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Statistical Considerations in the Design of Clinical Trials Targeting Prodromal Parkinson Disease

Eric A. Macklin, PhD,* Christopher S. Coffey, PhD,* Michael C. Brumm, MS, and John Peter Seibyl, MD

Neurology® 2022;99:S68-S75. doi:10.1212/WNL.0000000000200897

Correspondence
Dr. Macklin
emacklin@mgh.harvard.edu

Abstract

Clinical trials testing interventions for prodromal Parkinson disease (PD) hold particular promise for preserving neuronal function and thereby slowing or even forestalling progression to overt PD. Selection of the appropriate target population and outcome measures presents challenges unique to prodromal PD. We propose 3 clinical trial designs, spanning phase 2a, phase 2b, and phase 3 development, that might serve as templates for prodromal PD trials. The proposed phase 2a trial is of a 3-arm design of short duration and focuses on proof of concept with respect to target engagement and change in a motor outcome in a subset of prodromal participants who already manifest asymptomatic but measurable motor dysfunction as an exploratory aim. The proposed phase 2b trial suggests progression of dopamine transporter imaging specific binding ratio as a primary outcome evaluated annually over 2 years with phenoconversion to PD as a key secondary outcome. The proposed phase 3 trial is a large, simple design of a nutraceutical or behavioral intervention with remote administration and phenoconversion as the primary outcome. We then consider what additional data are needed in the short term to better design prodromal PD trials and examine what longer-term goals would accelerate discovery of safe and effective therapies for individuals at risk of PD. Clear and potentially context-specific definitions of phenoconversion and validation of intermediate endpoints are needed in the short term. The use of adaptive trial designs, master protocols, and research registries would help accelerate therapy development in the long term.

*These authors contributed equally to this work.

From the Biostatistics Center (E.A.M.), Massachusetts General Hospital and Harvard Medical School, Boston; Department of Biostatistics (C.S.C., M.C.B.), College of Public Health, University of Iowa, Iowa City; and Institute for Neurodegenerative Disorders (J.P.S.), New Haven, CT.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

The Article Processing Charge was funded by Massachusetts General Hospital.

Glossary

DAT = dopamine transporter; **DaTscan** = DAT imaging with 123-I Ioflupane SPECT; **DLB** = dementia with Lewy bodies; **iRBD** = idiopathic REM behavior disorder; **FDA** = Food and Drug Administration; **MDS** = Movement Disorder Society; **MSA** = multiple system atrophy; **PARS** = Parkinson Associated Risk Syndrome; **PD** = Parkinson disease; **PPMI** = Parkinson Progression Markers Initiative; **SBR** = specific binding ratio; **UPSIT** = University of Pennsylvania Smell Identification.

Clinical manifestation of Parkinson disease (PD) occurs only after substantial loss of dopaminergic neurons. Interventions started earlier in the course of disease, during the prodromal phase of PD when neuronal loss is less extensive, should have greater opportunity to preserve neuronal function and thereby slow or even forestall progression to overt PD.

Clinical trials targeting prodromal PD share elements common to any clinical trial of a progressive disease, elements unique to secondary prevention trials, and elements unique to prodromal PD. In Section 1, we describe the basic elements of trial design, review the outcomes available for assessing progression in prodromal PD, and then consider 3 alternative designs: (1) an early-phase design using remote assessments of motor outcomes, (2) a midphase design using imaging as a primary end point and phenoconversion to PD as a key secondary end point, and (3) a large, simple design of a low-risk intervention using phenoconversion as the primary end point. In Section 2, we discuss some of the complexities and trade-offs and what is needed to move the field forward in designing prodromal PD trials.

Basic Design Elements

Clinical trial design is structured around the trial's aims, target population, intervention, methods, and outcomes (including their schedule of assessment). Broadly, trial aims differ according to trial phase: phase 1 trials focus on pharmacokinetics and dosing, phase 2a on proof of concept, phase 2b on preliminary efficacy and safety, phase 3 on efficacy and more extensive safety, and phase 4 on real-world effectiveness. Features of unique concern for prodromal PD trials are specific to phases 2 and 3: what population to target and what outcomes to assess.

