

## **Chapter 19. Parkinson's Disease and Other Extrapyrarnidal Disorders**

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## **I. INTRODUCTORY REMARKS**

Parkinson's disease (PD) is the second most common neurodegenerative disorder of later life. The primary areas of neuropathologic injury are pigmented aminergic neuronal populations - the substantia nigra, locus ceruleus and others. PD causes progressive disability. Disability associated with PD includes not only motor dysfunction, but for many dysautonomia, cognitive changes (ranging from loss of executive function to frank dementia) and depression. There is no known cure nor is there a recognized method for slowing the ongoing degenerative process.

### **I.1. Unfulfilled therapeutic needs**

Currently available therapies are most effective in minimizing the motor dysfunction of PD, through increasing the activity of the nigrostriatal dopamine system, although overall benefit is partial, and not sustained over the years of disease. Development of a treatment with sustained therapeutic benefit over the decades of the disease would be invaluable. In addition, these standard therapies also have disabling and/or dose limiting adverse effects. Acute adverse effects include nausea and hypotension. Chronic adverse effects include dyskinesias (involuntary movements), somnolence, hallucinations or psychosis. In more advanced disease, a progressive diminution in the overall motor benefit, and in the duration of the treatment effect is an additional limitation of some therapeutic approaches. Methods for preventing the development of these disabling adverse effects, or for treating them effectively once developed, are needed. Treatments for the nonmotoric disabilities of PD (such as dysautonomia, cognitive changes and depression) are few, and none are universally effective. Developing effective therapies for these nonmotor features of PD is an emerging area of interest.

Much effort has been directed to the development of treatments that can stop or slow the progression of established disease (neuroprotection), but so far such an agent has not been identified unequivocally. Similarly, no cure is available, and there is no way to delay the onset of PD. These latter questions are the most critical, since they address preventive or curative goals, rather than symptom amelioration.

Other related areas of importance involve pharmacogenetic investigations in PD and developing treatments for "atypical" parkinsonism. Little work has been done to determine whether the genetic makeup of the individual in part determines response to therapy. This would include investigating subgroups with genetic forms of parkinsonism, as well as PD patients with genetic variants of elements of the dopaminergic system (such as metabolic enzymes or receptors). The "atypical" parkinsonian syndromes include less common chronic neurodegenerative disorders with prominent parkinsonian features, such as multiple system atrophy and progressive supranuclear palsy. In contrast to PD, there are no effective therapies for these devastating disorders, although existing antiparkinsonian therapies may provide short-lived partial benefit for a minority of patients.

### **I.2. Unclarified issues related to current treatments**

The majority of studies of antiparkinsonian agents have compared single agents to placebo in order to demonstrate efficacy. Few controlled studies provide evidence to guide the choice of a treatment regimen among the many existing therapies. Controlled studies have rarely compared existing therapies of any type, either those with proposed neuroprotective effects or those with symptomatic effects, either alone or in combination. In addition, little is known regarding the effects of existing therapies within clinical subgroups, defined by demographic characteristics such as age, gender or race/ethnicity or by disease features such as tremor predominance, cognitive function or age at onset. Little is known regarding the benefit of any therapeutic agent for a period of more than a few years. A review of all trials up until the end of 2001 found that the median follow-up period per trial was two years and only 40% of trials in early PD went beyond 12 months. Only two trials (DATATOP and UKPDRG) followed up patients for up to 10

years with only the latter being designed to test differences in mortality. Whether the choice of therapeutic regimen can prevent the development of adverse effects or alter the course of disease remains unresolved. Almost nothing is known regarding the relative effects of any individual therapy on survival in PD.

### **I.3. Needs and justification for developing new drugs**

Despite the number of agents approved for use in PD, neither a risk-free treatment with sustained benefit nor a preventive or curative agent has been identified. Therefore, there is a need for new drug development in all aspects of PD therapy. Moreover, because PD and other late-life neurodegenerative disorders, such as Alzheimer's disease, are thought to share common pathogenic features, there may be potential overlap of effect in some areas – either for primary neuroprotection, or treatment of common symptoms such as cognitive impairment or depression. Moreover, the potential number of cases of PD worldwide is expected to increase with the aging of the population. Most studies from the USA and Western Europe indicate PD prevalence to range from 1 – 2 % among individuals 65 and older, and age-specific prevalence appears to double about every 5-7 years after the age of 65. The numbers of persons in the age group at risk for PD is expected to increase progressively over the next several decades in both the developed and developing world. This expected increase in the numbers of persons affected is also expected for other neurodegenerative disorders such as the atypical parkinsonisms and Alzheimer's disease. A second, unrelated area of potential overlap for dopaminergic agents is in the treatment of restless legs syndrome, estimated to affect between 5 – 15% of the adult population.

### **I.4. Particularities of PD that will influence the protocol of investigation of the drug**

There is no diagnostic test for PD, and diagnosis is based solely on the expertise of the examiner. The greater the expertise of the examiner, the more accurate the diagnosis, as compared to post-mortem examination, but even in the hands of experts, some diagnostic error is expected. This potential for error is greater when the PD is of short duration, and clinical signs are few. Because PD is disabling, most persons can function without therapy only within the first one or two years after diagnosis. This hampers the evaluation of agents proposed to slow, but not stop, disease progression, as the addition of symptomatic therapy confounds the evaluation of a neuroprotective effect judged by clinical criteria. Recently, imaging approaches targeting the nigrostriatal dopamine system have been proposed as adjunctive means for assessing progression of PD, although these, too, may not be independent of the potentially confounding pharmacologic effects of PD treatments. A second aspect of the requirement for symptomatic therapy in moderate or more severe PD is that the efficacy of any agent in this patient population must be evaluated as an adjunct to an established therapy, because comparison to placebo alone would not be ethical. However, comparison of a new drug to placebo is appropriate for patients receiving symptomatic therapy for the first time (sometimes called “de novo” patients), and this design is preferred by both the FDA and the EMEA for new drugs intended for registration as monotherapy. In this special setting, provision for “rescue” with a symptomatic agent may be advisable.

The response to some antiparkinsonian agents, notably those including l-dopa, can vary dramatically over time. Variation can occur over hours or even minutes during the course of a single dose, and can be further modified by conditions such as the time of day, the number of prior doses, the type of concurrent therapy, and the timing and protein content of meals. Similarly, the adverse effects of antiparkinsonian therapies, such as dyskinesias, typically wax and wane during the course of a day. These features must be taken into consideration when choosing the most appropriate outcome measure.

Newer therapies may show modest improvements in motor functions. However, without the collection of data on activities of daily living and quality of life, it is hard to evaluate whether such benefits make much difference to patients and are cost-effective.

