, which is a jerky resistance to passive movement.
- **3: Tremor (Describe):** Defined as a neurological symptom that includes involuntary repetitive, rhythmic, regular shaking or oscillation of a body part involving opposing muscles. Measurable in terms of frequency and amplitude. When answering "present" to tremor, a new variable makes itself available to describe the tremor in terms of type (kinetic, postural, rest), constancy, frequency, amplitude, and lateral predominance.

- **4: Postural Instability or Failing (not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction)** Postural Instability defined as the inability to maintain balance in static and dynamic conditions, such as when preparing to move, standing still, or when there are positional perturbations.
- **5: Gait disturbance (shuffling, festinating):** Referring to a disruption in the usual and energetically efficient pattern of walking or movement. Among all of the types of gait disturbances, shuffling gait (dragging feet or without lifting the feet fully from the ground) and festinating gait (rapid, small steps, done in an attempt to keep the center of gravity (COG) in between the feet while the trunk leans forward involuntarily and shift the COG forward) are especially suggestive of parkinsonism.
- **6: Hypomimia (masked facies):** Defined as a limitation of the accurate expression of emotion in the face due to decreased speed and coordination with which the facial musculature is activated. This results in a lack of facial emotional display and the persistence of a neutral position.
- 7= Other (Specify)

  When answered as “present,” an additional variable is opened to describe any associated symptom other than the previously described.

Supportive Prospective Positive Criteria for PD (UK PD BB Criteria)

This section outlines the variables that support the diagnosis of Parkinson's Disease based on the Imperial College (UK) Parkinson Disease Brain Bank Criteria (Hughes et al. JNNP 1992). These categorical variables have four possible outcomes (Not Present / Present / Maybe / Unknown).

- **Unilateral Onset:** The onset of symptoms is asymmetrical, occurring only in one of the body's halves.
- **Rest Tremor Present:** Tremor is present when the person is not doing any volitional movement.
- **Progressive Disorder:** An illness that increases in severity in a determined range of time.
- **Persistent Asymmetry Affecting the Side of Onset Most:** Over time, the disturbance continues to be predominant on the same onset side of the body, even if it becomes bilateral.
- **Excellent Response (70%-100%) to Levodopa:** Refers to a significant improvement in motor symptoms of Parkinson's disease after administration of levodopa medication by at least 70 – 100% and a perceived improvement in quality of life.
- **Excellent Response (70%-100%) to Dopamine Agonist:** Refers to a significant improvement in motor symptoms of Parkinson's disease after administration of levodopa medication by at least 70 – 100% and a perceived improvement in quality of life.
- **Severe Levodopa-Induced Chorea:** Refers to the onset of involuntary, rapid jerky, and irregular movements that are not repetitive or rhythmic as a side effect of the chronic use of levodopa.
- **Levodopa Response for 5 Years or More:** This refers to clinically documented improvement of Parkinson’s disease motor symptoms, by history or by exam, due to pharmacological treatment with Levodopa that lasts for more than five years or more.

- **Clinical Course of 10 Years or More:** Refers to the natural history of the disease from the onset of symptoms to the present or death date of more than ten years.
- **Other:** If present, there is an additional "Specify" variable to describe

Status of Case Review

This section outlines any additional comments/confirmatory data not otherwise coded and the case's status (e.g., reviewed, positive PD).

Last Date Normal with Respect to PD

This section includes the Month, Day, and Year that the participant was last known to be at baseline functioning. If insufficient information supports a normal last date or only the year is known, then the rest of the variables (e.g., month or year) are coded as 99 and 9999, respectively.

Sources supporting last date of documented normal

As part of the data collection form, we include the Last Normal Date (Month, Day, and Year) if available. This section provides the opportunity to list all sources used to determine the participant's last known baseline functioning date.

- **FHS Cycle Exam Records:** this includes the MMSE, CERAD/Stroop, Medical History Updates (MHU), comments by Core study staff, chart summaries, and any other information obtained from the Core study research activities.
- **Neurological examination** refers only to neurology exams done as part of FHS research activities; exams done by outside neurologists go in the Medical Records category.
- **Medical Records:** This includes all records generated from non-FHS-related activities, such as hospital/ED notes, doctor notes, nursing home notes, neuropsych/neurology consults, etc.
- **Other**: This variable is categorical, with three possible outcomes (Yes/No/Unknown), and it allows the description of additional sources of information leading to diagnosis.
- Other (Specify). Open variable to specify the nature of additional information sources.

Subject classified as a PD case (PD review outcome)

This variable informs the review board's decision regarding the diagnosis of PD. It is a categorical variable with three possible outcomes (Yes/No/? PD). This classification is based on the two diagnostic criteria (See following variables).

- Is the subject classified as a PD or? PD case: page 2 is filled out, and page 3 is blank. See Appendix A for the complete form, including page 2. This section includes information such as medications, family history of extrapyramidal disease, diagnosis date [1], etc.
- If the subject is not classified as a PD case, page 2 is skipped, and page 3 is filled out. Page 3 lists a different diagnosis and indicates whether the subject may still be at risk for developing PD.

Criteria for PD confirming diagnosis (Yes/No Determination)

This section summarizes the previous symptomatic recount leading up to a diagnosis. It is based on two diagnostic criteria systems. The first is based on the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria reproduced per 1992 Hughes description.[1] This diagnosis system consists of a three-step process: the first refers to diagnosing Parkinsonian syndrome, Step 2 refers to the exclusion criteria for PD, and Step 3 refers to the prospective supportive criteria for PD. The second one refers to the Boston University Parkinson's Disease Center criteria of 1992.[2] Therefore, these two variables have been included as dichotomous (Yes/No) variables.

- Bradykinesia + 1 Cardinal Symptom (#2-5) (As per UK PD BB Clinical diagnostical criteria, 1992). **Note** The variable name includes a typo because the original diagnostic criteria mention Bradykinesia plus symptoms 2-3-4. However, all reviewed cases have used the correct criteria (2-4). An additional variable was added in the addendum of July 2023 to correct this typo. Due to the longevity of the data, it was decided to keep the original variable and fill out the new one prospectively.
- 1 Cardinal symptom (1-3) + one other Symptom (1-6) (As per BU PD Center 1992 criteria) [2]

Medications

This section codes any medications the subject may be taking that are relevant to PD. These are also categorical variables with four possible outcomes (No / Yes, now / Yes, not now / Unknown). These medications are coded if the subject was prescribed them at any time, not if they are just being used at present.

1 = Carbidopa-Levodopa (Specify)

2 =Dopamine Agonists – Bromocriptine, Pergolide, Pramipexole, Ropinirole, etc.

3 =Amantadine (Symmetrel)

4 =Anticholinergics – Cogentin, Artane, etc.

5 =COMT Inhibitors – Entacapone, Tolcapone, etc.

6 =MAO-B Inhibitors (Specify)

7 =Other PD Meds (Specify

If answering yes to medications Sinemet, L-dopa, and MAO-Inhibitors, there is another variable to include the medication dose. The "Other" variable codes any other medications deemed relevant by the adjudication panel.

Family History of Extrapyramidal Disease

This section includes any known family history of extrapyramidal disease. These are also categorical variables with three possible outcomes (No / Yes / Unknown).

1 =Mother

2 =Father

3 =Siblings

- Number of Siblings with Extrapyramidal Disease

4 =Spouse

5 =Other (Specify)

Year of Onset of PD

This section includes the year of onset of PD, which is determined by the adjudication panel during the review meeting based on available records. If no information is available to determine the year of onset, this variable is coded as unknown.

