Who to Enroll in Parkinson Disease Prevention Trials?  
The Case for Composite Prodromal Cohorts  
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Abstract  
Significant progress has been made in expanding our understanding of prodromal Parkinson disease (PD), particularly for recognition of early motor and nonmotor signs and symptoms. Although identification of these prodromal features may improve our understanding of the earliest stages of PD, they are individually insufficient for early disease detection and enrollment of participants in prevention trials in most cases because of low sensitivity, specificity, and positive predictive value. Composite cohorts, composed of individuals with multiple co-occurring prodromal features, are an important resource for conducting prodromal PD research and eventual prevention trials because they are more representative of the population at risk for PD, allow investigators to evaluate the efficacy of an intervention across individuals with varying prodromal feature patterns, are able to produce larger sample sizes, and capture individuals at different stages of prodromal PD. A key challenge in identifying individuals with prodromal disease for composite cohorts and prevention trial participation is that we know little about the natural history of prodromal PD. To move toward prevention trials, it is critical that we better understand common prodromal feature patterns and be able to predict the probability of progression and phenocversion. Ongoing research in cohort studies and administrative databases is beginning to address these questions, but further longitudinal analyses in a large population-based sample are necessary to provide a convincing and definitive strategy for identifying individuals to be enrolled in a prevention trial.
Glossary

AHS = Agricultural Health Study; B-SIT = brief smell identification test; DAT = dopamine transporter; HAAS = Honolulu-Asia Aging Study; HPFS = Health Professional’s Follow-Up; NHS = Nurses’ Health Study; PD = Parkinson disease; PPV = positive predictive value; pRBD = probable RBD; PRIPS = Prospective evaluation of Risk factors for Idiopathic Parkinson’s Syndrome; RBD = REM sleep behavior disorder; THIN = The Health Improvement Network; TREND = Tübingen Evaluation of Risk Factors for Early Detection of Neurodegeneration.

In the recent years, substantial progress has been made in expanding our understanding of prodromal Parkinson disease (PD). An important part of this progress is improved recognition of motor and nonmotor symptoms that commonly occur during prodromal PD. Indeed, although some individuals predominantly experience tremor or other motor signs (asymmetric arm swing,1 gait changes,2 and parkinsonism-related motor changes3) in the years preceding their PD diagnosis, many experience nonmotor symptoms at an increased rate during this period, including sensory impairments (olfactory loss4 and impaired color vision5), sleep-related disorders (REM sleep behavior disorder [RBD]6 and excessive daytime sleepiness7), autonomic dysfunction (constipation,7 orthostatic hypotension,8 erectile dysfunction,9 and urinary dysfunction9), and neuropsychiatric conditions (subjective cognitive complaints,10 depression,11 and anxiety11). Experiences of these features during prodromal PD are highly heterogeneous: Individuals may exhibit few or many of these features in distinct combinations and for varying lengths of time before clinical PD diagnosis. Beyond these signs and symptoms, possible biomarkers, including hyperechogenicity of the substantia nigra on transcranial sonography,3 reduced dopaminergic transporter activity (dopamine transporter [DAT] deficit),12 and phosphorylated α-synuclein depositions in skin,13 have been linked with prodromal PD. Here, we discuss how these features and biomarkers could be used to identify and enroll participants in PD prevention trials. We further address the advantages of a composite cohort vis a vis a genetic or RBD cohort, provide a summary of progress made in identifying prodromal PD in population-based cohorts, and discuss some of the challenges and potential solutions.