Earlier articles in this supplement have elaborated on the target population and the outcomes to assess. In brief, it is critical to enrich the sample to be responsive to treatment on the chosen outcome measure. This generally means identifying individuals who are predicted to be close to phenoconversion to overt PD or are expected to experience rapid progression of a continuous primary outcome measure.[1] Although some design considerations are similar between primary prevention trials of individuals at high risk for PD and secondary prevention trials in prodromal PD, in this article, we have chosen to focus on secondary prevention among individuals with high probability of prodromal PD based on the Movement Disorder Society (MDS) research criteria.[2,3] In either case, it is important that the risk of phenoconversion or the trajectory of progression is still modifiable. This tension between starting earlier in the disease course when an intervention may be more likely to benefit an individual vs starting later when progression is more rapid and any favorable treatment effort would be easier to detect is central to the potential and the difficulty of designing prodromal PD trials.

Options for outcomes in prodromal PD trials include phenoconversion, functional changes, and biological changes. Phenoconversion, generally confirmed diagnosis of PD by a trained neurologist, ideally a movement disorder specialist, is the most objectively clinically relevant outcome, and thus, the outcome most likely to satisfy regulatory interest in determining whether a treatment improves how patients feel, function, or survive, but complexities of phenoconversion as a research outcome remain and are discussed below. Functional changes reflect how a patient functions by definition, but clinically relevant thresholds of functional change require prior validation. The domains of functional change include motor function, cognitive capacity, and autonomic function associated with PD (e.g., constipation, orthostasis, and hyposmia). Biological changes (assessed by imaging or biofluid analysis) are typically the most sensitive outcomes but are the most remote from patient clinical experience. Dopamine transporter (DAT) imaging assessing deficits in dopamine binding in the striatum is the most mature biological assessment of features closely linked to PD.[4] Quantification of neurofilament levels (typically neurofilament light chain or phosphorylated neurofilament heavy chain) in plasma or CSF, α-synuclein aggregates in tissue, and seeding of α-synuclein aggregation in CSF are all promising biofluid measures that are believed to relate to PD pathology but still await validation as pharmacodynamic outcomes.[5-7]

Design Options

Phase 1 trials to investigate pharmacokinetics and maximum tolerated dosages would be pursued for potential therapies for prodromal PD the same as for any other novel therapeutic and are not covered here. Similarly, phase 4 postmarketing trials of approved therapies are not covered here given the lack of such compounds. In the middle, interventions targeting mechanisms believed to underly disease progression during prodromal PD fall into 2 broad categories: narrowly targeted small molecule or biologic interventions with specific molecular or pathology-targeting mechanisms and greater potential safety concerns and broadly targeted nutraceutical or

behavioral interventions with diffuse mechanisms of action and limited safety concerns.

Clinical trials of narrowly targeted small molecule or biologic interventions with specific molecular or pathologic mechanisms could plausibly be pursued in either early, phase 2a designs or later, phase 2b designs depending on existing data on safety and target engagement from other populations and on how aggressively development of the intervention is being pursued. For interventions with limited or only short-term safety data and a need for clear target engagement or proof of concept before further development, a phase 2a trial would be most appropriate. For interventions with existing long-term safety data, often repurposed drugs or drugs being pursued for multiple indications with long-term exposure outside of prodromal PD, and a need for preliminary data on clinical efficacy, evaluation of alternative dosages, dosing regimens, or modes of administration, and other preparation for phase 3 trials, a phase 2b trial would be most appropriate. During phase 2 development, regulatory agencies are primarily concerned with ensuring that adequate safety data support the planned dosages and exposure durations and otherwise permit investigators flexibility in trial design.

For interventions with adequate long-term safety data already in-hand, investigators could move directly to phase 3 confirmatory trials in prodromal PD with small molecule or biologic interventions, but the most plausible scenario for phase 3 trials in prodromal PD currently are trials of low-risk nutraceutical or behavioral interventions that would not be brought to a regulatory agency for approval. Given the more diffuse mechanism of action of these interventions, early phase trials focused on target engagement are less applicable although investigation of dosage and participant engagement can be essential steps before launch of large-scale trials. Large samples would typically be required because the treatment effects would be expected to be small (otherwise epidemiologic data would suffice to motivate implementation). Furthermore, given the large sample sizes required, a focus on remote and self-report assessment is expected.