Date of Diagnosis of PD & Diagnosis Confirmed By

- The first variable is the date of diagnosis of PD and includes Month, Day, and Year if known. If unknown, this variable is coded as 99 for the month or 9999 for the year.
- The second variable codes are by which the PD diagnosis is confirmed. There are four categorical variables for this which include (1 =Neurologist, 2 =Other Physician, 3 =Movement Disorders Specialist, 9 =Unknown)
- Suppose multiple medical records are available for review, and the diagnosis is confirmed by more than one type of physician. In that case, the following priority is listed below for coding purposes:
  - 3 (Movement Disorder Specialist) > 1 (Neurologist) > 2 (Other Physician)

Length of PD at the time of this documentation

This variable is coded as the (Year of Disability Rating – Year of Onset of PD + 1). If either the year of disability rating or the year of onset is missing, then 99 is entered

Disability Rating Scale

This variable is calculated during the adjudication meeting by the panel of neurologists using the most recent motor examination available from either medical records or FHS testing. The disability rating scale used is the modified Hoehn and Yahr and is listed below:[3]

Stage 0.0 = No signs of disease

Stage 1.0 = Unilateral disease

Stage 1.5 =Unilateral plus axial involvement

Stage 2.0 = Bilateral disease, without impairment of balance

Stage 2.5 = Mild bilateral disease, with recovery on pull test

Stage 3.0 = Mild to moderate bilateral disease; some postural instability; physically independent

Stage 4.0 = Severe disability, still able to walk or stand unassisted

Stage 5.0 = Wheelchair bound or bedridden unless aided

Date of Disability Rating

The date of disability rating is coded as the date of the last physical examination available for review (Month, Day, Year). If unknown, 99 or 9999 is entered.

Still at Risk for developing PD

This section is completed for participants with a negative PD diagnosis but who have a disease with similar symptoms. Where possible, use of current consensus diagnostic criteria are used as guidance but are not adhered to strictly for determining whether a disease is present or not. These clinical references are indicated below. For each diagnosis, four categorical options are coded as follows (0=Not Present, 1=Present, 2=Maybe, 9=Unknown).

1= Drug-induced Parkinsonism – Refers to the occurrence of Parkinsonian syndrome likely caused by the use of a therapeutic drug. The following criteria define this clinical syndrome: 1) Presence of parkinsonism, 2) No history of parkinsonism before the use of the offending drug, and 3) Onset of parkinsonism during use of the offending drug. In this section, we also specify the medication and dose duration.[4]

2= Multiple System Atrophy: This refers to the presence of the clinical entity that comprises an adult-onset, progressive neurodegenerative disease characterized by a heterogeneous severity of parkinsonian features, cerebellar ataxia, autonomic failure, urogenital dysfunction, and corticospinal disorders and historically called Shy-Drager syndrome, striatonigral degeneration, or olivopontocerebellar atrophy. The PD review team is guided by the criteria described in the Movement Disorders Society Criteria for the Diagnosis of MSA.[5]

3= Diffuse Lewy body disease: Refers to a clinical syndrome including dementia or cognitive impairment with the presence of other core symptoms such as fluctuating cognition with pronounced variations in attention and alertness, recurrent visual hallucinations, REM sleep behavior disorder, and one or more spontaneous cardinal features of parkinsonism. For this diagnosis to be present, it is important that cognitive symptoms onset should be at the same, or soon after motor symptom onset, commonly in a one-year period (see also Appendix L). [6,7]

4= Normal Pressure Hydrocephalus: Refers to the clinical syndrome comprising symptoms of increased intracranial pressure such as cognitive impairment, motor gait disturbances, and urinary function dysfunction in the presence of cerebrospinal fluid (CSF) opening pressure measured by lumbar puncture in the range of 60-240 mmH2O. Ventricular enlargement is not entirely attributable to cerebral atrophy or congenital enlargement (Evan's Index > 0.3 or callosal angle of 40 degrees or more).[8]

5= Essential / Familial Tremor: It refers to the clinical syndrome of bilateral, postural /action tremor. Involving the forearms and hand, being persistent and visible, and possibly associated with isolated head tremors of at least three years. It cannot be explained by other parkinsonism types or structurally congruent anatomic disturbance and is perhaps related to a familiar genetic tendency. Diagnosis could be supported by the Diagnostic Criteria by the Tremor Taskforce of the International Parkinson's Disease and Movement Disorders Society (IPMDS) or similar criteria.[9]

6= **Primary dystonia disorder:** A movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. They are usually initiated or worsened by voluntary action and associated with overflow muscle activation.[10]

7= Other (describe)

No Longer at Risk for Developing PD

This section is also completed for participants with a negative PD diagnosis but who have a disease with similar symptoms. Four categorical options are coded as (0=Not Present, 1=Present, 2=Maybe, 9=Unknown).

8= Vascular Parkinsonism: Defined as a condition that presents with the clinical features of parkinsonism that are presumably caused by cerebrovascular disease and classically described as symmetrical, lower-body parkinsonism with gait instability and absence of tremors and usually associated with pyramidal signs.[11]

9= Alzheimer's disease with Parkinsonism: Referring to the presence of clinical signs, symptoms, and criteria for Alzheimer's disease and the presence of Parkinsonian symptoms. The cognitive impairment not being explained by dementia due to Parkinson's disease.

10= Progressive supranuclear palsy: Refers to a clinical entity defined by a core of clinical manifestations such as ocular motor dysfunction, postural instability, akinesia, and cognitive dysfunction, In the presence or not of supportive features such as levodopa-resistance, hypokinetic, spastic dysarthria. Dysphagia, and photophobia. Imaging findings include predominant midbrain atrophy, hypometabolism, and postsynaptic striatal dopaminergic degeneration.[12]

11= Corticobasal degeneration: Refers to the clinical syndrome with clinical features of motor and cognitive symptoms. Asymmetrical, levodopa-resistant in long-term treatments that can overlap with Parkinson's, Progressive supranuclear palsy, and Alzheimer's disease. Probable corticobasal syndrome can be defined clinically as the asymmetric presentation of two of the following: limb rigidity or akinesia, limb dystonia, and limb myoclonus in addition to 2 of the following: orobuccal or limb apraxia, cortical sensory deficit, and alien limb phenomena.[13]

12= Wilson's disease: Presence of hepatic manifestations, neuropsychiatric disorders, ophthalmic signs, and episodes of hemolysis coexisting with acute liver failure because of an abnormal deposition of hepatocellular copper.

13= Huntington's disease: Formally defined as a person who carries a known CAG-expanded allele of the Huntington disease gene (HTT) or family history of HD and develops motor symptoms that are as described in the Diagnostic Confidence Level of the Unified Huntington Disease Rating Scale (UHDRS).

14= Other (Describe)

Participant Had Brain Autopsy

If the subject is alive, then this section is left blank. There are four categorial options which include (0=No autopsy, 1=Yes, autopsy-confirmed Parkinson's disease, 2=Yes, autopsy did not confirm PD, and 9=unknown)

- If the person donated the brain to FHS, and we have received it, mark "yes" (whether or not the neuropath team has completed the autopsy).
- The brain autopsy report for our neuropath cases should never be available for the DR meeting; the panel should be blind to these results.
- If the person had a brain autopsy performed by a different agency, and so the participant is not an FHS neuropath case, then the autopsy report can be made available to the panel for review.

Addendum – 2023

In July 2023, an addendum was added to include relevant cognitive variables from the Dementia Review and relevant variables from the newly implemented FHS Neurology Exam.

Additional Cognitive Variables

The following variables come from the Dementia Review form. The Dementia Review Diagnostic Manual of Procedures also describes details about these variables and how they are coded.