Advantages of Composite Cohorts

PD is a highly heterogeneous disease, as evidenced by the differing risk factor profiles and prodromal feature patterns that individuals ultimately developing PD display. Indeed, no single prodromal feature is experienced by all individuals in the prodromal period. Similarly, although several genetic risk factors for PD have been identified, it is estimated that only 5%–10% of cases can be attributed to monogenic causes.14 In the case of RBD cohorts, participants are often recruited from among patients seeking medical care for their RBD; this will tend to select for individuals with RBD severe enough to seek care rather than those with milder cases who do not. In certain situations, defining an at-risk population based solely on pathogenic genetic variations or clinically diagnosed RBD may be advantageous.15,16 As we move toward developing interventions for prodromal PD populations, however, composite cohorts may become preferable for several reasons. First, composite cohorts better reflect the frequency and severity of prodromal features in the general population of individuals at risk of PD and enable evaluation of the efficacy of an intervention across individuals with different prodromal features. This could be critical because specific features may define different subtypes,17,18 correlate with rates of disease progression,18 reflect different etiologies, as suggested by different risk factor profiles of RBD and PD,19 and respond differently to different interventions. Second, composite cohorts have the potential to identify much larger numbers of individuals with prodromal PD than genetic or RBD cohorts. Finally, composite cohorts capture individuals at different stages of prodromal PD, which has important implications for the type of intervention and how to measure prevention.

Challenges of Composite Cohorts

A key challenge in identifying individuals with prodromal disease for prevention trials is that we know little about the natural history of prodromal PD, including its stages and duration. Although prodromal PD is heterogeneous in duration and manifestation, it would be useful to identify common patterns and predict the probability of progression and phenocconversion over time. Extrapolating backward from functional imaging data of the striatum, it is estimated that brain pathology may start more than 10 years before the clinical PD diagnosis.20 However, the disease process may start earlier, particularly in the setting of the “gut first” paradigm, which suggests that in some patients the disease initiates in the gut and only reaches the CNS at a relatively late stage.17 This is supported by the observation that constipation may precede PD diagnosis by up to 19 years and is among the first identifiable features of prodromal PD.7 Hyposmia, which precedes manifest PD by several years, appears in most individuals at a later stage than constipation.3 Finally, RBD, at least in forms severe enough to prompt sleep clinic consultation and diagnosis, is strongly predictive of an α-synucleinopathy within 5–12 years and may thus identify individuals closer to phenocconversion.6 How often constipation, hyposmia, and RBD occur in this sequence remains uncertain because we lack longitudinal follow-up on a sufficiently large cohort to document the incidence and temporal relation between these features. Similarly, we have insufficient evidence to delineate different trajectories of prodromal PD progression incorporating psychiatric, autonomic, and other features. In most individuals, some nonmotor
features precede the onset of motor parkinsonism, which becomes manifest close to phenoconversion. More subtle motor signs, however, such as difficulty with balance,21 frequency of falls,72 and variations in gait2,21 have been identified years before PD diagnosis.

Another challenge is that several prodromal PD features commonly occur among older adults without prodromal PD. As such, any individual prodromal feature has a very low predictive value. The likelihood of multiple prodromal features co-occurring in the same individual, however, is low unless there is an underlying shared pathology causing them. This suggests that prodromal feature combinations may be useful for identifying individuals with prodromal PD, a concept supported by a growing body of research. In the Honolulu-Asia Aging Study (HAAS), individuals with 2 or more co-occurring nonmotor PD features had a 10-fold higher risk for developing PD.23 Consistent results have been obtained in several cross-sectional studies, comparing individuals without PD to individuals with early PD. In the Agricultural Health Study (AHS), the odds ratio of PD was 16.1 for men with 2 nonmotor features and 32.6 for those with 3 as compared with men without prodromal features; comparable figures in women were 4.0 and 17.1.24 In our recent analyses in the Health Professional’s Follow-Up (HPFS) ProPD subcohort, the odds of prevalent, diagnosed PD increased exponentially with the number of co-occurring nonmotor features, with those experiencing 1, 2, or, at the extreme, 6 or more concurrent features having 2.7-fold, 13-fold, and 1,325-fold higher odds of PD, respectively25; similar results were observed in the Nurses’ Health Study (NHS) ProPD study.26 Longitudinal monitoring for new prodromal features may provide a better approach to identifying individuals with prodromal PD than a 1-time assessment. Long-standing, stable hyposmia, for example, even if co-occurring with other prodromal features, could be less likely to indicate prodromal PD than incident or worsening hyposmia with the same accompanying features. This hypothesis, however, remains untested.