## **II. PHASE II STUDIES FOR REGISTRATION OF NEW DRUGS**

### **II.1. Outline a typical development plan**

During Phase II of drug development, candidate therapies are usually tested against placebo, though occasionally other existing treatments, in the disease population of question. Generally, PD clinical trials address two primary impairments, either parkinsonism itself or motor complications that occur as part of the disease and its chronic treatment and take the form of dyskinesias (involuntary movements) or motor fluctuations (poor response to medications). For each, the primary focus can be on the delay of development of impairment or treatment of impairment once developed. Patient selection depends on the primary clinical problem being addressed. For example, studies of delay in clinical progression of parkinsonism focus on early disease and patients are usually on no other medications for Parkinson's disease, whereas treatment protocols for dyskinesias and motor fluctuation usually focus on patients with more advanced disease who are already on multiple antiparkinsonism drugs. Almost all randomized, double-blind, controlled trials in PD are parallel in design.

### **II.2. Short-term studies**

Short-term efficacy trials are usually three to six months with built-in titration and withdrawal phases. In some of these studies, long-term open label continuation phases are included for the acquisition of safety data.

#### **II.2.A. Objectives**

Studies usually are aimed at treating impairment and therefore focus on alleviating parkinsonism itself or improving existing dyskinesias or motor fluctuations.

#### **II.2.B. Primary Endpoints**

For parkinsonism:

- a. Comparison of the Unified Parkinson's Disease Rating Scale (UPDRS) total score in relation to baseline scores.
- b. Comparison of the UPDRS Motor Examination (Part III) can be used as well, or the combined Activities of Daily Living and Motor Examination score (Parts II and III) in relation to baseline scores.
- c. The UPDRS is internationally utilized and has largely replaced earlier scales like the Columbia and Webster scales.
- d. The Hoehn and Yahr scale was formerly used, but it is a non-continuous scale, poorly responsive to interventions, and therefore more frequently used currently to describe patient groups and define entry criteria, rather than serving as a primary end-point.

For motor fluctuations:

- a. Dyskinesias are usually rated with the Abnormal Involuntary Movement Scale, or the Rush Dyskinesia Scale.
- b. Motor fluctuations are measured with at-home diaries for which patients undergo training in the study center on the operational definitions of "ON" (good medication response), "ON with disabling dyskinesias" (good medication response, but with superimposed involuntary movements that interfere with activities), and "OFF" (poor medication response). Reductions in overall OFF time without an increase in ON with dyskinesias indicate improved motor fluctuations. Global measures on motor fluctuations and dyskinesias can be obtained from UPDRS Part IV.

#### **II.2.C. Secondary endpoints**

For parkinsonism:

- a. Hoehn and Yahr stage, the Schwab and England rating scale

- b. Dyskinesias and motor fluctuation as secondary outcomes are measured as described in Primary endpoints
- c. Global scales like the Clinical Global Impression Severity and Clinical Global Impression Change scores are also used. More studies now include disease specific Quality of Life measures, such as the PDQ-39, and PDQUALIF or generic measures such as EuroQol and the SF-36. (It can be argued that quality of life measures should be primary rather than secondary outcomes)

For motor fluctuations or dyskinesias:

- a. Secondary endpoints include UPDRS and all primary endpoints listed under Parkinsonism.

#### **II.2.D. Exploratory endpoints**

Depending on the chemistry of the intervention, exploratory endpoints can include non-motor elements of Parkinson's disease such as depression, cognition, hallucinations, and dysautonomia. Rating scales for all of these are derived from standard scales in the medical literature and have not been developed specifically for Parkinson's disease in most instances.

#### **II.2.E. Study Design**

Randomized double-blind placebo controlled parallel studies are the gold standard. After screening and entry criteria are verified, subjects are randomized and are seen regularly during study-drug intervention and then withdrawn from the drug and seen at a close-out visit. Some studies assign patients to a fixed dose (or doses) of the study drug or placebo and others allow dose titration to a maximal tolerated dose that is pre-determined. Patients are usually seen weekly for the first four weeks or through the titration phase, then at longer intervals during chronic treatment with an end-of-exposure visit and a final visit one week after drug-exposure cessation.

#### **II.2.F. Study population**

The study population depends on the question being addressed:

**Parkinsonism:** In early disease, the subjects are usually on no treatment for parkinsonian signs at the time of enrollment and receive monotherapy with either placebo or study drug. In moderate and advanced disease, patients are enrolled who have inadequate efficacy from their current drug therapy and can often be on levodopa or another agent with a pharmacological mechanism that is different from the study drug under question.

**Motor complications:** In advanced disease where the focus is usually on motor complications, patients must have dyskinesias and/or motor fluctuations of sufficient severity to warrant intervention.

Patients with another illness sufficiently severe as to jeopardize participation in the study or interpretation of results are excluded. Patients must pass screening tests for depression or dementia.

#### **II.2.G. Specific Inclusion Criteria**

Parkinson's disease is defined clinically based on various diagnostic standards, such as the UK Brain Bank criteria. Inclusion criteria for admitting mild, moderate or advanced patients with PD are primarily based on Hoehn and Yahr stage and medication exposure. Early monotherapy studies restrict subjects to Stage I-III (unilateral or bilateral disease that may include mild balance problems but no spontaneous falling) and sometimes to Stage I-II only (no balance problems). Studies of drugs that are added to current treatment in moderate Parkinson's disease usually restrict patients to Stage II-IV, and therefore include patients with poor balance. For studies of motor complications, inclusion criteria usually require baseline scores for the target problem sufficiently severe enough so that patients are likely to deteriorate during the trial. For dyskinesias, a minimal baseline score on the AIMS (variably 7-10) is often used, and for motor fluctuations, inclusion often requires a minimal 25% or more OFF time on diaries or the UPDRS Part IV for study entry. These criteria are introduced to avoid "floor effects".

### **II.2.H. Specific Exclusion Criteria**

In each trial, patients cannot have an allergy to the product being tested. Current exposure to various medications and past exposure to levodopa may exclude subjects from the early monotherapy trials. Because dopamine is a precursor to melanin, studies of drugs that alter levodopa bioavailability or metabolism exclude patients with a past history of melanoma. Almost no intervention studies permit Stage V patients who are wheelchair-bound at their peak treatment. Those with parkinsonian syndromes other than PD are typically excluded.

### **II.2.I. Tools for assessing Primary Endpoints**

- b. For Parkinsonism: UPDRS, total or Part III, or Parts II + III
- c. For Dyskinesias: AIMS, Rush Dyskinesia Scale
- d. Motor Fluctuations: Home diaries, Part IV of UPDRS

### **II.2.J. Specific criteria for early withdrawal and discontinuation**

The investigator will discontinue a subject before completion of the study if consent is withdrawn, if the double-blind code is broken, if it is medically unacceptable to continue treatment due to adverse events or other reasons, or if pregnancy occurs.

### **II.2.K. Data analysis methods**

The analysis of efficacy variables is based on the intention-to-treat strategy. All statistical tests are two-sided and p values <0.05 are considered statistically significant, though sometimes adjusted p-values are used to account for multiple comparisons. Many statistical methods can be used for the primary and secondary endpoints and include analysis of variance, analysis of covariance, and logistic regression.

## **II.3. Long-term studies**

Long-term efficacy trials are usually nine months to five years.

### **II.3.A. Objectives**

Studies are usually aimed at delaying the development of impairment, e.g. progressive parkinsonism, motor fluctuations or dyskinesias.

