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Enrollment of Participants From Marginalized Racial and Ethnic Groups

A Comparative Assessment of the STEADY-PD III and SURE-PD3 Trials

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Abstract

Background and Objectives

Representation of persons from marginalized racial and ethnic groups in Parkinson disease (PD) trials has been low, limiting the generalizability of therapeutic options for individuals with PD. Two large phase 3 randomized clinical trials sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), STEADY-PD III and SURE-PD3, screened participants from overlapping Parkinson Study Group clinical sites under similar eligibility criteria but differed in participation by underrepresented minorities. The goal of this research is to compare recruitment strategies of PD participants belonging to marginalized racial and ethnic groups.

Methods

A total of 998 participants with identified race and ethnicity consented to STEADY-PD III and SURE-PD3 from 86 clinical sites. Demographics, clinical trial characteristics, and recruitment strategies were compared. NINDS imposed a minority recruitment mandate on STEADY-PD III but not SURE-PD3.

Results

Ten percent of participants who consented to STEADY-PD III self-identified as belonging to marginalized racial and ethnic groups compared to 6.5% in SURE-PD3 (difference = 3.9%, 95% confidence interval [CI] 0.4%–7.5%, p value = 0.034). This difference persisted after screening (10.1% of patients in STEADY-PD III vs 5.4% in SURE-PD 3, difference = 4.7%, 95% CI 0.6%–8.8%, p value = 0.038).

Discussion

Although both trials targeted similar participants, STEADY-PD III was able to consent and recruit a higher percentage of patients from racial and ethnic marginalized groups. Possible reasons include differential incentives for achieving minority recruitment goals.

Trial Registration Information

This study used data from The Safety, Tolerability, and Efficacy Assessment of Isradipine for Parkinson Disease (STEADY-PD III; NCT02168842) and the Study of Urate Elevation in Parkinson's Disease (SURE-PD3; NCT02642393).

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Parkinson disease (PD) is a chronic neurodegenerative condition that affects at least 1% of individuals older than 60 years and occurs in all races and ethnic groups.[1–3] Despite recent developments, there are no effective disease-modifying therapies in PD, necessitating large clinical trials evaluating new therapeutics.

Recruitment into randomized controlled trials (RCTs) in neurology is often challenging due to complexities in protocol design.[4] Recruitment of participants belonging to marginalized racial and ethnic groups has been low in several National Institute of Neurological Disorders and Stroke (NINDS)-funded and other clinical trials evaluating a broad range of neurologic conditions, including movement disorders.[5,6] In the case of PD, representation of such patients in clinical trials has historically fallen below their proportional prevalence, lessening the generalizability of therapeutics development for individuals with PD.[7]

The Safety, Tolerability, and Efficacy Assessment of Isradipine for Parkinson Disease (STEADY-PD III; NCT02168842) and the Study of Urate Elevation in Parkinson's Disease (SURE-PD3; NCT02642393) trials were NINDS-funded, phase 3 randomized clinical trials, which included participants from an overlapping set of Parkinson Study Group (PSG) clinical sites. In this study, we compare the different recruitment efforts and enrollment of persons from marginalized racial and ethnic groups in STEADY-PD III and SURE-PD3 trials to understand how their differences may inform efforts to improve inclusivity of future trials and observational studies.

Methods

Trial Participants, Organization, and Design

Both trials were conducted at PSG sites. The PSG is an independent consortium of scientific investigators committed to the cooperative planning, implementation, analysis, and reporting of controlled clinical trials and other research in PD and related disorders.

STEADY-PD III was a phase 3, randomized, 2-arm, parallel-group, placebo-controlled, double-blind, multicenter clinical trial designed to assess the disease-modifying potential of isradipine in patients with early PD not receiving or requiring symptomatic therapy at baseline other than a stable dose of amantadine or anticholinergics. Participants were randomized 1:1 to receive either isradipine 5 mg twice daily or placebo for 36 months. Northwestern University served as the Clinical Coordination Center (CCC); the University of Rochester Clinical Trials Coordination Center served as the Data Coordination Center (DCC).[8] Inclusion criteria included age greater than 30 years, a PD diagnosis made within 3 years of screening, and not receiving excluded symptomatic PD therapy.[9] Exclusion criteria included history of significant cardiovascular disease, unstable medical or psychiatric conditions, significant cognitive impairment, use of calcium channel blockers, or other use of antihypertensives that would make exposure to isradipine unsafe.