As discussed below, increasing the number of features required for identifying prodromal PD decreases the sensitivity because an increasing number of true cases will not meet the diagnostic requirement. The optimal combination should, therefore, be determined empirically and may depend on the purpose of the study. For instance, an algorithm with high sensitivity and low-to-moderate predictive value could be used if those who screen positive will be further vetted by DAT imaging. Conversely, if the algorithm is intended to identify individuals eligible for a trial without further confirmation, a higher positive predictive value (PPV) may be required, even if it can only be obtained at the expense of low sensitivity.

Composite Cohorts and Prevention Trials

Before enrolling individuals in a prevention trial, it is important to identify a suitable outcome and be able to estimate the frequency of that outcome without intervention. These challenges, detailed by Coffey and Macklin,27 are related to the criteria used for identifying prodromal PD. There is a clear tension between the need to identify individuals in the earliest stages of the disease process, when there is little pathologic damage and more time to change the disease course before the appearance of disabling symptoms, and the need to have clinically meaningful and measurable outcomes within the trial duration, which will likely be less than 5 years. The efficacy of an early intervention that delays phenoconversion from 10 to 20 years, for example, could only be assessed using surrogate markers, such as prodromal feature progression or biomarker changes (e.g., body fluids composition, changes in gait, and imaging). DAT, which is discussed by Seibyl and Kuo28 will likely play a critical role in identifying and monitoring the progression of prodromal PD, but because of its cost and requirement for in-person visits to specialized centers, it is unsuitable for screening large populations in which the prevalence of prodromal PD is typically <3%.29 As such, we will focus on strategies being developed to identify individuals with prodromal PD in the general population of older adults, including cohort studies and studies of administrative databases.

Cohort Studies

Cohort studies can be categorized into 2 groups: (1) studies exploiting existing cohorts that were designed for other purposes and (2) cohorts specifically designed to investigate prodromal PD (Table). Examples in the first group are the HAAS,23 the Rotterdam Study,10,21 the HPFS,25 the NHS,30 and the AHS.24 These are very efficient because there is no cost of recruitment, there are well established mechanisms for follow-up, and they typically have large sample sizes and long duration. Such cohorts have provided important insights on risk factors for PD and several prodromal features, including constipation and hyposmia. Their main limitation is that they only include a limited set of prodromal features and thus do not have sufficient information to derive comprehensive diagnostic algorithms.

Prodromal PD cohorts are generally smaller and have shorter follow-up than established cohorts but conduct in-depth in-person assessments of clinical features, repeated neurologic examinations, and neuroimaging. Among the earliest of these cohorts is the Tübingen Evaluation of Risk Factors for Early Detection of Neurodegeneration (TREND),31 which used public advertising to recruit individuals age older than 50 years without diagnosed neurodegenerative diseases and with symptoms suggestive of depression, hyposmia, or RBD. Overall, 698 individuals are being followed up with biennial screening; 16 have been diagnosed with PD during 7 years of follow-up.7 A similar cohort without enrichment for prodromal features is the Prospective evaluation of Risk factors for Idiopathic Parkinson’s Syndrome (PRIPS),32 which recruited individuals age 50 years or older to 2 centers in Germany using public advertising. Overall, 1,847 individuals were included in PRIPS and followed prospectively; to date,
21 PRIPS participants have developed PD during 5 years of follow-up. TREND and PRIPS stand out for their comprehensive test batteries, including standardized neurologic examinations and transcranial sonography of the substantia nigra. In both cohorts, the Movement Disorder Society research criteria were used to estimate the probability that an individual has prodromal PD. Pooled analyses of data from these cohorts and other smaller studies in Germany have been recently reported; the PPV for PD diagnosis in the full sample during the follow-up ranged from 27% (0.38 sensitivity) to 80% (0.12 sensitivity) (Figure). Importantly, each of these studies’ algorithms included information on motor features, such as parkinsonism, which primarily occur in the late stages of prodromal PD.