### **II.3.B. Primary Endpoints**

For delay in progression of parkinsonism:

- a. Need to start dopaminergic therapy.
- b. Prespecified increase in a standard measurement tool of parkinsonism (UPDRS)

For delay in development of motor fluctuations and dyskinesias

- a. Time to development of these complications
- b. % of the population at given time points who have the complication

### **II.3.C. Secondary endpoints**

- a. For Delay in Parkinsonism Progression: secondary endpoints can include the primary endpoints for Delay in Development of Motor Fluctuations and Dyskinesias described above.
- b. For Delay in Development of Motor Fluctuations and Dyskinesias, secondary endpoints can include the primary endpoints for Delay in Parkinsonism Progression described above
- c. For all studies, other secondary endpoints are UPDRS scores, Hoehn and Yahr stage, Schwab and England rating scale score at specified time points.
- d. For all studies, global secondary endpoints include Clinical Global Impression Severity and Clinical Global Impression Change scores as well as disease specific Quality of Life measures, such as the PDQ-39, and PDQUALIF or generic measures, such as the EuroQol and SF-36.

- e. Increasingly, long-term studies are being accompanied by neuroimaging markers using beta CIT SPECT scanning or 18-F-dopa PET scanning indices.

#### **II.3.D. Exploratory endpoints**

Depending on the chemistry of the intervention, exploratory endpoints can include non-motor elements of Parkinson's disease such as depression, cognition, hallucinations, and dysautonomia. Rating scales for all of these are derived from standard scales in the medical literature and have not been developed specifically for Parkinson's disease in most instances.

#### **II.3.E. Study design**

Randomized double-blind placebo controlled parallel studies are the gold standard. Studies usually involve the enrollment of several hundred patients and therefore multiple centers are usually involved. After screening and entry criteria are verified, subjects are randomized and are seen usually one month after study entry and thereafter on a three or six month schedule regularly. A final visit shortly after drug-exposure cessation is standard for safety monitoring and allows the detection of withdrawal effects on primary and secondary outcomes.

#### **II.3.F. Study population**

The study population depends on the question being addressed: Delay in Parkinsonism: In early disease, the subjects are usually on no treatment for parkinsonian signs at the time of enrollment and receive monotherapy with either placebo or study drug. In moderate disease, patients are enrolled who have inadequate efficacy from their current drug therapy and can often be on levodopa or another agent with a pharmacological mechanism that is different from the study drug under question. Because these studies are long in duration, some protocols permit addition of levodopa or other drugs with continuation in the study even after the primary endpoint is reached (e.g. need for starting dopaminergic therapy) so that secondary endpoints can still be measured.

Delay in Motor complications: These studies enroll patients who at baseline are in need of dopaminergic therapy. The study randomizes patients to standard dopaminergic therapy, usually levodopa, or the new study drug. Because these studies are long in duration, some protocols permit addition of additional levodopa in both groups if inadequate efficacy of treatment is encountered in the midst of the study period.

#### **II.3.G. Specific Inclusion Criteria**

Parkinson's disease is defined clinically with diagnostic standards, such as UK Brain Bank criteria. Other parkinsonian syndromes that are not PD are not intentionally included.

- a. Delay in Progression of Parkinsonism: Inclusion criteria for long-term studies are primarily based on short duration of PD (less than five years of symptoms or diagnosis), Hoehn and Yahr stage (usually less than Stage III, meaning no significant postural reflex compromise) and medication exposure (no dopaminergic medication and often other requirements such as no Coenzyme Q, no antidepressants).
- b. Delay in Development of motor complications: Inclusion criteria for long-term studies of this type enroll PD patients starting dopaminergic therapy because of need to treat the symptoms of PD. Such patients must be Stage I-III (unilateral or bilateral disease that may include mild balance problems but no spontaneous falling). Because the studies examine the onset time to motor complications, patients must not have any of these signs at baseline.
- c. For both types of studies, neuroimaging data are often an intrinsic part of the protocol, so patients must be able and willing to undergo these scans, and must not have claustrophobia or other limits that preclude participation in these tests.

#### **II.3.H. Specific Exclusion Criteria**

In each trial, patients cannot have an allergy to the product being tested. Past medication exposure, especially to levodopa, may exclude subjects. Because dopamine is a precursor to melanin, some studies

exclude patients with a past history of melanoma. Those with parkinsonian syndromes other than PD are typically excluded. Patients with another illness sufficiently severe as to jeopardize participation in the study or interpretation of results are excluded. Patients who fail screening tests for dementia and depression are typically excluded.

### **II.3.I. Tools for assessing Primary Endpoints**

- a. For Delay in Parkinsonism: Clinician's assessment of the necessity to start dopaminergic therapy (for patient safety, job security, or quality of life), UPDRS, total or Part III, or Parts II + III
- b. For Dyskinesias: Onset of first dyskinesias as assessed by diaries or by Part IV of the UDPRS, AIMS, Rush Dyskinesia Scale
- c. Motor Fluctuations: Onset of first OFF period by Home diaries or by Part IV of UPDRS

### **II.3.J. Specific criteria for early withdrawal and discontinuation**

The investigator will discontinue a subject before completion of the study if consent is withdrawn, if the double-blind code is broken, if it is medically unacceptable to continue treatment due to adverse events or other reasons, or if pregnancy occurs.

### **II.3.K. Data analysis methods**

The analyses are usually based on the intention-to-treat strategy. All statistical tests are two-sided and p values  $<0.05$  are considered statistically significant. The primary analysis for studies involving Delay in the Development of Clinical Progression of Parkinsonism or Motor Complications evaluate survival and calculate cumulative probability of reaching each end point. Differences in outcome are expressed as hazard functions, usually with the Kaplan-Meier estimate, which can be displayed graphically. It is important to censor individuals who either drop out or have limited follow-up. Hypothesis testing between groups can use the log-rank test or Cox's proportional hazard regression modeling, which allows adjustment for multiple covariates.

## **III. PHASE III STUDIES FOR REGISTRATION OF NEW DRUGS**

### **III.1. Outline a typical development plan**

Phase III trials are conducted after initial demonstration of safety and efficacy of a drug. These trials investigate larger numbers of patients, to obtain further information on efficacy and safety. A primary goal of the Phase III development plan is to obtain the information necessary for product registration. Typical studies extend the observations from Phase II studies, often employing similar study designs, but with larger numbers of subjects and longer periods of observation. Because Parkinson's disease is relatively uncommon, Phase III studies must invariably involve multiple centers in order to allow timely accrual.

Phase III trials will address the same two primary impairments – parkinsonism, or motor complications associated with chronic treatment (dyskinesias, motor fluctuations). The aim can be either to delay or prevent the development or slow the progression of the impairment or to provide symptomatic relief.