1. Cognitively Intact?
    a. If no, date last cognitively intact
2. Cognitive Impairment?
    a. If yes, date of cognitive impairment onset
3. Dementia?
    a. If yes, code dementia diagnosis:
        i. Mild
        ii. Moderate
        iii. Severe
4. Date of Dementia Diagnosis
5. Dementia Subtype

    0 = None
    1 = Alzheimer's Disease Without Stroke: Presence of Alzheimer Disease based on the NINCDS-ADRDA.
    2 = Alzheimer's Disease with Stroke
    3 = Vascular Dementia Without Alzheimer's Disease

4 = Mixed Dementia Type (Alzheimer's Disease + Vascular Dementia)
5 = Frontotemporal Dementia
6 = Dementia with Lewy Bodies
7 = Dementia that does not fit any other Category (progressive)
8 = Dementia that does not fit any other Category (non-progressive)
9 = Cognitive Impairment – No Dementia
10 = Dementia – Uncertain
99 = Unknown

FHS-BAP Neurology Exam

If a participant has completed the FHS Neurology testing, the following two variables are coded:

1. Date of FHS Neurology Exam
2. MDS-UPDRS Part III Total Score

**Note: If the participant has not been in for Neurology testing or is deceased, these two variables are left blank.

Updated UK PD Brain Bank Clinical Diagnostic Criteria

As outlined in a previous section of this document, the original PD form has a variable confirming the PD diagnosis, which includes a label for the variable, including gait disturbance as a cardinal symptom. This variable was included to correctly outline the three cardinal symptoms (rigidity, tremor, postural instability/falling), encompassing variables 2-4 on the PD form.

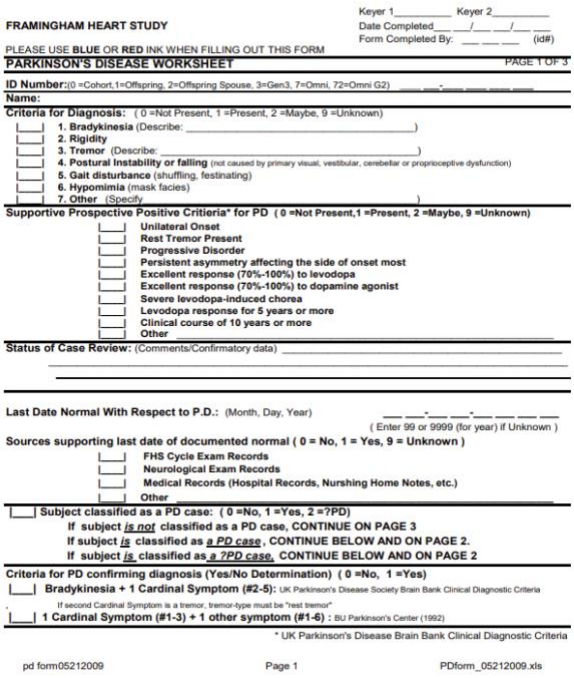
Supporting Symptoms/Diagnoses

To capture additional PD/Parkinsonism symptoms, we added seven additional variables described below. The data for these variables comes from the PDRCS, which includes information from medical records (including supporting biomarkers), Core exams, and FHS Neurology testing.

1. REM Sleep Behavior Disorder
2. Fluctuating Cognition
3. Visual Hallucinations
4. Auditory Hallucinations
5. Orthostatic Hypotension
6. Neurogenic Bladder
7. Other Supporting Biomarkers?
    - Nuclear Medicine (e.g., SPECT/PET)
    - Tissue Sample (e.g., skin biopsy)
    - Fluids (e.g., CSF, blood saliva)
    - Other (If other, specify)

Variables 1-6 are coded as "yes/no." If marked "yes," an additional variable includes the age of onset for each symptom present. If additional supporting biomarkers exist (variable 7), a drop-down includes three options and a variable for "Other," which consists of a text box to describe.

Appendix A. Parkinson's Disease Review Paper form used through March 2021



FRAMINGHAM HEART STUDY

Keyer 1_____ Keyer 2_____
Date Completed___ ___/___ ___/___ ___
Form Completed By: ___ ___ ___ (id#)

PLEASE USE **BLUE** OR **RED** INK WHEN FILLING OUT THIS FORM

PARKINSON'S DISEASE WORKSHEET PAGE 1 OF 3

ID Number:(0 =Cohort,1=Offspring, 2=Offspring Spouse, 3=Gen3, 7=Omni, 72=Omni G2) ___ ___-___ ___ ___ ___

Name:

Criteria for Diagnosis: (0 =Not Present, 1 =Present, 2 =Maybe, 9 =Unknown)

|___| 1. **Bradykinesia** (Describe: _____)
|___| 2. **Rigidity**
|___| 3. **Tremor** (Describe: _____)
|___| 4. **Postural Instability or falling** (not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction)
|___| 5. **Gait disturbance** (shuffling, festinating)
|___| 6. **Hypomimia** (mask facies)
|___| 7. **Other** (Specify _____)

Supportive Prospective Positive Critieria* for PD (0 =Not Present,1 =Present, 2 =Maybe, 9 =Unknown)

|___| **Unilateral Onset**
|___| **Rest Tremor Present**
|___| **Progressive Disorder**
|___| **Persistent asymmetry affecting the side of onset most**
|___| **Excellent response (70%-100%) to levodopa**
|___| **Excellent response (70%-100%) to dopamine agonist**
|___| **Severe levodopa-induced chorea**
|___| **Levodopa response for 5 years or more**
|___| **Clinical course of 10 years or more**
|___| **Other** _____

Status of Case Review: (Comments/Confirmatory data) _____

Last Date Normal With Respect to P.D.: (Month, Day, Year) ___ ___-___ ___-___ ___ ___ ___
(Enter 99 or 9999 (for year) if Unknown)

Sources supporting last date of documented normal (0 = No, 1 = Yes, 9 = Unknown)

|___| **FHS Cycle Exam Records**
|___| **Neurological Exam Records**
|___| **Medical Records (Hospital Records, Nurshing Home Notes, etc.)**
|___| **Other** _____

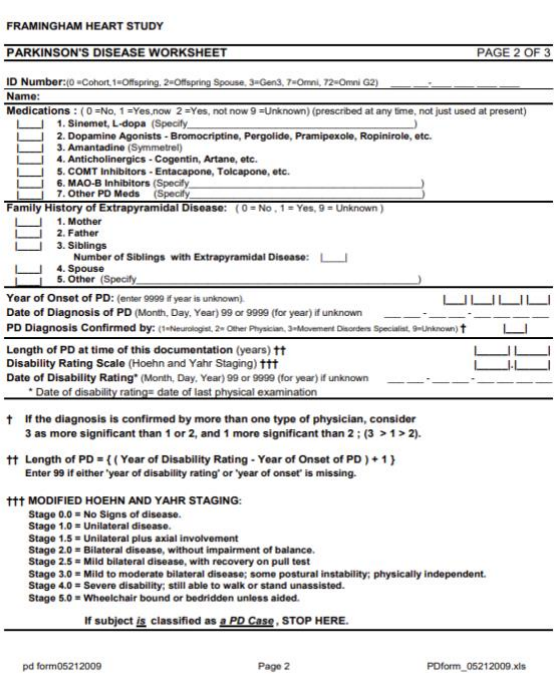
|___| **Subject classified as a PD case: (0 =No, 1 =Yes, 2 =?PD)**
If subject *is not* classified as a PD case, CONTINUE ON PAGE 3
If subject *is* classified as *a PD case*, CONTINUE BELOW AND ON PAGE 2.
If subject *is* classified as *a ?PD case*, CONTINUE BELOW AND ON PAGE 2

Criteria for PD confirming diagnosis (Yes/No Determination) (0 =No, 1 =Yes)

|___| **Bradykinesia + 1 Cardinal Symptom (#2-5):** UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria
If second Cardinal Symptom is a tremor, tremor-type must be "rest tremor"
|___| **1 Cardinal Symptom (#1-3) + 1 other symptom (#1-6) :** BU Parkinson's Center (1992)