Plausible Phase 2a Proof-of-Concept Trial

Phase 2a trials focus on ensuring the absence of important safety concerns and confirming proof of concept. Operational aims would include evaluation of recruitment strategies, participant retention, and other factors related to feasibility. A plausible design of a phase 2a prodromal PD trial would focus on safety and proof of concept with respect to target engagement and an exploratory analysis of change in a measure of motor function. To ensure some potential for detecting changes in motor function, participants should already be experiencing findings suggestive of some degree of neurodegeneration. Eligibility criteria might include idiopathic REM behavior disorder (iRBD), hyposmia, constipation, deficit of DAT density by SPECT, bradykinesia, or a combination of all 5. In the Parkinson Associated Risk Syndrome (PARS) study, 67% of subjects with hyposmia and DAT deficit phenoconverted within 4 years.[8] Ongoing research is aimed at identifying improved screening criteria for patients with prodromal PD.[9,10]

Evaluation of target engagement is generally evaluated by tracking change in biomarkers specific to the biological mechanism of the planned intervention and not further discussed here. Exploratory analysis of change in motor function could take several directions. Because patients with prodromal PD have at most asymptomatic impairments in motor function insufficient to diagnose PD, measures of motor function for consideration in small proof-of-concept trials must be sufficiently sensitive to detect subclinical changes in motor function. Options for assessment of motor function include in-clinic tapping and pegboard tasks, remote task-oriented smartphone assessments of tapping and gait (e.g., mPower[11] and the PD Mobile app[12]), measures of mobility tracked through passive data collection using a wearable device or smartphone, and in-clinic or smartphone-based assessments of speech.[13,14]

A phase 2a proof-of-concept trial in prodromal PD might be designed for 3–6 months of follow-up of a sample of 36–75 individuals randomized 1:1:1 to placebo and 2 active dosages. Participants should have a high probability of prodromal PD based on the MDS research criteria. Features that could be identified by remote prescreening include possible iRBD by bed-partner report, hyposmia by self-administered University of Pennsylvania Smell Identification Test (UPSIT), self-report of constipation, and remote assessment of asymptomatic but measurable motor dysfunction (e.g., using smartphone tapping tasks or tracking keyboard typing dynamics[15]). Secondary in-clinic assessment of DAT deficit would be desirable. Such a design could effectively compare target engagement biomarkers with a true effect size between 1.0 and 0.70 for n = 36 and 75, respectively, under standard conditions (80% power when tested at 2-tailed $p < 0.05$). Given those sample sizes, such a trial would have an 80% probability of observing a numerical mean difference in favor of active treatment for a true effect size between 0.30 and 0.21 for exploratory end points. The primary limitation in pursuing such a design with respect to evaluating progression to PD is lack of knowledge that participants selected by the criteria above or similar criteria will experience measurable change in motor symptoms over a relatively short duration and the relationship between that progression and risk of future phenoconversion. No remote motor assessments have thus far been validated to identify patients at high risk of developing PD. Nevertheless, some interventions will need to accumulate shorter-term safety data, supportive evidence of target engagement, and preliminary data on efficacy before moving to a phase 2b trial.

Plausible Phase 2b Trial

Phase 2b trials focus on ensuring the absence of important safety concerns and preparing for confirmatory phase 3 trials.

As with phase 2a prodromal PD trials, participants must have sufficiently advanced underlying pathology for changes in disease course to be detected in a reasonable sample size. A plausible design could track disease progression by DAT imaging with 123-I ioflupane SPECT (DaTscan) as a primary end point and phenoconversion as the key secondary end point in preparation for a future phase 3 trial in which phenoconversion would be the primary end point.