### **III.2 Long-term studies to slow or halt progression of parkinsonism**

Conclusive demonstration that a drug can stop or slow progression of parkinsonism remains a challenge. The design of a trial with this objective must take into account some limitations. First, there is no biomarker of Parkinson's disease progression. Primary endpoints are based on clinical measures of parkinsonism. Because most people with Parkinson's disease require symptomatic therapy within several months to a few years of diagnosis, such studies typically enroll only those early in the course of disease who do not require symptomatic therapy. This design avoids the confounding effect of symptomatic

treatment on the efficacy endpoint measures. No alternative marker of disease has yet been accepted as a primary endpoint to assess progression of parkinsonism.

Demonstration of efficacy in slowing or stopping progression in those with more advanced disease, who require symptomatic therapy, presents even greater challenges. Few studies have attempted to demonstrate efficacy in this population. In those with more advanced parkinsonism, clinical measures of parkinsonism are confounded by the effects of symptomatic therapy, but withdrawal of the therapy is potentially harmful. Follow-up of those with more advanced disease until death or severe disability may pose practical difficulties. Some countries are fortunate in enabling research study participants to be prospectively “flagged” on a central database (e.g. National Health Service Central Register, UK) that automatically informs researchers when a participant has died and supplies a copy of the death certificate. A typical development plan to investigate a drug proposed to slow the progression of parkinsonism will include several multicenter, double blind, placebo-controlled trials investigating the safety and efficacy of one or several doses of the drug. Monotherapy trials are the norm. Patients are recently diagnosed and not in need of symptomatic therapy. Prior exposure to symptomatic antiparkinsonian therapy is precluded, or limited to a short time, to avoid confounding. Other agents proposed to slow the progression of parkinsonism are excluded. Because this type of drug would be expected to be used for many years, or even for the entire duration of disease, safety monitoring should allow detection of events expected to occur at moderate frequency (0.5 – 5%). In general, around 1200-1500 persons exposed in short and long term studies should be adequate to detect differences of around 2 to 3% across groups. To detect adverse events occurring after prolonged use of the drug, duration of monitoring should be at least 12 months for some subjects. Depending on the specific agent, special safety monitoring may be indicated.

### **III.2.A. Objectives**

Study goals typically are to slow or stop progression of parkinsonism

### **III.2.B. Primary Endpoints**

Efficacy:

- a. Need to start symptomatic antiparkinsonian therapy; or
- b. A prespecified worsening in a standard clinical assessment instrument, usually the UPDRS

Safety:

- a. All adverse events;
- b. Depending on the specific agent, monitoring special safety endpoints may be indicated. For example, agents thought to block apoptotic neuronal cell death may conceivably also present an increased risk of neoplasm, and special monitoring procedures for cancer may be appropriate.

### **III.2.C. Secondary Endpoints**

- a. Clinical assessment measures of parkinsonism, including UPDRS (if not a primary endpoint measure), Hoehn and Yahr stage, Schwab and England;
- b. Global measures such as need to start symptomatic therapy (if not a primary endpoint), Clinical Global Impression Severity or Change, and disease-specific Quality of Life measures, such as the PDQ-39 or PDQUALIF or generic measures such as EuroQol and SF-36;
- c. Neuroimaging outcomes measuring uptake of ligands specific to the dopamine system, such as [<sup>123</sup>I]β-CIT (2β-carbomethoxy-3β-[4-iodophenyl]) and single photon positron emission tomography (SPECT) or [<sup>18</sup>F]-dopa and positron emission tomography (PET) scanning indices.

### **III.2.D. Exploratory endpoints**

- a. Endpoints targeting nonmotor features of Parkinson’s disease, such as cognition, dysautonomia, depression;
- b. Endpoints investigating response to symptomatic therapy once initiated;

- c. Endpoints investigating development of the complications of chronic dopaminergic therapy (dyskinesias, fluctuations, hallucinations or psychosis)
- d. Although death is a logical endpoint when investigating agents thought to alter the course of disease, the long disease duration (10 or more years on average, depending on the age at onset), makes death an impractical outcome for many drug development plans.

### **III.2.E. Study Design**

Randomized double-blind placebo controlled parallel studies are the gold standard. Individual studies generally involve the enrollment of at least 300 patients and therefore multiple centers are needed.

Because there is inevitable subjectivity in endpoint determination, it is almost always desirable to require that the primary outcome measure be determined by the same rater, at a minimum for key time points (such as enrollment and endpoint). It may be desirable to identify specific raters within a center and/or to specify a required level of expertise with the primary efficacy measure. A blocked randomization, either by investigator or by center, is another approach to minimize the effect of between-rater variability in end point determination.

To avoid “unblinding” and the potential for biased end point assessment, two raters may be used -- a “treating” investigator who evaluates the patient at each visit, and a “blinded” investigator who determines performance on study primary outcome measures only at key visits, and is otherwise prohibited from knowledge of the subject. The use of video-assessment enables a core group of central raters to assess patients across a wide geographical distribution, but may be problematic for some impairments e.g. rigidity

Subjects are typically assessed 1 – 6 weeks after the initiation of study drug, depending on the safety and pharmacology of the specific agent. Subsequent visits typically occur at 3-6 month intervals. Telephone follow up for safety monitoring may be planned between in-person visits. The duration of exposure for any one individual will vary depending on the proposed mechanism of the drug under development, but a minimum of 9 months follow up is though necessary to demonstrate efficacy in slowing the progression of parkinsonism.

One or more visits after drug-exposure cessation is standard for safety monitoring. When the drug has known or suspected symptomatic benefit in parkinsonism, the primary outcome measurement may be most easily interpreted only after study drug has been withdrawn. The symptomatic benefit may be mild, and only identifiable when symptoms worsen after drug withdrawal. The primary efficacy outcome may at times be determined at an interval after withdrawal of the drug under development. When planning the timing of post-treatment assessments, it will be important to consider the pharmacology of the drug under study, so that the study drug is washed out when assessments are performed.

Follow up is often continued after primary efficacy data have been obtained. Extended follow up can be especially valuable in monitoring safety, and to assess secondary outcomes such as the development of dyskinesia, motor fluctuations or psychosis.

### **III.2.F. Study population**

Subjects typically have recently diagnosed Parkinson’ disease, not requiring symptomatic therapy and with little or no prior exposure to symptomatic or proposed neuroprotective therapies. Because Parkinson’s disease is diagnosed only by clinical criteria, and the full complement of diagnostic signs may not manifest for several years, it is expected that a percentage of those meeting diagnostic criteria with recently diagnosed Parkinson’s disease will be misclassified. Experts with greater familiarity with Parkinson’s disease have greater long-term diagnostic accuracy, but some error is inevitable. The greater potential for misclassification in early disease should be considered in determining sample size. Whilst misclassification may result in attenuated effect estimates, assuming no therapeutic benefit for the patients

who have been misdiagnosed, this result may be a more realistic estimate of treatment benefits outside trials, where expert diagnosis may not always be available prior to initiating therapy.