The Parkinson At Risk Syndrome study in the United States targeted 10,000 individuals at elevated PD risk because of an affected first-degree relative. Of them, 4,999 completed an olfactory test and 669 with hyposmia were invited to participate in a clinical and imaging (DAT) cohort. The 203 hyposmic individuals who consented were included in the study with 100 normosmic controls. The PPV for PD diagnosis in the full sample during the follow-up ranged from 27% (0.38 sensitivity) to 80% (0.12 sensitivity) (Figure). Importantly, each of these studies’ algorithms included information on motor features, such as parkinsonism, which primarily occur in the late stages of prodromal PD.

Our team has taken another approach to establishing a cohort of individuals with high probability of prodromal PD. We estimated that fewer than 50 incident cases of PD would be expected within 4 years in a cohort of 10,000 individuals aged 70–79 years. To capture prodromal PD at younger ages and considering the imperfect performance of any screening algorithm, more than 100,000 individuals need to be screened to identify a few hundred individuals eligible for a prevention trial. This can only be accomplished using multistage screening approaches in which 1 or 2 very low-cost screening rounds are used to enrich the population with individuals at high enough risk of prodromal PD to justify applying more expensive, invasive, or burdensome specialized diagnostics.

### Table: Characteristics of Selecteda Studies on Prodromal PD

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<th>Participants, No.</th>
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<th>Follow-up, y</th>
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<td>574</td>
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<td>PRIPS32,33</td>
<td>Yes</td>
<td>1,847</td>
<td>21</td>
<td>3–5</td>
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<tr>
<td>TREND2,31</td>
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<td>698</td>
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<td>EPIPIR34,48</td>
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<td>715</td>
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<td>4,999/303b</td>
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<td>6</td>
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<td>HPFS/NHS ProPD25</td>
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<td>53,765/20,769</td>
<td>140/86c</td>
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<td>HAAS23,49</td>
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<td>Medicare25</td>
<td>No</td>
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<td>89,790</td>
<td>5*</td>
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Abbreviations: HAAS = Honolulu-Asia Aging Study; HPFS = Health Professional’s Follow-Up; NHS = Nurses’ Health Study; PARS = Parkinson at-risk syndrome; PD = Parkinson disease; PRIPS = Prospective evaluation of Risk factors for Idiopathic Parkinson’s Syndrome; THIN = The Health Improvement Network; TREND = Tubingen Evaluation of Risk Factors for Early Detection of Neurodegeneration.

a Table is not all-inclusive of prodromal PD studies but rather includes a selected sample to illustrate different study designs.
b Initial report in the PARS described 4,999 participants; subsequent analyses have focused on a subset of 303.
c Unpublished, PD case counts among those with partial and full screening for nonmotor features, respectively.
d Unpublished, total PD case count between NHS and HPFS cohorts to date.
e Follow-up years reflect 5 years used to evaluate prodromal period in analyses.

DAT. This study demonstrates that the combination of hyposmia, positive family history of PD, and DAT deficit is strongly predictive of phenoconversion within 4 years. Notably, however, the sensitivity of this screening strategy is probably low because all PD cases among individuals without a family history of PD (~85% of cases) or among normosmic individuals would be missed.