Consider a phase 2b prodromal PD trial with prescreening for iRBD and hyposmia, eligibility defined by DAT deficit, annual DAT imaging over 2 years, and rate of DAT specific binding ratio (SBR) progression as the primary end point. Although DAT imaging is subject to interference from other DAT-binding medications and a relationship between low DAT SBR and loss of nigrostriatal neurons has been controversial,[16,17] several studies document associations between change in DAT SBR and risk of subsequent phenoconversion to PD.[18,19] Power depends on the mean rates of DAT SBR progression and person-to-person variation. In a sample of 39 patients with iRBD, Shin et al.[18] reported rates of DAT SBR progression of −0.19 (SD = 0.27) units/year over 4 years of follow-up with DAT imaging at 2-year intervals. Estimates of DAT SBR progression and variance of −0.19 (SD = 0.24) units over 2 years are suggested by preliminary data from the Parkinson Progression Markers Initiative (PPMI) prodromal PD cohort of 39 participants aged 60 years or older with baseline striatal DAT SBR less than 65% of age-specific and sex-specific norms followed for 3 years with annual DAT imaging. Among the subset of 22 iRBD patients also with hyposmia and DAT deficit at baseline in Shin et al., the mean rate of progression was 30% slower and the variance reduced by 75% at −0.13 (0.13) units/year.[18] Using these estimates, a simple 2-group *t* test of group mean rates would suggest a required total sample size of 128 to have 80% power to detect 50% slowing. If we accommodate uncertainty in the estimated standard deviation of 0.13 units/year by convoluting the power calculations over a scaled inverse chi-square with 21 degrees of freedom and assume up to 10% loss to follow-up over 2 years (vs 5% and 8% in the STEADY-PD III[20] and SURE-PD3[21] trials, respectively), the required sample size increases to 160. Power for detecting a treatment-dependent slowing in DAT SBR progression would be somewhat higher using a shared-baseline, mixed-model repeated measures analysis that accounts for covariance among repeated DAT SBR estimates assuming some correlation between baseline and follow-up assessments and incremental loss to follow-up.

In addition to estimating DAT progression rates among patients with prodromal PD, Shin et al.[18] reported 7.3%–13.3% annual phenoconversion rates among all iRBD patients and among those also with hyposmia and DAT deficit at baseline, respectively, suggesting 14%–25% cumulative rates over 2 years of follow-up. Alotaibi et al.[22] estimated a 20% phenoconversion rate over 2 years of follow-up among a cohort of 101 iRBD patients. Data from 64 participants in the combined iRBD and hyposmic prodromal cohorts of the PPMI and a subset of 39 participants aged 60 years or older with DAT SBR below 65% of that predicted by age and sex indicate 2-year phenoconversion rates of 13% and 18%, respectively.

Assuming a 15% phenoconversion rate over 2 years of follow-up with 1 year to complete recruitment and accommodating up to 10% loss to follow-up, a phase 2b prodromal PD trial with phenoconversion as a key secondary end point and a sample size of 160 would have an 80% probability to observe a numerically lower proportion of active-arm participants phenoconverting if the true relative risk was reduced at least 30%. Note that this is a numerical comparison of rates in the observed data, not an inferential test. For 80% power to detect a statistically significant reduction in risk of phenoconversion with 2-tailed *p* values of 0.10 or 0.05, the true relative risk would have to be reduced by 73% and 79%, respectively. Note that detection of a 50% or 30% reduction in phenoconversion in a trial with 1 year of accrual, a minimum of 2 years of follow-up and 10% loss to follow-up requires sample sizes of 570 and 1,860, respectively, under standard conditions.

Although phenoconversion is in principle a continuous time-to-event outcome, in practice, phenoconversion will be interval censored. Trials can increase their power by increasing the frequency of evaluation for phenoconversion and following participants to a common time point to extend follow-up of early enrollees.

Plausible Large, Simple Phase 3 Trial

Phase 3 trials focus on ensuring the absence of important safety concerns and demonstrating clinical effectiveness. Phenoconversion is the most plausible primary end point for regulatory approval given our currently limited data on the clinical relevance of more proximal measures of disease progression. An alternative would be sustained worsening in motor or cognitive function of a magnitude that was accepted as clinically relevant.[22] In either case, given relatively slow disease progression on average among even carefully selected individuals with high probability of prodromal PD, such trials are expected to require 2–5 years of follow-up.