### **III.2.G. Specific Inclusion Criteria**

- a. Parkinson's disease is defined clinically using published diagnostic standards, such as the UK Brain Bank and NIH criteria. These criteria exclude those with signs suggesting other parkinsonian syndromes.
- b. Disease duration is typically less than five years after diagnosis. Symptom duration may be used, although this measure is dependent on patient report and may be less reliable.
- c. Symptomatic treatment must not be needed in the opinion of the subject and the investigator. Enrolling subjects would need to be comfortable without symptomatic therapy if parkinsonism did not progress.
- d. Mild disease severity defined using clinical criteria, such as Hoehn and Yahr stage less than III. Other clinical measures such as tremor scores or Schwab and England scores may also be used.
- e. No or limited prior treatment with drugs proposed to slow disease progression (e.g., selegiline, coenzyme Q10).
- f. No or limited prior treatment with symptomatic antiparkinsonian treatments.
- g. If imaging is a secondary outcome, patients must be able and willing to undergo these scans, and must not have claustrophobia or other limits that preclude participation in these tests. In many cases, only a subgroup of subjects participate in the imaging study.

### **III.2.H. Specific Exclusion Criteria**

- a. Current treatment with drugs that could alleviate parkinsonism (e.g., dopaminergic, anticholinergic drugs). In early Parkinson's disease, the appropriate washout period for the available symptomatic therapies is not well established. Generally a washout period of at least 4 weeks is desirable, in order to avoid excess early terminations due to enrollment of subjects not able to function without antiparkinsonian treatment.
- b. Current treatment with drugs that could worsen (e.g., most antipsychotics, some antiemetics) parkinsonism
- c. Any serious illness that may affect participation
- d. Known allergy to study drug or related compounds
- e. Use of medication thought to interact with study drug
- f. At risk for an adverse effect of a specific drug

### **III.2.I. Tools for assessing Primary Endpoints**

The endpoints are determined by the investigator using clinical skills. Familiarity with the disease and the specific instruments used is therefore critical to the integrity of the study endpoint. Training in the use of the endpoint instruments is desirable.

### **III.2.J. Specific criteria for early withdrawal and discontinuation**

The investigator will discontinue a subject before completion of the study if consent is withdrawn, if the double-blind code is broken, if it is medically unacceptable to continue treatment due to adverse events or other reasons, or if pregnancy occurs. A special case occurs when the primary endpoint measure is the investigator-determined need for symptomatic therapy. If the subject initiates symptomatic therapy prior to the investigator-determined end point, it may be preferable to continue to observe the subject on study drug and symptomatic therapy when possible, in order to obtain additional safety information.

### **III.2.K. Data analysis methods**

The primary analyses are based on the intention-to-treat strategy. All statistical tests are two-sided. Generally p values <0.05 are considered statistically significant. The primary analysis approach typically evaluates survival and calculates cumulative probability of reaching each end point. Differences in

outcome are expressed as hazard functions, usually with the Kaplan-Meier estimate, which can be displayed graphically. It is important to censor individuals who either drop out or have limited follow-up. Hypothesis testing between groups can use the log-rank test or Cox's proportional hazard regression modeling, which allows adjustment for multiple covariates.

### **III.3 Long term studies to provide symptomatic improvement in parkinsonism**

While there are a number of agents with demonstrated antiparkinsonian efficacy, none provides sustained symptomatic benefit throughout the course of this lifelong disorder. The acute and chronic side effects of established therapies are additional sources of concern. Trials of new therapies should be designed to address these concerns, with the goal of developing new drugs with more favorable efficacy and side effect profiles.

A typical development plan to investigate a drug proposed to provide symptomatic improvement of parkinsonism will include several multicenter, double blind, placebo-controlled trials investigating the safety and efficacy of one or several doses of the drug. Monotherapy trials, comparing the study drug to placebo, will in most cases be limited to early disease, enrolling "de novo" patients receiving symptomatic therapy for the first time. In advanced Parkinson's disease, the study-drug will typically be given as adjunctive therapy, and compared to placebo given adjunctively, as it would be unethical to withdraw existing therapies. Most commonly, the efficacy of the new agent when given in combination with a dopaminergic agent (usually l-dopa plus decarboxylase inhibitor) is compared to the efficacy of placebo combined with the same agent. The addition of an adjunctive antiparkinsonian agent can result not only in improvement of parkinsonism, but also in the new onset of dopaminergic side effects, or the worsening of existing side effects, such as dyskinesias or psychosis. Specific monitoring for this possibility, and provisions for adjustment of therapies, appropriate to the specific drugs, should be included in the study protocol. In addition a global measure such as a disease specific quality of life measure is essential as it is otherwise impossible to interpret an improvement in motor function coupled with a deterioration in side effects. An alternative design compares the new drug to standard therapy. Design of such studies is often difficult due to uncertainty regarding equivalence of dosage. Some regulatory agencies may be less receptive to comparison study designs. As for all development plans, close contact with scientists in the regulatory agencies is essential.

Safety evaluations should take into account the chronic use expected for most drugs in this category. Therefore, safety monitoring should allow detection of events expected to occur at moderate frequency (0.5 – 5%). In general, around 1200-1500 persons exposed in short and long term studies should be adequate to detect differences of around 2 to 3% across groups. To detect adverse events occurring after prolonged use of the drug, duration of monitoring should be at least 12 months for some subjects. Depending on the specific agent, special safety monitoring may be indicated.

#### **III.3.A. Objectives**

Studies are aimed at treating impairment due to parkinsonism or improving existing dyskinesias or motor fluctuations.

#### **III.3.B. Primary Endpoints**

For parkinsonism:

- a. Comparison of the Unified Parkinson's Disease Rating Scale (total score) relative to baseline scores.
- b. Comparison of the UPDRS Motor Examination (Part III) can be used as well, or the combined Activities of Daily Living and Motor Examination score (Parts II and III) relative to baseline scores. The UPDRS Part I includes nonmotor features and does not distinguish between primary features of disease and drug-induced side effects. For this reason, some prefer not to use Part I when assessing a new drug as adjunctive therapy along with a dopaminergic agent.
- c. The UPDRS is internationally utilized and has largely replaced earlier scales like the Columbia and Webster scales.

- d. The Hoehn and Yahr scale was formerly used, but it is a non-continuous scale, poorly responsive to interventions, and therefore more frequently used currently to describe patient groups and define entry criteria, rather than serving as a primary end-point.

For motor fluctuations:

- a. Dyskinesias are usually rated with the Abnormal Involuntary Movement Scale (AIMS), or the Rush Dyskinesia Scale. Dyskinesias are often intermittent, and an at-home diary may be used. However, a self-report diary will likely identify only dyskinesias of moderate to severe intensity, as mild dyskinesias may be missed by the patient experiencing them.
- b. Motor fluctuations are measured with at-home diaries for which patients undergo training in the study center on the operational definitions of “ON” (good medication response), “ON with disabling dyskinesias” (good medication response, but with superimposed involuntary movements that interfere with activities), and “OFF” (poor medication response). Decrease in overall OFF time without an increase in ON with dyskinesias indicate improved motor fluctuations.
- c. Global measures on motor fluctuations and dyskinesias can be obtained from UPDRS Part IV.