Our team has taken another approach to establishing a cohort of individuals with high probability of prodromal PD. We estimated that fewer than 50 incident cases of PD would be expected within 4 years in a cohort of 10,000 individuals aged 70–79 years. To capture prodromal PD at younger ages and considering the imperfect performance of any screening algorithm, more than 100,000 individuals need to be screened to identify a few hundred individuals eligible for a prevention trial. This can only be accomplished using multistage screening approaches in which 1 or 2 very low-cost screening rounds are used to enrich the population with individuals at high enough risk of prodromal PD to justify applying more expensive, invasive, or burdensome specialized diagnostics. We have explored this strategy among participants in the HPFS25 and NHS. The first stage used 2 questions on self-administered questionnaires on constipation and 1 question on RBD. Individuals with either constipation or probable RBD (pRBD) and a random sample without either feature
were mailed the brief smell identification test (B-SIT)\textsuperscript{37} and self-administered questionnaires to further capture depressive symptoms and body pain using questions from the Short-Form Health Survey,\textsuperscript{38} color discrimination using a version of the Roth color discrimination test,\textsuperscript{39} excessive daytime sleepiness using the Epworth sleepiness scale,\textsuperscript{40} and parkinsonism using a set of 9 questions on changes in motor function.\textsuperscript{41} Including a sufficiently large random sample of individuals without prodromal features is critical to estimate the true sensitivity of the proposed strategy—without this sample, it is impossible to know how many true cases of prodromal PD in the source population have been missed. This enriched cohort (ProPD) comprises 20,769 individuals who are now being followed for changes in prodromal features and PD phenoconversion. To estimate preliminary upper bounds of the sensitivity, specificity, and PPV of different diagnostic algorithms, we estimated the association of different combinations of prodromal features with diagnosed PD. As expected, an increasing number of features resulted in higher odds of PD but reduced sensitivity.\textsuperscript{25} Extrapolating these findings to a hypothetical population of 10,000 men with a 2% prevalence of PD (i.e., 200 true cases) and assuming these features always precede clinical diagnosis, the combination of constipation, pRBD, and hyposmia would identify 59 of the 200 true cases (29% sensitivity) with a PPV of 35%, whereas the use of 6 nonmotor features would identify only 23 of the true cases (11% sensitivity) but achieve a 70% positive predictive value (Figure). These are reasonable enrichment levels considering the features were measured using mailed questionnaires that are inexpensive and low burden to participants. In a similar pilot study in Italy, 392 participants were recruited in the waiting room of 4 general practitioners and completed a 1-page self-administered questionnaire and an adapted self-administered B-SIT.\textsuperscript{42} Among these individuals, 24 (6.1%) had at least a 40% probability of having prodromal PD as defined by the updated Movement Disorder Society research criteria.\textsuperscript{43} The cost for collecting these data was 13 euros per subject, largely because of cost of B-SIT booklet and a 5 euro incentive per recruited participant for the physicians. Although screening with self-administered questionnaires is subject to measurement error and insufficient for diagnosis, individuals with high prodromal PD probability can be further screened using more specific tools, such as polysomnography for RBD confirmation, clinical assessment of motor symptoms, or imaging for DAT levels.

**Administrative Databases**

Existing administrative data sources have been leveraged to identify individuals with prodromal PD (Table). This approach is faster and logistically simpler than recruiting an ad hoc cohort and relies on very large study populations, thus providing stable PPV estimates. An initial attempt to identify prodromal PD was conducted in The Health Improvement Network (THIN) UK primary care database,\textsuperscript{44} which contains longitudinal medical records for more than 11 million individuals. Over 8,000 incident PD cases (defined by a first time PD diagnosis and 2+ antiparkinsonian drug prescriptions) and 46,000 controls were included in these analyses. The investigators searched the database for codes of symptoms associated with prodromal PD, including motor signs, autonomic and psychiatric features, and anosmia. The search focused on the 5 years preceding the index date, defined as the first reported date of PD diagnosis or antiparkinsonian medication prescription. The optimized algorithm for predicting PD achieved a PPV of 37% (95% CI 35%–39%), with a sensitivity of 43%. These results, however, were largely driven
by tremor—after excluding tremor, the PPV dropped to 9%. This highlights the difficulty of recognizing prodromal PD in a premotor phase, which is particularly challenging in administrative data because key nonmotor features, such as hyposmia and RBD, are grossly underreported. In this study, for example, anosmia was reported by only 0.37% of PD cases (as compared with ~70% in cohort studies) and was not associated with PD in multivariate analyses; RBD was not mentioned in the report, presumably because of its rarity. Furthermore, the actual diagnosis date likely precedes the index date in this study, suggesting that the “prodromal period” evaluated includes time when PD cases met diagnostic criteria. This limitation could be partially offset in future investigations by considering, for example, a period between 5 and 10 years before the index date, but lack of reliable information on hyposmia and RBD will remain an important obstacle until these features are routinely assessed during general medicine examinations.