Given an absence of pharmaceuticals with advanced development in prodromal PD currently, the most plausible design of a phase 3 trial in prodromal PD currently is 1 testing the potential benefit of a nutraceutical or behavioral intervention. Epidemiologic studies suggest that the most potent interventions of this nature might reduce annual phenoconversion rates in the range of only 10% or so. For example, moderate to vigorous exercise is associated with 30% reduction in the risk of developing PD over a median of 12 years.[23]

Detection of treatment benefits as small as 10% with high power requires very large sample sizes. For example, with a mean of 5 years of follow-up and a constant background phenoconversion rate of 20% and accommodating 20% loss to follow-up and 20% nonadherence over 5 years, the sample size required to detect a 10% reduction in relative risk of

phenoconversion is approximately 10,000 with 1:1 randomization and minimal α-spending on interim analyses under standard conditions.

A trial of this scale would likely require a remote design with electronic consent and self-evaluation for outcomes. The sample size of 10,000 stated above assumes continuous evaluation of phenoconversion, perhaps achieved through self-assessment and self-referral to a staged program of virtual evaluation followed by in-person assessment by movement disorder specialists. Differentiation between phenoconversion to PD vs phenoconversion to a range of similar movement disorders or synucleinopathies (e.g., multiple system atrophy [MSA] and dementia with Lewy bodies [DLB]) may be a complication for pharmaceutical trials with phenoconversion to PD as the primary outcome, but evidence of reduced rates of phenoconversion to any movement disorder or synucleinopathy may be sufficient to establish a nutraceutical or behavioral intervention as a new standard of care.

The prior section presents several options for designing prevention trials in PD based on current knowledge. However, given the uncertainty in optimal eligibility criteria and choice and characteristics of outcome measures, it is helpful to consider what additional data are needed to better design such trials and to examine what longer-term goals should be for trial designs in this area.

What Do We Need to Move Forward?

One critical aspect required to advance prodromal PD trials is to validate a definition of "phenoconversion" as a research outcome. In particular, should the first instance of phenoconversion be accepted? Or should some level of sustained progression be required, and if so, how long should progression be sustained? How should progression to non-PD conditions (e.g., MSA, DLB, and progressive supranuclear palsy) be considered as part of the definition of phenoconversion. For some interventions, for example, interventions targeting α-synuclein aggregation, phenoconversion to a diagnosis of another synucleinopathy may be considered equivalent to phenoconversion to PD, whereas for other interventions, for example, interventions targeting recycling of dopamine receptors, phenoconversion to a non-PD diagnosis might not be considered equivalent. It will also be critical to align research and clinical definitions as much as possible. A situation where a research outcome works well in the clinical trial setting but does not correlate well with clinical interpretation would complicate, rather than help, prodromal PD trials.

Even with a fully specified and clinically relevant definition of phenoconversion, trials using phenoconversion as the primary outcome are likely to require large sample sizes and long follow-up times. Early phase trials require more efficient outcomes for which meaningful change can be assessed over short time intervals (e.g., 2 years or less). Validation of early end points, for example, by associating with subsequent phenoconversion, will be critical for their use in early phase trials and for potential regulatory approval under the US Food and Drug Administration (FDA) Accelerated Approval Program.[24] Using data from the prodromal cohort of the PPMI study, Chahine et al.[19] suggested that changes in DAT values within the first 2 years of enrollment are strongly associated with the risk of long-term development of PD. Nevertheless, association does not equal causation. Determining causation from short-term end points to longer-term phenoconversion requires the following: temporality (cause precedes effect), strong association, biological plausibility, coherence (consistency with other knowledge), consistency (repeatability), and specificity (cause results in a single effect).

The temptation to choose unvalidated end points in prodromal PD only because they are familiar to PD researchers should be avoided. For example, motor progression has traditionally been used as an end point for PD clinical trials, but motor progression may or may not be useful for prodromal PD because of the much smaller expected change in such measures in this population—even among those who will go on to phenoconvert. Estimates of person-to-person variation in longitudinal change of a such motor end points, compliance with such assessments, and the expected mean magnitude of change in the absence of treatment among prodromal PD patients are not yet available but are actively being acquired in several studies: PPMI 2.0 prodromal cohort,[25] the Tübingen Evaluation of Risk Factors for Early Detection of Neurodegeneration study,[26] and PREDICT-PD.[27] Observed rates of change in such measures and the balance of within-person vs among-person variance will inform decisions about an optimal trade-off between duration of follow-up and number of participants required.