### **III.3.C. Secondary endpoints**

For parkinsonism:

- a. Hoehn and Yahr stage, the Schwab and England rating scale
- b. Dyskinesias and motor fluctuation as secondary outcomes are measured as described in Primary endpoints
- c. Global scales like the Clinical Global Impression Severity and Clinical Global Impression Change scores are also used, as well as disease specific Quality of Life measures, such as the PDQ-39, and PDQUALIF and generic measures such as the EuroQol and SF-36.

For motor fluctuations or dyskinesias:

- a. Secondary endpoints include UPDRS and all primary endpoints listed under Parkinsonism.

### **III.3.D. Exploratory endpoints**

Depending on the chemistry of the intervention, exploratory endpoints can include non-motor elements of Parkinson’s disease such as depression, cognition, somnolence, hallucinations or dysautonomia. Rating scales for all of these are derived from standard scales in the medical literature. In most cases these have not been developed specifically for Parkinson’s disease.

### **III.3.E. Study Design**

Randomized, double-blind, placebo-controlled, parallel group studies are the standard. After screening and entry criteria are verified, subjects are randomized and are seen regularly during study-drug intervention and then withdrawn from the drug and seen at a close-out visit. Some studies assign patients to one or more fixed doses or placebo. Other designs allow dose titration to an efficacy endpoint (e.g., loss of motor fluctuations) or to a pre-determined maximum, if tolerated. Visit frequency is determined in part by the pharmacologic and safety profile of the study drug, and the endpoint(s) of interest. Weekly or biweekly visits are typical during the titration phase, followed by longer between visit intervals, such as 4 – 12 weeks. There is an end-of-exposure visit and a final visit one week after drug-exposure cessation.

Because there is inevitable subjectivity in endpoint determination, it is almost always desirable to require that the primary outcome measure be determined by the same rater, at a minimum for key time points (such as enrollment and endpoint). It may be desirable to identify specific raters within a center and/or to specify a required level of expertise with the primary efficacy measure. A blocked randomization, either by investigator or by center, is another approach to minimize the effect of between-rater variability in end point determination.

To avoid “unblinding” and the potential for biased end point assessment, two raters may be used -- a “treating” investigator who evaluates the patient at each visit, and a “blinded” investigator who determines performance on study primary outcome measures only at key visits, and is otherwise prohibited from knowledge of the subject. The use of video-assessment enables a core group of central raters to assess patients across a wide geographical distribution, but may be problematic for some impairments e.g. rigidity.

Follow up is often continued after primary efficacy data have been obtained. Extended followup can be especially valuable in monitoring safety, and to assess chronic efficacy.

### **III.3.F. Study population**

The study population depends on the question being addressed:

**Parkinsonism:** In early disease, the subjects are usually on no treatment for parkinsonian signs at the time of enrollment and receive monotherapy with either placebo or study drug. In moderate and advanced disease, patients are enrolled who have inadequate efficacy from their current drug therapy. Current therapy is typically levodopa or another agent with a pharmacological mechanism that is different from the study drug under question. When developing a drug for adjunctive use, the determination of what standard therapies will be acceptable must be made. Most commonly new adjunctive treatments are compared to placebo in patients receiving levodopa.

**Motor complications:** In advanced disease where the focus is usually on motor complications, patients must have dyskinesias and/or motor fluctuations of sufficient severity to warrant intervention.

Patients with another illness sufficiently severe as to jeopardize participation in the study or interpretation of results are excluded. Patients who fail screening tests for dementia and depression are typically excluded.

### **III.3.G. Specific Inclusion Criteria**

Parkinson’s disease is defined clinically based on various diagnostic standards, such as UK Brain Bank criteria. Inclusion criteria for admitting mild, moderate or advanced patients with PD are primarily based on Hoehn and Yahr stage and medication exposure. Early monotherapy studies restrict subjects to Stage I-III (unilateral or bilateral disease that may include mild balance problems but no spontaneous falling) and sometimes to Stage I-II only (no balance problems). Studies of drugs that are added to standard treatment in moderate Parkinson’s disease usually restrict patients to Stage II-IV, and therefore include patients with poor balance. For studies of motor complications, inclusion criteria usually require baseline scores for the target problem sufficiently severe enough to allow change determination during the trial. For dyskinesia, a minimal baseline score on the AIMS (variably 7-10) is often used, and for motor fluctuations inclusion often requires a minimal 25% or more OFF time on diaries or the UPDRS Part IV for study entry. These criteria are introduced to avoid “floor effects”. The existing antiparkinsonian drug regimen should be optimized before determining eligibility.

### **III.3.H. Specific Exclusion Criteria**

In each trial, patients cannot have an allergy to the product being tested. Current exposure to various medications and past exposure to levodopa may exclude subjects from the early monotherapy trials. Because dopamine is a precursor to melanin, studies of drugs that alter levodopa bioavailability or metabolism exclude patients with a past history of melanoma. Almost no intervention studies permit Stage V patients who are wheelchair-bound at their peak treatment. Those with parkinsonian syndromes other than PD are typically excluded.

### **III.3.I. Tools for assessing Primary Endpoints**

- b. For Parkinsonism: UPDRS, total or Part III, or Parts II + III
- c. For Dyskinesias: AIMS, Rush Dyskinesia Scale
- d. Motor Fluctuations: Home diaries, Part IV of UPDRS

### **III.3.J. Specific criteria for early withdrawal and discontinuation**

The investigator will discontinue a subject before completion of the study if consent is withdrawn, if the double-blind code is broken, if it is medically unacceptable to continue treatment due to adverse events or other reasons, or if pregnancy occurs.

### **III.3.K. Data analysis methods**

The analysis of efficacy variables is based on the intention-to-treat strategy. All statistical tests are two-sided and p values <0.05 are considered statistically significant. Many statistical methods can be used for the primary and secondary endpoints and include analysis of variance, analysis of covariance, and logistical regression.

## **III.4. Long term studies to delay the development of dyskinesias or motor fluctuations**

Dyskinesias and motor fluctuations are inevitable side effects for most patients requiring levodopa. These side effects are much less commonly associated with other antiparkinsonian agents. However, the majority of persons with Parkinson's disease eventually require levodopa therapy.

### **III.4.A. Objectives**

Studies usually are aimed at delaying the development of motor fluctuations, dyskinesias or both.

### **III.4.B. Primary Endpoints**

- a. Time to development of these complications
- b. % of the population at given time points who have the complication

### **III.4.C. Secondary endpoints**

- a. Measures of parkinsonian impairment, such as UPDRS scores, Hoehn and Yahr stage, Schwab and England rating scale
- b. Clinical Global Impression Severity and Clinical Global Impression Change
- c. Quality of Life measures, such as the PDQ-39, and PDQUALIF.
- d. Neuroimaging outcomes measuring uptake of ligands specific to the dopamine system, such as [<sup>123</sup>I]β-CIT (2β-carbomethoxy-3β-[4-iodophenyl]) and single photon positron emission tomography (SPECT) or [<sup>18</sup>F]-dopa and positron emission tomography (PET) scanning indices.

### **III.4.D. Exploratory endpoints**

Depending on the chemistry of the intervention, exploratory endpoints can include non-motor elements of Parkinson's disease such as depression, cognition, hallucinations, and dysautonomia. Rating scales for all of these are derived from standard scales in the medical literature and have not been developed specifically for Parkinson's disease in most instances.