* UK Parkinson's Disease Brain Bank Clinical Diagnostic Criteria

pd form05212009 Page 1 PDform_05212009.xls



FRAMINGHAM HEART STUDY

PARKINSON'S DISEASE WORKSHEET PAGE 2 OF 3

ID Number:(0 =Cohort,1=Offspring, 2=Offspring Spouse, 3=Gen3, 7=Omni, 72=Omni G2) ___ ___-___ ___ ___ ___

Name:

Medications : (0 =No, 1 =Yes,now 2 =Yes, not now 9 =Unknown) (prescribed at any time, not just used at present)

|___| 1. **Sinemet, L-dopa** (Specify_____)
|___| 2. **Dopamine Agonists - Bromocriptine, Pergolide, Pramipexole, Ropinirole, etc.**
|___| 3. **Amantadine** (Symmetrel)
|___| 4. **Anticholinergics - Cogentin, Artane, etc.**
|___| 5. **COMT Inhibitors - Entacapone, Tolcapone, etc.**
|___| 6. **MAO-B Inhibitors** (Specify_____)
|___| 7. **Other PD Meds** (Specify_____)

Family History of Extrapyramidal Disease: (0 = No , 1 = Yes, 9 = Unknown)

|___| 1. **Mother**
|___| 2. **Father**
|___| 3. **Siblings**
Number of Siblings with Extrapyramidal Disease: |___|
|___| 4. **Spouse**
|___| 5. **Other** (Specify_____)

Year of Onset of PD: (enter 9999 if year is unknown). |___|___|___|___|

Date of Diagnosis of PD (Month, Day, Year) 99 or 9999 (for year) if unknown ___ ___ - ___ ___ - ___ ___ ___ ___

PD Diagnosis Confirmed by: (1=Neurologist, 2= Other Physician, 3=Movement Disorders Specialist, 9=Unknown) † |___|

Length of PD at time of this documentation (years) †† |___|___|

Disability Rating Scale (Hoehn and Yahr Staging) ††† |___|.|___|

Date of Disability Rating* (Month, Day, Year) 99 or 9999 (for year) if unknown ___ ___ - ___ ___ - ___ ___ ___ ___
* Date of disability rating= date of last physical examination

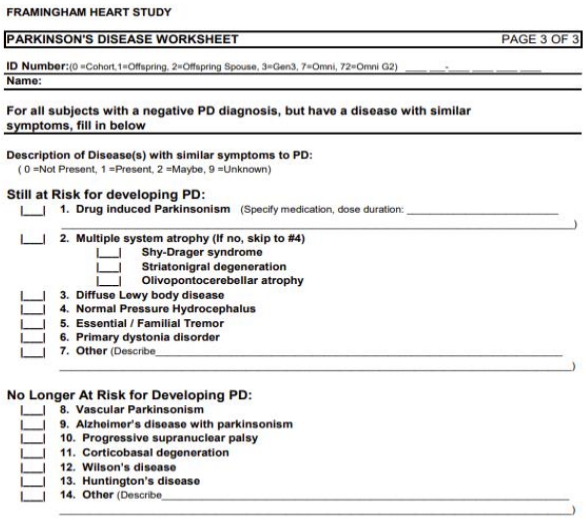
† **If the diagnosis is confirmed by more than one type of physician, consider 3 as more significant than 1 or 2, and 1 more significant than 2 ; (3 > 1 > 2).**

†† **Length of PD = { (Year of Disability Rating - Year of Onset of PD) + 1 }**
Enter 99 if either 'year of disability rating' or 'year of onset' is missing.

††† **MODIFIED HOEHN AND YAHR STAGING:**
Stage 0.0 = No Signs of disease.
Stage 1.0 = Unilateral disease.
Stage 1.5 = Unilateral plus axial involvement
Stage 2.0 = Bilateral disease, without impairment of balance.
Stage 2.5 = Mild bilateral disease, with recovery on pull test
Stage 3.0 = Mild to moderate bilateral disease; some postural instability; physically independent.
Stage 4.0 = Severe disability; still able to walk or stand unassisted.
Stage 5.0 = Wheelchair bound or bedridden unless aided.

If subject *is* classified as *a PD Case*, STOP HERE.

pd form05212009 Page 2 PDform_05212009.xls



FRAMINGHAM HEART STUDY

PARKINSON'S DISEASE WORKSHEET PAGE 3 OF 3

ID Number:(0 =Cohort,1=Offspring, 2=Offspring Spouse, 3=Gen3, 7=Omni, 72=Omni G2) ___ ___-___ ___ ___ ___

Name:

For all subjects with a negative PD diagnosis, but have a disease with similar symptoms, fill in below

Description of Disease(s) with similar symptoms to PD:
(0 =Not Present, 1 =Present, 2 =Maybe, 9 =Unknown)

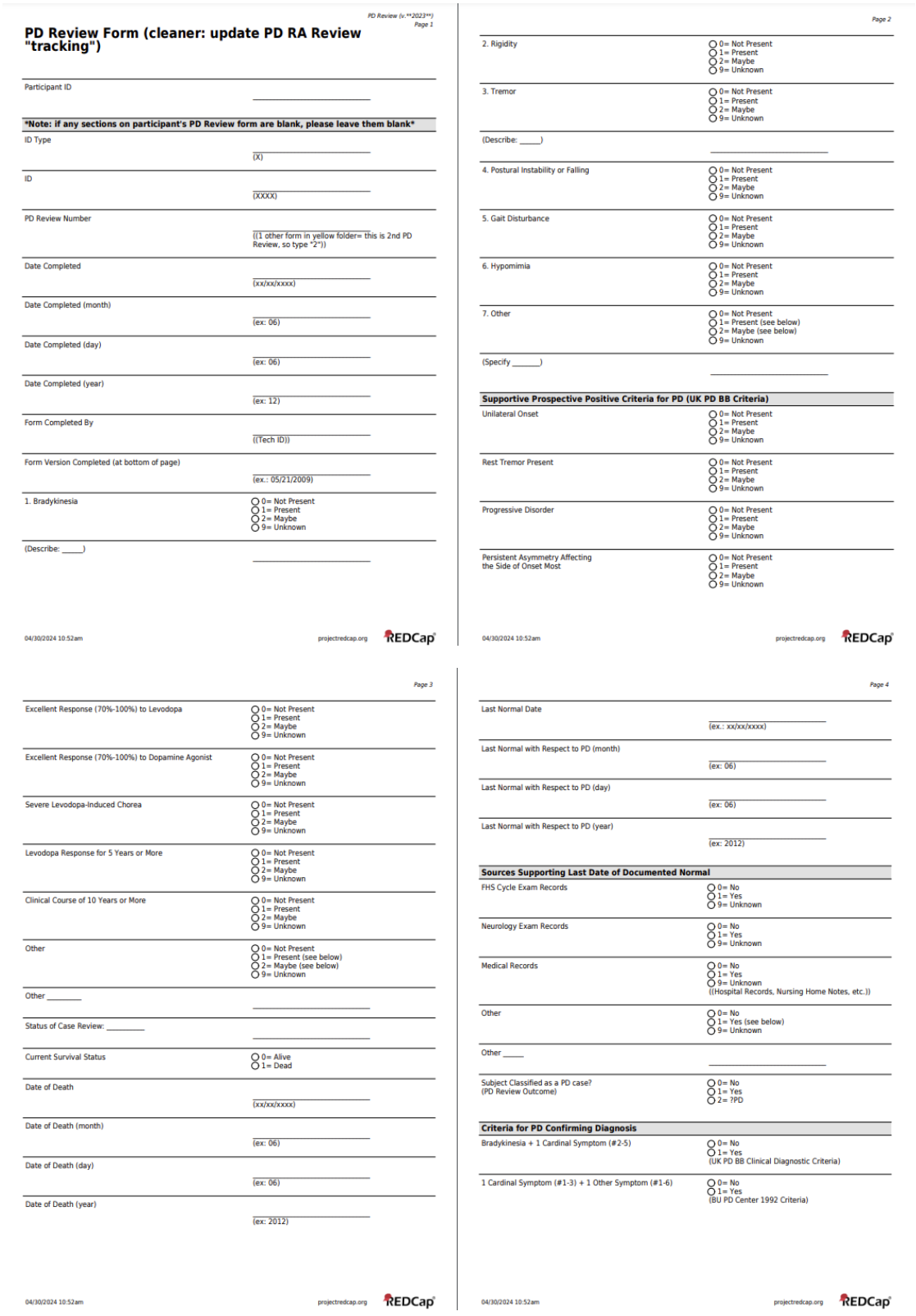
Still at Risk for developing PD:

|___| 1. **Drug induced Parkinsonism** (Specify medication, dose duration: _____)
|___| 2. **Multiple system atrophy (If no, skip to #4)**
|___| **Shy-Drager syndrome**
|___| **Striatonigral degeneration**
|___| **Olivopontocerebellar atrophy**
|___| 3. **Diffuse Lewy body disease**
|___| 4. **Normal Pressure Hydrocephalus**
|___| 5. **Essential / Familial Tremor**
|___| 6. **Primary dystonia disorder**
|___| 7. **Other** (Describe_____)

No Longer At Risk for Developing PD:

|___| 8. **Vascular Parkinsonism**
|___| 9. **Alzheimer's disease with parkinsonism**
|___| 10. **Progressive supranuclear palsy**
|___| 11. **Corticobasal degeneration**
|___| 12. **Wilson's disease**
|___| 13. **Huntington's disease**
|___| 14. **Other** (Describe_____)

Appendix B. REDCap form launched on July 7, 2023



PD Review (v.**2023**)
Page 1

PD Review Form (cleaner: update PD RA Review "tracking")

Participant ID

Note: if any sections on participant's PD Review form are blank, please leave them blank

ID Type
(X)

ID
(XXXX)

PD Review Number
((1 other form in yellow folder= this is 2nd PD Review, so type "2"))

Date Completed
(xx/xx/xxxx)

Date Completed (month)
(ex: 06)

Date Completed (day)
(ex: 06)

Date Completed (year)
(ex: 12)

Form Completed By
((Tech ID))

Form Version Completed (at bottom of page)
(ex.: 05/21/2009)

1. Bradykinesia
○ 0= Not Present
○ 1= Present
○ 2= Maybe
○ 9= Unknown

(Describe: _____)

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2. Rigidity
○ 0= Not Present
○ 1= Present
○ 2= Maybe
○ 9= Unknown

3. Tremor
○ 0= Not Present
○ 1= Present
○ 2= Maybe
○ 9= Unknown

(Describe: _____)

4. Postural Instability or Falling
○ 0= Not Present
○ 1= Present
○ 2= Maybe
○ 9= Unknown

5. Gait Disturbance
○ 0= Not Present
○ 1= Present
○ 2= Maybe
○ 9= Unknown

6. Hypomimia
○ 0= Not Present
○ 1= Present
○ 2= Maybe
○ 9= Unknown

7. Other
○ 0= Not Present
○ 1= Present (see below)
○ 2= Maybe (see below)
○ 9= Unknown

(Specify _____)

Supportive Prospective Positive Criteria for PD (UK PD BB Criteria)

Unilateral Onset
○ 0= Not Present
○ 1= Present
○ 2= Maybe
○ 9= Unknown

Rest Tremor Present
○ 0= Not Present
○ 1= Present
○ 2= Maybe
○ 9= Unknown

Progressive Disorder
○ 0= Not Present
○ 1= Present
○ 2= Maybe
○ 9= Unknown

Persistent Asymmetry Affecting the Side of Onset Most
○ 0= Not Present
○ 1= Present
○ 2= Maybe
○ 9= Unknown

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Excellent Response (70%-100%) to Levodopa
○ 0= Not Present
○ 1= Present
○ 2= Maybe
○ 9= Unknown

Excellent Response (70%-100%) to Dopamine Agonist
○ 0= Not Present
○ 1= Present
○ 2= Maybe
○ 9= Unknown

Severe Levodopa-Induced Chorea
○ 0= Not Present
○ 1= Present
○ 2= Maybe
○ 9= Unknown

Levodopa Response for 5 Years or More
○ 0= Not Present
○ 1= Present
○ 2= Maybe
○ 9= Unknown

Clinical Course of 10 Years or More
○ 0= Not Present
○ 1= Present
○ 2= Maybe
○ 9= Unknown

Other
○ 0= Not Present
○ 1= Present (see below)
○ 2= Maybe (see below)
○ 9= Unknown

Other _____

Status of Case Review: _____

Current Survival Status
○ 0= Alive
○ 1= Dead

Date of Death
(xx/xx/xxxx)

Date of Death (month)
(ex: 06)

Date of Death (day)
(ex: 06)

Date of Death (year)
(ex: 2012)

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Page 4

Last Normal Date
(ex.: xx/xx/xxxx)

Last Normal with Respect to PD (month)
(ex: 06)

Last Normal with Respect to PD (day)
(ex: 06)

Last Normal with Respect to PD (year)
(ex: 2012)

Sources Supporting Last Date of Documented Normal

FHS Cycle Exam Records
○ 0= No
○ 1= Yes
○ 9= Unknown

Neurology Exam Records
○ 0= No
○ 1= Yes
○ 9= Unknown

Medical Records
○ 0= No
○ 1= Yes
○ 9= Unknown
((Hospital Records, Nursing Home Notes, etc.))

Other
○ 0= No
○ 1= Yes (see below)
○ 9= Unknown

Other _____

Subject Classified as a PD case? (PD Review Outcome)
○ 0= No
○ 1= Yes
○ 2= ?PD

Criteria for PD Confirming Diagnosis

Bradykinesia + 1 Cardinal Symptom (#2-5)
○ 0= No
○ 1= Yes
(UK PD BB Clinical Diagnostic Criteria)

1 Cardinal Symptom (#1-3) + 1 Other Symptom (#1-6)
○ 0= No
○ 1= Yes
(BU PD Center 1992 Criteria)

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Medications

1. Sinemet, L-dopa	○ 0= No ○ 1= Yes, now ○ 2= Yes, not now ○ 9= Unknown
(Specify _____)	_____
2. Dopamine Agonists	○ 0= No ○ 1= Yes, now ○ 2= Yes, not now ○ 9= Unknown
3. Amantadine	○ 0= No ○ 1= Yes, now ○ 2= Yes, not now ○ 9= Unknown
4. Anticholinergics	○ 0= No ○ 1= Yes, now ○ 2= Yes, not now ○ 9= Unknown
5. COMT Inhibitors	○ 0= No ○ 1= Yes, now ○ 2= Yes, not now ○ 9= Unknown
6. MAO-B Inhibitors	○ 0= No ○ 1= Yes, now ○ 2= Yes, not now ○ 9= Unknown
(Specify _____)	_____
7. Other PD Meds	○ 0= No ○ 1= Yes, now (see below) ○ 2= Yes, not now (see below) ○ 9= Unknown
(Specify _____)	_____

Family History of Extrapyramidal Disease

1. Mother	○ 0= No ○ 1= Yes ○ 9= Unknown
2. Father	○ 0= No ○ 1= Yes ○ 9= Unknown

3. Siblings	○ 0= No ○ 1= Yes ○ 9= Unknown
Number of Siblings with Extrapyramidal Disease	_____
4. Spouse	○ 0= No ○ 1= Yes ○ 9= Unknown
5. Other	○ 0= No ○ 1= Yes (see below) ○ 9= Unknown
(Specify _____)	_____
Date of Diagnosis of PD	_____ (xx/xx/xxxx)
Year of Onset of PD	_____ (XXXX)
Date of Diagnosis of PD (month)	_____ (ex: 06)
Date of Diagnosis of PD (day)	_____ (ex: 06)
Date of Diagnosis of PD (year)	_____ (ex: 06)
PD Diagnosis Confirmed By	○ 1= Neurologist ○ 2= Other Physician ○ 3= Movement Disorders Specialist ○ 9= Unknown
Length of PD at time of this documentation	_____
Disability Rating	_____ (Use modified Hoehn and Yahr)
Date of Disability Rating	_____ (xx/xx/xxxx)
Date of Disability Rating (month)	_____ (ex: 06)