A separate study leveraged administrative medical claims data to identify patients with incident PD among Medicare beneficiaries in the United States. As in the UK study, the investigators focused on the 5 years preceding the first-recorded PD diagnosis. Over 89,000 individuals with incident PD, representing all newly diagnosed PD cases in 2009, and 118,000 controls were included. Rather than focusing on PD-related feature codes, the US investigators considered all procedure and diagnosis codes and used machine learning methods to develop a prediction model, which ultimately included 536 codes. Although this approach identified individuals with a higher than average probability of future PD diagnosis, the sensitivity (73.5%) and specificity (83.2%) reported, when applied to a population with 2% prevalence of prodromal PD, would yield a PPV of only 8.2%. Furthermore, the limitations of the THIN study also apply to this investigation. Because of their limitations, administrative databases are unsuitable on their own to select individuals for a prevention trial, but, if individuals have free and easy access to their records, these data could complement information from other sources.

Current Status and Future Directions

In summary, composite cohorts represent an ideal resource for conducting prodromal PD research and should be further used as we move toward planning PD prevention trials. Although we do not yet have sufficient longitudinal data to provide a convincing and definitive strategy for identifying individuals to be enrolled in a prevention trial, it may be useful to imagine a hypothetical scenario, which will highlight the challenges that remain to be resolved. Assuming investigators wish to identify individuals for a 5-year prevention trial and with phenoconversion to manifest PD as the primary outcome, eligible individuals could be recruited as follows (numbers inferred from the HPFS ProPD cohort screening data):

**Stage 1:** Screen a general population sample of 100,000 individuals older than 60 years of age who have a sleep partner using 2 questions on constipation and 1 on pRBD (targeting a population at higher risk, because of even greater age, family history, or other risk factors would be more efficient but would exclude many prodromal PD cases). This screening, which could be done at minimal cost online through ad hoc advertising or primary health care physicians, would identify ~3,830 (3.83%) individuals with concurrent constipation and pRBD. Although focusing screening on individuals older than 60 years of age will miss cases with younger age at onset, such an age cutoff will also greatly improve the efficiency of screening a large population for potential cases of prodromal PD by focusing screening efforts on age groups at highest risk, thereby balancing the need to identify a sufficiently large study population with the practical and financial logistics of participant recruitment for a prevention trial.

**Stage 2:** Administer an olfactory test to these 3,830 individuals to identify those with hyposmia. Approximately 1,425 would be expected to be hyposmic, of whom ~500 should be true cases of prodromal PD, either in the premotor or early motor stage. A parkinsonism questionnaire could be used to further identify those individuals with motor symptoms and, therefore, higher probability of phenoconversion within 5 years. Approximately 296 (21%) of the 1,425 individuals with constipation, pRBD, and hyposmia are expected to screen positive for parkinsonism.

**Stage 3:** Use DAT imaging to identify individuals with evidence of dopaminergic deficit. If the purpose is to identify individuals in an advanced stage of prodromal PD, imaging could be restricted to the ~296 individuals with motor signs. Alternatively, individuals without parkinsonism could be of interest for trials targeting individuals in the earliest prodromal stage, with appearance and progression of motor signs or changes in DAT as the outcome. Although few other conditions are likely to cause multiple prodromal PD features, particularly with the co-occurrence of imaging evidence of a dopaminergic deficit, individuals selected for prevention trial participation whose symptoms are determined to be caused by a different etiology should be excluded from trial participation. Such exclusions could be based on the individual being diagnosed with such an alternative condition or on biomarker-based evidence, as appropriate.

A limitation of this plan is that it still excludes the 2/3 of individuals with prodromal PD without all the selected features. It is, therefore, important to conduct further research on prodromal PD and to gain a better understanding of its natural history and potential biomarkers. Among the latter are noninvasive imaging techniques, such as transcranial sonography and novel magnetic resonance methods. Promising results have also been obtained examining the volatilome and with the use of wearables to detect early gait changes. Rather than a one-size-fits-all approach, different strategies...
will need to be tailored to the specific needs of each trial, including the population being targeted and the type of intervention.

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**Disclosure**

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**Appendix Authors**

**References**

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