SURE-PD3 was a phase 3, randomized, 2-arm, parallel-group, placebo-controlled, double-blind, 2-period, multicenter clinical trial designed to assess the disease-modifying potential of inosine in patients with early PD not receiving or requiring symptomatic therapy at baseline other than a stable dose of a monoamine oxidase–B inhibitor. Participants were randomized 1:1 to receive either oral inosine titrated to achieve a serum urate level from 7.1 to 8.0 mg/dL or placebo for 24 months. Massachusetts General Hospital served as the CCC; the University of Rochester served as the DCC.[10] Inclusion criteria included age greater than 30 years, a PD diagnosis made within 3 years of the screening visit, not receiving excluded symptomatic PD therapy, and serum urate ≤5.7 mg/dL. Exclusion criteria included history of significant cardiovascular disease, unstable medical or psychiatric conditions, significant cognitive impairment, use of thiazide diuretics, and history of crystallopathy or increased risk of crystallopathy due to low urine pH or renal impairment.

Minority Recruitment

STEADY-PD III and SURE-PD3 shared similar methodologies and strategies to improve the enrollment of persons belonging to marginalized racial and ethnic groups. Participants were consented from a total of 86 clinical sites between the 2 trials, 25 unique to STEADY-PD III, 31 unique to SURE-PD3, and 30 shared between the 2 trials. Sites were selected based on multiple performance criteria including their capacity and experience in enrollment of marginalized participants. The trials also developed a Recruitment Toolkit composed of patient and clinician engagement materials that encouraged recruitment of patients from marginalized racial and ethnic groups, such as cards, site brochures, posters, thank you cards, and primary care physician notification and physician outreach letters (eFigures 1–4, links.lww.com/CPJ/A395). Recruitment periods for STEADY-PD III and SURE-PD3 occurred sequentially but within a few years of each other, from November 2014 to November 2015 and from July 2016 to December 2017, respectively.

A major difference between the trials was a funding mandate requiring 10% inclusion of patients belonging to a marginalized racial and ethnic group for STEADY-PD III, whereas a 10% minority inclusion was only encouraged for SURE-PD3. Based on the internal discussions by the STEADY-PD III Steering Committee, the sites and research coordinators received direct communication regarding marginalized group recruitment goals as set by the sponsor that stipulated additional minority recruitment initiatives.

Uniquely, STEADY-PD III leadership also created a Minority Recruitment Application to which sites could apply for additional funding to support local outreach of marginalized participants. Site coordinators launched other local initiatives, such as a contacting regional professional and lay organizations and organizing events where information regarding the trial would be shared. Finally, STEADY-PD III was part of The Randomized Recruitment Intervention Trial (RECRUIT), in which clinical sites were randomized to receive an intervention based on enhanced trust levels between investigators and marginalized groups

serving physicians compared with control.[11] A total of 14 clinical sites (7 intervention and 7 control sites) and 88 participants were enrolled. There was a trend toward greater recruitment of marginalized persons in the intervention arm, although the confidence interval (CI) included 1 (odds ratio 2.2, CI 0.6–8.0).

On the other hand, SURE-PD3 focused on other targeted strategies. For instance, it included a network-based recruitment initiative to use medical records to reach out directly to primary care physicians who had diagnosed PD as an attempt to overcome specialist referral barrier that disproportionately affects candidates from belonging to marginalized racial and ethnic groups. Moreover, it also created a participant reimbursement debit card system (estimated around $1,000 total per participant completing all visits) to potentially eliminate barriers to participation that disproportionately limit the enrollment of candidates from marginalized racial and ethnic groups. Although both trials translated materials into Spanish to facilitate enrollment of marginalized groups, SURE-PD3 only did that for consent form and clinical scales, whereas STEADY-PD III also encouraged sites to perform translations of recruitment materials prior to consent.