Date of Disability Rating (day)	_____ (ex: 06)
Date of Disability Rating (year)	_____ (ex: 2012)

Still at Risk for Developing PD Criteria

1. Drug induced Parkinsonism	○ 0= Not Present ○ 1= Present ○ 2= Maybe ○ 9= Unknown
(Specify medication, dose duration: _____)	_____
2. Multiple System Atrophy	○ 0= Not Present ○ 1= Present ○ 2= Maybe ○ 9= Unknown
Shy-Drager Syndrome	○ 0= Not Present ○ 1= Present ○ 2= Maybe ○ 9= Unknown
Striatonigal Degeneration	○ 0= Not Present ○ 1= Present ○ 2= Maybe ○ 9= Unknown
Olivopontocerebellar Atrophy	○ 0= Not Present ○ 1= Present ○ 2= Maybe ○ 9= Unknown
3. Diffuse Lewy Body Disease	○ 0= Not Present ○ 1= Present ○ 2= Maybe ○ 9= Unknown
4. Normal Pressure Hydrocephalus	○ 0= Not Present ○ 1= Present ○ 2= Maybe ○ 9= Unknown
5. Essential/Familial Tremor	○ 0= Not Present ○ 1= Present ○ 2= Maybe ○ 9= Unknown
6. Primary Dystonia Disorder	○ 0= Not Present ○ 1= Present ○ 2= Maybe ○ 9= Unknown

7. Other	○ 0= Not Present ○ 1= Present (see below) ○ 2= Maybe (see below) ○ 9= Unknown
(Describe _____)	_____

No Longer At Risk for Developing PD Criteria

8. Vascular Parkinsonism	○ 0= Not Present ○ 1= Present ○ 2= Maybe ○ 9= Unknown
9. Alzheimer's Disease with Parkinsonism	○ 0= Not Present ○ 1= Present ○ 2= Maybe ○ 9= Unknown
10. Progressive Supranuclear Palsy	○ 0= Not Present ○ 1= Present ○ 2= Maybe ○ 9= Unknown
11. Corticobasal Degeneration	○ 0= Not Present ○ 1= Present ○ 2= Maybe ○ 9= Unknown
12. Wilson's Disease	○ 0= Not Present ○ 1= Present ○ 2= Maybe ○ 9= Unknown
13. Huntington's Disease	○ 0= Not Present ○ 1= Present ○ 2= Maybe ○ 9= Unknown
14. Other	○ 0= Not Present ○ 1= Present (see below) ○ 2= Maybe (see below) ○ 9= Unknown
(Describe _____)	_____

Addendum (only present if deceased)

Participant Had Brain Autopsy	○ 0= No autopsy ○ 1= Yes, autopsy confirmed Parkinson's disease ○ 2= Yes, autopsy did not confirm PD ○ 9= Unknown

Addendum V. *2023*

Cognitively Intact?	○ Yes ○ No
Date Last Cognitively Intact?	_____ (xx/xx/xxxx)
Cognitive Impairment?	○ Yes ○ No
Date of Cognitive Impairment Onset?	_____ (xx/xx/xxxx)
Dementia?	○ Yes ○ No
Dementia Diagnosis	○ Mild ○ Moderate ○ Severe
Date of Dementia Diagnosis	_____ (xx/xx/xxxx)
Dementia Subtype	○ 0 = None ○ 1 = Alzheimer's Disease Without Stroke ○ 2 = Alzheimer's Disease With Stroke ○ 3 = Vascular Dementia Without Alzheimer's Disease ○ 4 = Mixed Dementia Type (Alzheimer's Disease + Vascular Dementia) ○ 5 = Frontotemporal Dementia ○ 6 = Dementia with Lewy Bodies ○ 7 = Dementia that does not fit any other Category (progressive) (if yes, fill box below) ○ 8 = Dementia that does not fit any other Category (non-progressive) (if yes, fill box below) ○ 9 = Cognitive Impairment- No Dementia (MCI) ○ 10 = Dementia present - Uncertain Etiology(10) ○ 99 = Unknown (99)

FHS-BAP Neurology Exam

Date of FHS Neurology Exam	_____ (xx/xx/xxxx)
MDS-UPDRS III Total Score	_____
Bradykinesia + 1 Cardinal Symptom (#2-4)	○ 0= No ○ 1= Yes (UK PD BB Clinical Diagnostic Criteria)
REM Sleep Behavior Disorder	○ Yes ○ No
REM Sleep Behavior Disorder Age Onset	_____
Fluctuating Cognition (CJS or Similar)	○ Yes ○ No
Fluctuating Cognition Age Onset	_____
Visual Hallucinations	○ Yes ○ No
Visual Hallucinations Age Onset	_____
Auditory Hallucinations	○ Yes ○ No
Auditory Hallucinations Age Onset	_____
Orthostatic Hypotension	○ Yes ○ No
Orthostatic Hypotension Age Onset	_____
Neurogenic Bladder	○ Yes ○ No
Neurogenic Bladder Age Onset	_____
Other Supporting Biomarkers?	☐ Nuclear Medicine (eg SPECT/PET) ☐ Tissue Sample (eg skin biopsy) ☐ Fluids (eg CSF, Blood Saliva) ☐ Other
If Other, Specify	_____

Appendix C. DSM-IV Criteria for Dementia

A. Development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances
    a. Aphasia
    b. Apraxia
    c. Agnosia
    d. Disturbance in executive functioning
B. The cognitive deficits are sufficiently severe to cause impairment in occupational or social functioning.
C. The cognitive deficits must represent a decline from a previously higher level of functioning.

DSM-IV Criteria for the Diagnosis of Alzheimer's Disease

A. The development of multiple cognitive deficits manifested by both:
    1. Memory impairment (impaired ability to learn new information or to recall previously learned information).
    2. One (or more) of the following cognitive disturbances:
    a. Aphasia (language disturbance)
    b. Apraxia (impaired ability to carry out motor activities despite intact motor function
    c. Agnosia (failure to recognize or identify objects despite intact sensory function)
    d. Disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a substantial decline from a previous level of functioning.
C. The course is characterized by gradual onset and continuing cognitive decline.
D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
    1. Other central nervous systems, conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
    2. 2. Systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B12 or folic acid deficiency, neurosyphilis, HIV infection)
    3. Substance-induced conditions
E. The deficits do not occur exclusively during delirium.
F. The disturbance is not better accounted for by another disorder (e.g., major depressive disorder, schizophrenia).

DSM-IV criteria for the diagnosis of vascular dementia

A. The development of multiple cognitive deficits manifested by both:

1. Memory impairment (impaired ability to learn new information or to recall previously learned information)
2. One or more of the following cognitive disturbances:
   (a) aphasia (language disturbance)
   (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
   (c) agnosia (failure to recognize or identify objects despite intact sensory function)
   (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. Focal neurological signs and symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicative of cerebrovascular disease (e.g., multiple infarctions involving cortex and underlying white matter) that are judged to be etiologically related to the disturbance.

D. The deficits do not occur exclusively during delirium.

Appendix D. Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) definition of dementia

Dementia is a **deterioration** from a known or estimated prior level of **intellectual function** sufficient to interfere broadly with the conduct of the patient's **customary affairs of life,** which is **not isolated to a single narrow category of intellectual performance** and is independent of the **level of consciousness.** This deterioration should be supported by **historical evidence** and documented by either bedside mental status testing or, ideally, by more detailed neuropsychological examination using quantifiable, reproducible tests for which normative data are available.