Furthermore, we need to distinguish changes that reflect progression to PD vs those that reflect other diseases or normal aging. This will require large, observational cohorts that include both PD and non-PD participants. The PPMI study recently expanded to enroll prodromal PD participants, enriched for dopaminergic loss using DaTscan, iRBD, or hyposmia, along with de novo PD participants and healthy controls to address these questions.[25] PPMI 2.0 uses a multilayered approach to recruitment that leverages online scalable screening platforms, such as Fox Insight, to find possible "at risk" cohorts because of iRBD, hyposmia, or rare genetic mutations. Potential participants who meet at least one of the above criteria are invited for a DaTscan to determine whether they have evidence of a dopaminergic deficit and thus are at higher risk for developing motor features soon after enrollment. In addition to providing critical information to inform future trial designs, such observational cohorts could also serve as registries from which prescreened participants could be drawn for future trials and against which progression could be compared as a natural history cohort to strengthen any observed differences observed within single-arm or double-blind intervention trials.

The optimal recruitment strategy for enrichment of prodromal PD trials is an open question. The complexity of an enrichment approach must be balanced against the benefits obtained. The PARS study implemented a funnel design consisting of a series of steps starting with direct mailings and online recruitment.[28] From over 10,000 respondents, UPSIT assessments were sent to 9,398 eligible first-degree relatives and nonrelatives of patients with PD. Just over half of these individuals returned their UPSIT assessments, of whom 669 met the enrichment criterion for olfactory loss (≤15th percentile based on age and sex). As previously mentioned, a more enhanced enrichment strategy is being used (and will be constantly assessed and modified) as part of PPMI 2.0. PPMI 2.0 aims both to enroll and follow a set of prodromal participants and also to evaluate strategies for enrichment of future prodromal PD trials. The current strategy focuses primarily on DAT loss, iRBD, and hyposmia and uses an online portal to allow high throughput screening of individuals. As participants enroll into PPMI 2.0 from the online portal and some phenoconvert, a series of predictive models will be updated to inform additional screening measures that might be used in future prodromal PD trials.

In addition to the concerns addressed above, several other questions must be addressed during design of prodromal PD trials. What are expected conversion/progression rates? How do these differ across various choices of enriched enrollment populations? What corresponds to a clinically meaningful change (in any of the end points under consideration) in this population? What are target treatment effects? How should the balance between toxicity and benefit be considered in trials that enroll individuals before a clinical diagnosis? What are the appropriate type I and type II errors for determining sample size requirements for prodromal PD trials?

Finally, it will be important to conduct clinical trial "postmortems"—especially after the initial prodromal PD trials are launched and completed. Although researchers will attempt to optimize the design of trials beforehand, a number of important questions should be examined after completing these initial trials. Did the placebo group progress as expected—e.g., do we have a good estimate of the phenoconversion rate? Did this study identify the correct target population? Did the intervention achieve target engagement? If the trial is negative, can we be confident that failure to see effects was due to lack of a therapeutic effect rather than insufficient study design?

Future?

Given the challenges of enrolling and following prodromal PD participants, stand-alone phase 2 and phase 3 clinical trials would likely be large, costly, and time-consuming. The greater need for efficiency suggests that innovative designs should be considered for prodromal PD trials. Adaptive designs permit midstudy review and modification of trial characteristics based on accumulating data. A recent FDA guidance document[29] defines an adaptive design as "…a clinical trial design that allows for prospectively planned modifications to 1 or more aspects of the design based on accumulating data from participants in the trial." The guidance document notes that any potential adaptation needs to be planned and described before the initiation of the trial. This permits the use of simulation studies to assess the operating characteristics of the design, identify potential bias that arise from data-dependent adaptations, and evaluate the effect of mitigation strategies to reduce bias that exists. Owing to the need for such simulation studies, implementation of an adaptive design typically involves a more extensive assessment and planning period vs standard trial designs, but adaptive trials can provide greater efficiency during trial conduct. A wide range of possible adaptations exist, including 2 that are well-suited to prodromal PD trials.