### **III.4.E. Study Design**

Randomized double-blind placebo controlled parallel studies are the standard. Studies usually involve the enrollment of several hundred patients and therefore multiple centers are usually involved. After screening and entry criteria are verified, subjects are randomized and are seen usually one month after study entry and thereafter at three or six month intervals. A final visit shortly after drug-exposure cessation is standard for safety monitoring and allows the detection of withdrawal effects on primary and secondary outcomes.

### **III.4.F. Study population**

These studies enroll patients who at baseline are in need of symptomatic antiparkinsonian therapy. The study randomizes patients to standard dopaminergic therapy, usually levodopa, or the new study drug. Because these studies are long in duration, some protocols permit addition of additional levodopa in both groups if inadequate efficacy of treatment is encountered in the midst of the study period.

#### **III.4.G. Specific Inclusion Criteria**

Parkinson's disease is defined clinically with diagnostic standards, including UK Brain Bank criteria. Other parkinsonian syndromes that are not PD are excluded. PD patients must be newly in need of symptomatic antiparkinsonian therapy, typically Hoehn and Yahr Stage II or III. Patients should have no prior exposure or very minimal prior exposure to dopaminergic drugs and should not have motor fluctuations or dyskinesias.

If neuroimaging endpoints are important to the study design, patients must be able and willing to undergo these scans, and must not have claustrophobia or other limitations that preclude participation in these tests.

#### **III.4.H. Specific Exclusion Criteria**

In each trial, patients cannot have an allergy to the product being tested. Past medication exposure, especially to levodopa, may exclude subjects. Because dopamine is a precursor to melanin, some studies exclude patients with a past history of melanoma. Parkinsonian patients who carry other diagnoses besides Parkinson's disease are excluded.

#### **III.4.I. Tools for assessing Primary Endpoints**

- a. For Dyskinesias: Onset of first dyskinesias as assessed by diaries or by Part IV of the UDPRS, AIMS, Rush Dyskinesia Scale
- b. Motor Fluctuations: Onset of first OFF period by Home diaries or by Part IV of UPDRS

#### **III.4.J. Specific criteria for early withdrawal and discontinuation**

The investigator will discontinue a subject before completion of the study if consent is withdrawn, if the double-blind code is broken, if it is medically unacceptable to continue treatment due to adverse events or other reasons, or if pregnancy occurs.

#### **III.4.K. Data analysis methods**

The analyses are based on the intention-to-treat strategy. All statistical tests are two-sided and p values <0.05 are considered statistically significant, though sometimes adjusted p-values are used to account for multiple comparisons. The primary analysis for studies involving Delay in the Development of Motor Complications evaluates survival and calculates cumulative probability of reaching each end point. Differences in outcome are expressed as hazard functions, usually with the Kaplan-Meier estimate, which can be displayed graphically. It is important to censor individuals who either drop out or have limited follow-up. Hypothesis testing between groups can use the log-rank test or Cox's proportional hazard regression modeling, which allows adjustment for multiple covariates.

### **IV. OTHER STUDIES (NEW INDICATION TRIALS, PRAGMATIC TRIALS)**

#### **IV.1 Special clinical problems**

Outside of the primary motor elements of PD (parkinsonism and motor complications), PD patients experience a number of other disabilities, including hallucinations, dementia, depression, dysautonomia, sexual dysfunction, and fatigue. Drugs that are useful in for treating these symptoms in other medical contexts can be tested in PD through randomized double-blind placebo-controlled trials of PD subjects with the target problem. The example of hallucinations is provided, as a prototype, because it has been studied more than the other special clinical problems listed. For each of the other conditions, similar studies can be performed using PD patients with the target problem and appropriately designed measurement tools adapted from other medical fields.

## **IV.2. Hallucinations**

### **IV.2.A. Objectives**

Reduce the frequency or severity of hallucinations in drug-treated patients with chronic PD and hallucinations.

### **IV.2.B. Primary Endpoints**

Change scores on standardized measures of hallucinations or global psychiatric disturbance.

### **IV.2.C. Secondary endpoints**

Because drugs that improve hallucinations generally block dopamine receptors, the risk of aggravating PD is substantive and therefore secondary endpoints include standard assessments of parkinsonism, including UPDRS and Hoehn and Yahr stage.

### **IV.2.D. Exploratory endpoints**

Scores on inventories for Depression, Cognition, and Quality of Life.

### **IV.2.E. Study Design**

Open label exploratory and double blind placebo-controlled or clozapine-controlled trials have been conducted. These studies are usually short-term (4 weeks to 3 months), and parallel in design.

### **IV.2.F. Patient sample**

Subjects with chronic hallucinations, with severity and frequency defined by clinical judgment as in need of treatment or by specific scores on screening tests like the Hallucination and Delusion items of the Neuropsychiatric Inventory, are enrolled in studies of agents shown to be useful against hallucinations in psychiatric populations, usually schizophrenia. Traditionally, drug dosage ranges in PD are up to 100 times less than in schizophrenia.

### **IV.2.G. Specific Inclusion Criteria**

Parkinson's disease is defined clinically based on various diagnostic standards, such as UK Brain Bank criteria. Inclusion criteria must establish that hallucinations began after chronic exposure to dopaminergic drugs in order to exclude the contamination of the sample by subjects with Dementia with Lewy Bodies. Entry criteria must establish that hallucinations are frequent and severe enough at baseline to warrant intervention and that scores on the baseline hallucination assessment are high enough to permit detection of change with the intervention.

### **IV.2.H. Specific Exclusion Criteria**

In each trial, patients cannot have an allergy to the product being tested. Current exposure to other treatments for hallucinations is not permitted and usually an abstinence from such drugs for a minimum of 4 weeks is required. Almost no intervention studies permit Stage V patients who are wheelchair-bound at their peak treatment. Parkinsonian patients who carry other diagnoses besides Parkinson's disease are excluded.

### **IV.2.I. Tools for assessing Primary Endpoints**

Specific hallucination scales includes the Scale for Positive Symptoms (SAPS), the Parkinson Psychosis Scale, Item I (Thought Disorder) of Part I of the UPDRS, and individual items on various scales including the Neuropsychiatric Inventory. Global scales include the Brief Psychiatric Rating Scale, total Part I score of the UPDRS, and the Clinical Global Impressions scale.

### **IV.2.J. Specific criteria for early withdrawal and discontinuation**

The investigator will discontinue a subject before completion of the study if consent is withdrawn, if the double-blind code is broken, if it is medically unacceptable to continue treatment due to adverse events or other reasons, or if pregnancy occurs.