Deterioration: Ideally, cognitive decline should be assessed using quantifiable and reproducible tests for which normative data are available**.** However, statistically derived cutoff scores should not be included in the definition of dementia because (1) age-, education-, and gender-specific norms are not available for many cognitive functions in older populations; (2) standard deviation cutoffs may be inappropriate because many test scores used to assess dementia do not have a normal distribution; and (3) statistical cutoffs are inconsistent with the core meaning of dementia as a decline in an *individual's* mentation because they establish arbitrary population standards to be applied to individuals with widely varying baseline function. Intellectual loss should remain a clinical decision.

Patient's customary affairs of life: Change is in functional impairment in *intellectual* activities of daily living rather than in social or occupational functioning. The degree of intellectual deterioration must be sufficient to interfere with the conduct of the patient's customary affairs of life.

Not isolated by a single narrow category: There is a significant gap between mental status testing and the biological status of the CNS and the intellectual activities of daily living[1]; thus, the *number* or *type* of cognitive deficits is not specified. However, most patients with dementia will exhibit deficits in more than one type of intellectual task, and a distinction must be retained between the patient who has an isolated impairment such as aphasia as opposed to the broader intellectual loss connoted by dementia.

Independent of the level of consciousness: In general, a diagnosis of dementia should not be made when there is a clouding of consciousness (e.g., a recent stroke). On the other hand, the presence of clouding of consciousness does not necessarily preclude a diagnosis of dementia. The critical issue for a diagnosis of dementia is the ability to establish that the mental deterioration is not due to impairment of consciousness.

Historical evidence: Given the limits of mental status testing, historical evidence and clinical judgment should be considered when diagnosing dementia.

[1]Some definitions of dementia require deficits in more than one “area of cognition.” Problems with this include: (1) these so-called areas of cognition (such as attention, concentration, memory, language, and visual-spatial functions) are theoretical constructs that help us to conceptualize brain function but have imperfect biologic validity; (2) while assessment of these areas of cognition is conventionally based upon neuropsychological testing, there is no a priori basis and no universal system by which performance on given tasks can be attributed explicitly to such discrete cognitive domains; and (3) in mental status testing, artificial challenges are substituted for actual intellectual activities of daily living; yet again, there is no one-to-one correlation between performance on such tasks and real-life intellectual function. Thus, criteria that attempt to operationalize the definition of dementia by specifying the number and types of cognitive or neuropsychological deficits may sacrifice the essential meaning of a decline in mental status in favor of an arbitrary number of deficits identified in artificially delineated areas of cognition by insufficiently specific tests.

Appendix E. Hachinski Ischemia Scale

Table 1. Hachinski Ischemia Score

Abrupt onset*	2
Stepwise progression*†	1
Fluctuating course†‡	2
Nocturnal confusion‡	1
Relative preservation of personality†	1
Depression	1
Somatic complaints*	1
Emotional incontinence*†	1
History of hypertension*	1
History of strokes*†	2
Evidence of associated atherosclerosis	1
Focal neurologic symptoms*†‡	2
Focal neurologic signs*	2

* Items significantly more common in MID than AD.[41]
† Items significantly more common in MID than AD.[42]
‡ Items that explained a significance portion of the variance in logistic regression.[42]

Appendix F. National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) NINCDS-ADRDA Update (2011)

All-Cause Dementia

1. Interferes with the functioning
2. Decline from previous levels of functioning
3. Not explained by delirium or a major psychiatric disorder
4. The cognitive or behavioral impairment involves a minimum of two of the following domains:
    a. Memory (Ability to acquire and remember new information)
    b. Reasoning and handling of complex tasks, poor judgment
    c. Visuospatial abilities—symptoms include
    d. Language functions (speaking, reading, writing)
    e. Personality, behavior, or comportment

Probable AD dementia

1. Insidious onset (months to years, not hours to days)
2. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.
    - Amnestic presentation
        - Impairment in learning and recall of recently learned information
    - Nonamnestic presentations (Most prominent deficits are…):
        - **Language presentation**: Word-finding
        - **Visuospatial presentation**: Spatial cognition -
        - **Executive dysfunction**: Reasoning, judgment, and problem solving.
3. The diagnosis of **probable AD dementia should NOT** be applied when there is evidence of
    - Substantial CVD (stroke temporally related, multiple/extensive infarcts or severe WMH
    - Core features of DLB other than dementia itself
    - Prominent features of behavioral variant FTD
    - Prominent features of semantic variant PPA or non-fluent/agrammatic variant PPA
    - Evidence for another concurrent, active neurological disease, non-neurological medical comorbidity, or use of meds that could have a substantial effect on cognition

Possible AD dementia: Core clinical criteria

1. Atypical course
    a. Sudden onset of cognitive impairment or
    b. Insufficient historical detail or objective cog. Documentation of progressive decline
2. Etiologically mixed presentation
    a. Concomitant CVD
    b. Features of DLB

c. Other neuro/medical comorbidity or meds

Dementia unlikely to be due to AD

1. Does not meet clinical criteria for AD dementia.
2. Sufficient evidence for an alternative diagnosis such as HIV dementia, dementia of Huntington's disease, or others that rarely, if ever, overlap with AD

Appendix G. Criteria for the Diagnosis of Ischemic Vascular Dementia

Table 2. Criteria for the diagnosis of ischemic vascular dementia (IVD)

I. Dementia

Dementia is a deterioration from a known or estimated prior level of intellectual function sufficient to interfere broadly with the conduct of the patient's customary affairs of life, which is not isolated to a single narrow category of intellectual performance, and which is independent of level of consciousness.

This deterioration should be supported by historical evidence and documented by either bedside mental status testing or ideally by more detailed neuropsychological examination, using tests that are quantifiable, reproducible, and for which normative data are available.

II. Probable IVD

A. The criteria for the clinical diagnosis of PROBABLE IVD include ALL of the following:

1. Dementia;
2. Evidence of two or more ischemic strokes by history, neurologic signs, and/or neuroimaging studies (CT or T_1-weighted MRI);

   or

   Occurrence of a single stroke with a clearly documented temporal relationship to the onset of dementia;
3. Evidence of at least one infarct outside the cerebellum by CT or T_1-weighted MRI.

B. The diagnosis of PROBABLE IVD is supported by

1. Evidence of multiple infarcts in brain regions known to affect cognition;
2. A history of multiple transient ischemic attacks;
3. History of vascular risk factors (eg, hypertension, heart disease, diabetes mellitus);
4. Elevated Hachinski Ischemia Scale (original or modified version).

C. Clinical features that are thought to be associated with IVD, but await further research, include

1. Relatively early appearance of gait disturbance and urinary incontinence;
2. Periventricular and deep white matter changes on T_2-weighted MRI that are excessive for age;
3. Focal changes in electrophysiologic studies (eg, EEG, evoked potentials) or physiologic neuroimaging studies (eg, SPECT, PET, NMR spectroscopy).

D. Other clinical features that do not constitute strong evidence either for or against a diagnosis of PROBABLE IVD include

1. Periods of slowly progressive symptoms;
2. Illusions, psychosis, hallucinations, delusions;
3. Seizures.

E. Clinical features that cast doubt on a diagnosis of PROBABLE IVD include

1. Transcortical sensory aphasia in the absence of corresponding focal lesions on neuroimaging studies;
2. Absence of central neurologic symptoms/signs, other than cognitive disturbance.