Adaptive phase 2/3 seamless designs allow combining objectives traditionally addressed in separate trials into a single trial. Participants enrolled in phase 2 are used to inform a "go"/"no go" decision that determines whether the trial should transition to phase 3. If this study proceeds to phase 3, the final analysis uses participants enrolled in both phases. Because adaptive designs are most useful with short-term outcomes, such seamless designs are most effective when a short-term biomarker is used for the interim "go"/"no go" decision while a longer-term clinical end point is used in the eventual phase 3 study (if the initial "go" criteria are met). The inclusion of phase 2 data that were used to inform the decision to move to phase 3 creates that potential for bias. Final analyses must guarantee control of type 1 error rates and other key statistical operating characteristics. Despite these challenges, this type of seamless adaptive design has appeal for prodromal PD trials if clear criteria for adaptations can be prespecified. In particular, such designs would allow the use of imaging, motor, or biological measures as the primary phase 2 end point with a prespecified "go"/"no go" criterion for determining whether to continue to phase 3 with phenoconversion as the end point.

Additional efficiencies can be gained by using a master protocol approach rather than conducting separate trials across different sponsors.[30] A recent FDA guidance document[31] defines a master protocol as "…a protocol designed with multiple substudies, which may have different objectives and involves coordinated efforts to evaluate 1 or more investigational drugs in 1 or more disease subtypes within the overall trial structure." There are 3 broad types of master protocols: basket trials in which a single investigational agent is tested across multiple diseases, umbrella trials in which multiple investigational agents are tested in a single disease, and platform trials in which multiple investigational agents are tested across multiple diseases. For prodromal PD trials, an umbrella trial to study multiple interventions alone or in combination can increase efficiency and reduce overall required sample size by permitting the use of a shared placebo against which all experimental interventions are tested. Such trials can accommodate asynchronous entries and exits of multiple interventions under a single protocol, avoiding the need to rebuild trial infrastructure to test each individual intervention. Given the many challenges described above, the efficiency of master protocols has appeal for prodromal PD trials.

Conclusions

There is increasing interest in developing therapies to prevent progression to PD among individuals with symptoms of prodromal PD. Simultaneously, there is substantial uncertainty with respect to optimal trial design in this setting. As described here, several plausible trial designs could currently be considered across the stages of clinical development. Each contains some uncertainty regarding the optimal choice of population, end points, and trial duration. The field of prodromal PD research will be aided by expansion of cohorts of individuals at risk for PD to identify appropriate eligibility criteria, collect pilot data on relevant end points, and to serve as registries of potential trial participants. In combination with adaptive and master protocol designs, efficient prodromal PD trials will hopefully lead to rapid development of therapeutics to prevent PD.

Study Funding

Supported in part by Award ID PF-MET-2011 from the Parkinson's Foundation.

Disclosure

E.A. Macklin reports the following interactions with industry over the previous 24 months: receiving grants by his institution on his behalf from AI Therapeutics, Alector, Amylyx, Biohaven, Calico Life Sciences, Clene Nanomedicine, Mitsubishi Tanabe Pharma America, Prilenia, Revalesio, Seelos, and UCB Ra Pharma; serving on Steering Committees for Biogen and Stoparkinson Healthcare; serving on a DSMB for Novartis and Sanofi; and serving on advisory boards for Alector, Bial Therapeutics, Cerevance, Cortexyme, Enterin, InTrance, nQ Medical, and Partner Therapeutics. J.P. Seibyl is a consultant to Biogen, Life Molecular Imaging, GE Healthcare, Roche, AbbVie, and LikeMinds, and holds equity in Invicro. The other authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* October 15, 2021. Accepted in final form May 13, 2022.

Appendix Authors

Name	Location	Contribution
Eric A. Macklin, PhD	Biostatistics Center, Massachusetts General Hospital and Harvard Medical School, Boston	Drafting/revision of the manuscript for content, including medical writing for content
Christopher S. Coffey, PhD	Department of Biostatistics, College of Public Health, University of Iowa, Iowa City	Drafting/revision of the manuscript for content, including medical writing for content
Michael C. Brumm, MS	Department of Biostatistics, College of Public Health, University of Iowa, Iowa City	Drafting/revision of the manuscript for content, including medical writing for content
John Peter Seibyl, MD	Institute for Neurodegenerative Disorders, New Haven, CT	Drafting/revision of the manuscript for content, including medical writing for content

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Neurology 2022;99;68-75
DOI 10.1212/WNL.0000000000200897