#### **IV.2.K. Data analysis methods**

The analysis of efficacy variables is based on the intention-to-treat strategy. All statistical tests are two-sided and p values <0.05 are considered statistically significant. Multiple statistical methods can be used for the primary and secondary endpoints and include analysis of variance, analysis of covariance, and logistic regression. Clozapine is the only drug that has been shown to have efficacy for hallucinations in double-blind placebo-controlled trials but it is expensive and has potentially dangerous side effects. As it is unlikely that a new drug will be superior to clozapine but may be cheaper and/or safer, a study of a new agent against clozapine could be designed as an equivalence trial as long as it is powered to detect sufficiently narrow confidence intervals around equivalence. It is generally the case that equivalence trials require a larger sample size for the same power than a conventional trial.

#### **IV.2. Surgical interventions: Deep brain stimulation, lesions, and cellular replacement therapies**

The increased knowledge of the disrupted anatomical circuitry in PD has prompted laboratory studies and clinical trials of surgical interventions. On the premise that the degeneration in PD leaves several nuclei overactive from loss of inhibition, lesions and high voltage electrical stimulation have been applied to several deep brain structures, including the globus pallidum, thalamus and subthalamic nucleus. Alternatively, cellular replacement therapies focus on transplanting dopaminergic cells into the striatum in an attempt to reinnervate denervated structures. These studies are designed to evaluate both short-term and long-term (one to two years) efficacy, having the same objectives, rating tools and analytic methods described above for the treatment of parkinsonism and motor complications. Only special issues that are particular to these surgical trials are listed below:

#### **IV.2.A. Study Design**

Whereas randomized double-blind controlled parallel studies are the standard design in medication trials, this model is more difficult to effect in surgical trials. Lesion studies have primarily been open-label observations, and only a few have used a prospectively followed comparison group that receives optimal medical care. A few have randomized patients between two different surgical procedures. For deep brain stimulation, blinded ratings with the stimulator turned on and turned off have been used for comparisons. In cellular replacement therapies, the randomized, double-blind placebo-controlled parallel design that is typical of medical trials has been most closely replicated. In these cases, subjects are randomized between treatment groups and those who are assigned the control group go to the operating room, have a skull burr hole placed, but no needle penetration or cellular placement into the brain occurs. The surgical investigator is the only person on the research team who is unblinded, and all ratings are performed by investigators who were not involved in the surgery. In all studies, subjects are evaluated at baseline (often with more than one baseline assessment) and then seen regularly after surgery, usually at one month, and every three months thereafter during the trial. The score at the final visit usually serves as the primary outcome measure having adjusted for baseline scores. Often the percentage change in baseline scores is presented across different interventions. A common feature of all these trials is that the sample size is much smaller given the complexity and expense of the interventions. This makes the use of standardized outcome measures even more important as, inevitably, pooling results through the use of meta-analysis will be required to reduce the likelihood of both type I and type II errors. One special feature of surgical trials is the ability to assess an intervention undertaken either unilaterally or bilaterally. If subjects are randomised to have a different procedure for each side then, they can act as their own controls and matched methods of analysis are required as in cross-over studies. More typically comparisons are made by side so that 20 patients treated bilaterally provide 40 outcome measures. In this case, it is important to remember that each observation is not truly independent as they clustered within individuals and more complex statistical methods are required to allow for this clustering.

#### **IV.2.B. Study population**

The study population for surgical interventions are subjects with advanced PD who have failed other therapies, but still show an objective improvement (even if for short intervals) to dopaminergic therapy. They have motor complications in the form of dyskinesias and/or motor fluctuations. During “on” periods, they must be Hoehn and Yahr Stage I-III and during “off” periods, they must be Stage III-V.

#### **IV.2.C. Specific Inclusion Criteria**

Because surgical intervention is a major medical treatment, patients must be in good health other than their PD. Most studies require good cognitive status (MMSE usually at least 24) and no hallucinations. They must clearly understand all surgical risks and have a caregiver who can participate in the program.

#### **IV.2.D. Specific Exclusion Criteria**

Parkinsonian patients who carry other diagnoses besides Parkinson’s disease are excluded. Dementia, hallucinations and other significant behavioral problems usually exclude patients from these trials.

### **V. SPECIAL CONSIDERATIONS**

Placebo effects are frequent and substantive in PD trials. The dopamine system is directly involved in the regulation of reward mechanisms, expectation, motivation and vigilance. Positron emission tomography [<sup>11</sup>C]-raclopride binding studies document evidence of increased striatal dopamine release in PD subjects responding to placebo treatment. Because most drugs or interventions being studied in PD share dopaminergic augmentation mechanisms, separating primary dopaminergic effects due to the intervention vs. dopaminergic effects due to study participation (placebo effects) must be delineated. Whereas a positive effect on parkinsonism is anticipated in both the control and study group in PD, the outcome scores, after adjusting for baseline scores, must be significantly better in the intervention arm than in the placebo-treated arm before one can conclude that improvement is due to the intervention.

### **VI. EXAMPLES OF LANDMARK TRIALS**

#### **Treatment of parkinsonism**

1. Shannon KM, Bennett JP, Friedman JH. Efficacy of pramipexole, a novel dopamine agonist as monotherapy in mild to moderate Parkinson’s disease. *Neurology* 1997;49:724-728.
2. Olanow CW, Fahn S, Muentner M, Klawans HL. A multicenter double-blind placebo-controlled trial of pergolide as an adjunct to Sinemet in Parkinson’s disease. *Mov Disord* 1994;9:40-47.
3. Parkinson Study Group. Pramipexole vs. levodopa as initial treatment for Parkinson’s disease: a randomized controlled trial. *JAMA* 2000;284:1931-1938.

#### **Treatment of motor complications**

1. Rajput AH, Martin W, Saint-Hilaire MH, Dorflinger E. Tolcapone improves motor function in parkinsonian patients with the “wearing off” phenomenon: a double blind placebo controlled multicenter trial. *Neurology* 1997;49:1066-1071.

#### **Prevention of clinical progression of parkinsonism**

1. Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson’s disease. *N Engl J Med* 1989;321:1364-1371.

#### **Prevention of disease mortality**

1. Lees AJ, Katzenschlager R, Head J, Ben-Shlomo Y, on behalf of the Parkinson’s Disease Research Group of the United Kingdom. Ten-year follow-up of three different initial treatments in de-novo PD: a randomized trial. *Neurology* 2001;57:1687-1694.

### **Prevention of development of motor complications**

1. Rascol O, Brooks DJ, Borczyk AD, De Deyn PP. A five-year study of the incidence of dyskinesias in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *N Engl J Med* 2000;342:1484-1491.

### **Treatment of special issues**

1. Parkinson Study Group. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. *N Engl J Med* 1999;340:757-763.

### **Surgical interventions**

1. Schuurman PR, Bosch DA, Bossuyt PM. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. *N Engl J Med* 2000;317:461-468.
2. Deep Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *N Engl J Med* 2001;345:956-963.
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## **VII. SUGGESTED READINGS**

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3. Tanner CM, PD or not PD?—that is the question. *Neurology* 2003;61:5-6.
4. Kieburtz K. Designing neuroprotection trials in Parkinson's disease. *Ann Neurol* 2003;53 (suppl 3):100-109.
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6. Brooks DJ. Imaging endpoints for monitoring neuroprotection in Parkinson's disease. *Ann Neurol* 2003;53 (suppl. 3): 110-119.
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