III. Possible IVD

A clinical diagnosis of POSSIBLE IVD may be made when there is

1. Dementia;

   and one or more of the following:

2a. A history or evidence of a single stroke (but not multiple strokes) without a clearly documented temporal relationship to the onset of dementia;

   or

2b. Binswanger's syndrome (without multiple strokes) that includes all of the following:

   i. Early-onset urinary incontinence not explained by urologic disease, or gait disturbance (eg, parkinsonian, magnetic, apraxic, or "senile" gait) not explained by peripheral cause,

   ii. Vascular risk factors, and

   iii. Extensive white matter changes on neuroimaging.

IV. Definite IVD

A diagnosis of DEFINITE IVD requires histopathologic examination of the brain, as well as

A. Clinical evidence of dementia;

B. Pathologic confirmation of multiple infarcts, some outside of the cerebellum.

Note: If there is evidence of Alzheimer's disease or some other pathologic disorder that is thought to have contributed to the dementia, a diagnosis of MIXED dementia should be made.

V. Mixed dementia

A diagnosis of MIXED dementia should be made in the presence of one or more other systemic or brain disorders that are thought to be *causally* related to the dementia.

The degree of confidence in the diagnosis of IVD should be specified as possible, probable, or definite, and the other disorder(s) contributing to the dementia should be listed. For example: mixed dementia due to probable IVD and possible Alzheimer's disease or mixed dementia due to definite IVD and hypothyroidism.

VI. Research classification

Classification of IVD for RESEARCH purposes should specify features of the infarcts that may differentiate subtypes of the disorder, such as

Location:	cortical, white matter, periventricular, basal ganglia, thalamus
Size:	volume
Distribution:	large, small, or microvessel
Severity:	chronic ischemia versus infarction
Etiology:	embolism, atherosclerosis, arteriosclerosis, cerebral amyloid angiopathy, hypoperfusion.

Appendix H. Diagnosis of Frontotemporal Dementia

The Lund-Manchester Research Criteria (LMRC)
Clinical diagnostic features of frontotemporal dementia[14]

- CORE DIAGNOSTIC FEATURES
  - Behavioral disorder
    - Insidious onset and slow progression
    - Early loss of personal awareness (neglect of personal hygiene and grooming)
    - Early loss of social awareness (lack of social tact, misdemeanors such as shoplifting)
    - Early signs of disinhibition (such as unrestrained sexuality, violent behavior, inappropriate jocularity, restless pacing)
    - Mental rigidity and inflexibility
    - Hyperorality (oral/dietary changes, overeating, food fads, excessive smoking and alcohol consumption, oral exploration of objects)
    - Stereotyped and preservative behavior (wandering, mannerisms such as clapping, singing, dancing, ritualistic preoccupation such as hoarding, toileting, and dressing)
    - Utilization behavior (unrestrained exploration of objects in the environment)
    - Distractibility, impulsivity, and persistence
    - Early loss of insight into the fact that the altered condition is due to a pathological change in one's mental state.

  - Affective symptoms
    - Depression, anxiety, excessive sentimentality, suicidal and fixed ideation, delusion (early and evanescent)
    - Hypochondriasis, bizarre somatic preoccupation (early and evanescent)
    - Emotional unconcern (emotional indifference and remoteness, lack of empathy and sympathy, apathy)
    - Amimia (inertia, aspontaneity)

  - Speech disorder
    - Progressive reduction of speech (aspontaneity and economy of utterance)
    - Stereotypy of speech (repetition of a limited repertoire of words, phrases, or themes)
    - Echolalia and perseveration

        - Late mutism.

    - Spatial orientation and praxis preserved (intact abilities to negotiate the environment)

    - Physical signs
        - Early primitive reflexes
        - Early incontinence
        - Late akinesia, rigidity, tremor
        - Low and labile blood pressure.

    - Investigations
        - Normal EEG despite clinically evident dementia
        - Brain imaging (structural or functional, or both): predominant frontal or anterior temporal abnormality, or both
        - Neuropsychology (profound failure on "frontal lobe" tests in the absence of severe amnesia, aphasia, or perceptual spatial disorder)

- SUPPORTIVE DIAGNOSTIC FEATURES
    - Onset before 65
    - Positive family history of similar disorder in a first-degree relative
    - Bulbar palsy, muscular weakness, and wasting, fasciculations (motor neuron disease)

- DIAGNOSTIC EXCLUSION FEATURES
    - Abrupt onset with ictal events
    - Head trauma related to onset
    - Early severe amnesia
    - Early spatial disorientation, loss in surroundings, defective localization of objects
    - Early severe apraxia
    - Logoclonic speech with rapid loss of train of thought
    - Myoclonus
    - Cortical bulbar and spinal deficits
    - Cerebellar ataxia
    - Choreo-athetosis
    - Early, severe, pathological EEG
    - Brain imaging (predominant post-central structural or functional deficit. Multifocal cerebral lesions on CT or MRI)

- Laboratory tests indicating brain involvement or inflammatory disorder (such as multiple sclerosis, syphilis, AIDS, and herpes simplex encephalitis).

- RELATIVE DIAGNOSTIC EXCLUSION FEATURES
  - Typical history of chronic alcoholism
  - Sustained hypertension
  - History of vascular disease (such as angina, claudication).

Appendix I. Diagnosis of Dementia with Lewy Bodies[7]

1. The central feature required for diagnosing DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits in tests of attention, frontal-subcortical skills, and visuospatial ability may be especially prominent.
2. Two of the following core features are essential for a diagnosis of probable DLB, and one is necessary for possible DLB:
    a. Fluctuating cognition with pronounced variations in attention and alertness
    b. Recurrent visual hallucinations that are typically well-formed and detailed
    c. Spontaneous motor features of Parkinsonism
3. Features supportive of the diagnosis are
    d. Repeated falls
    e. Syncope
    f. Transient loss of consciousness
    g. Neuroleptic sensitivity
    h. Systematized delusions
    i. Hallucinations in other modalities
4. A diagnosis of DLB is less likely in the presence of
    j. Stroke disease, evident as focal neurologic signs or on brain imaging
    k. Evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture

(See 2005 revision on the following page)

2005 Revision of criteria for diagnosing dementia with Lewy bodies[15]

Table 1 *Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB)*

1. *Central feature* (essential for a diagnosis of possible or probable DLB)

   Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent.

2. *Core* features (two core features are sufficient for a diagnosis of probable DLB, one for possible DLB)

   Fluctuating cognition with pronounced variations in attention and alertness

   Recurrent visual hallucinations that are typically well formed and detailed

   Spontaneous features of parkinsonism

3. *Suggestive features* (If one or more of these is present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features is sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.)

   REM sleep behavior disorder

   Severe neuroleptic sensitivity

   Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging

4. *Supportive features* (commonly present but not proven to have diagnostic specificity)

   Repeated falls and syncope

   Transient, unexplained loss of consciousness

   Severe autonomic dysfunction, e.g., orthostatic hypotension, urinary incontinence

   Hallucinations in other modalities

   Systematized delusions

   Depression

   Relative preservation of medial temporal lobe structures on CT/MRI scan

   Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity

   Abnormal (low uptake) MIBG myocardial scintigraphy

   Prominent slow wave activity on EEG with temporal lobe transient sharp waves

5. A diagnosis of DLB is *less likely*

   In the presence of cerebrovascular disease evident as focal neurologic signs or on brain imaging

   In the presence of any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture

   If parkinsonism only appears for the first time at a stage of severe dementia

6. *Temporal sequence* of symptoms

   DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if it is present). The term Parkinson disease dementia (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease. In a practice setting the term that is most appropriate to the clinical situation should be used and generic terms such as LB disease are often helpful. In research studies in which distinction needs to be made between DLB and PDD, the existing 1-year rule between the onset of dementia and parkinsonism DLB continues to be recommended. Adoption of other time periods will simply confound data pooling or comparison between studies. In other research settings that may include clinicopathologic studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as LB disease or alpha-synucleinopathy.

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