Data and Statistical Analysis

The proportions of consented and randomized participants who self-identified as a marginalized racial or ethnic group were compared between trials using the Fisher exact test and as differences and ratios with 95% Wald CIs. We considered a 2-tailed p value <0.05 statistically significant. SAS (version 9.4, SAS Institute Inc., Cary, NC) was used for all statistical analyses. Race and ethnicity were classified according to the US Federal standards[12] as American Indian or Alaska Native participants, Asian participants, Hispanic or Latino participants, Native Hawaiian or other Pacific Islander, or White participants.[13] For both trials, racial and ethnic data were self-identified by presenting the categories defined above. This did not differ between both trials. Multiracial individuals were classified according to the least prevalent race identified. Patients with missing data on race and ethnicity were omitted from the analysis.

Standard Protocol Approvals, Registrations, and Patient Consents

This study used data from STEADY-PD III (NCT02168842) and SURE-PD3 (NCT02642393) clinical trials. Each protocol was approved at applicable sites, and written informed consent was obtained from all participants in their respective trial prior to screening.

Data availability

De-identified data may be obtained from the clinical research archive administered by NINDS.

Results

A total of 998 consented participants were analyzed. Two SURE-PD3 participants who lacked data on race and ethnicity were omitted. STEADY-PD III consented a larger percentage of participants who self-identified as belonging to a marginalized racial or ethnic group than SURE-PD3 (10.4% vs 6.5%, difference = 3.9%, 95% CI 0.4%–7.5%, ratio = 1.60, 95% CI 1.06–2.43, Fisher $p = 0.034$; Table).

Most of the observed difference in minority recruitment occurred at the 30 overlapping sites. STEADY-PD III consented a larger percentage than SURE-PD3 of participants from overlapping sites (64% vs 50%, Fisher $p < 0.001$).

STEADY-PD III randomized a larger percentage than SURE-PD3 of participants who self-identified as part of a racial or ethnic marginalized group (10.1% vs 5.4%, rate difference = 4.7%, 95% CI 0.6%–8.8%, rate ratio = 1.87, 95% CI 1.06–3.32, Fisher $p = 0.038$). By design, STEADY-PD III randomized a larger percentage than SURE-PD3 of participants with screening serum urate >5.7 mg/dL. Even among those with screening serum urate ≤5.7 mg/dL, STEADY-PD III randomized a larger percentage than SURE-PD3 of participants who self-identified as belonging to a racial or ethnic marginalized group (10.3% vs 5.4%, rate difference = 4.9%, 95% CI 0.3%–9.5%, rate ratio = 1.90, 95% CI 1.04–3.48, Fisher $p = 0.035$). This was true for Black or African American participants in particular (2.5% in STEADY-PD III vs 0.8% in SURE-PD3).

Discussion

Despite recruiting participants over similar time periods, under similar eligibility criteria and from similar sites (including geographic location), STEADY-PD III was able to successfully enroll more participants belonging to marginalized racial and ethnic groups when compared with SURE-PD3. A number of factors may explain this discrepancy and could guide improvements in recruitment in future PD trials.

Although site selection was slightly different in both trials, nonoverlapping sites were responsible for a small percentage of consented patients from marginalized racial and ethnic groups. The difference in such enrollment does not appear to be driven by site selection.

Although largely similar, several important eligibility criteria differed between the trials. A nonfasting serum urate ≤5.7 mg/dL at the first screening visit was required for SURE-PD3 eligibility. Prior literature has suggested that African American patients may have higher serum urate levels.[14] Nevertheless, even after restricting the analysis to participants with screening serum urate ≤5.7 mg/dL, STEADY-PD III consented a larger percentage than SURE-PD3 of African American participants.

The milestone to achieve at least 10% minority recruitment increased attention to this topic by the STEADY-PD III leadership. Following internal discussion by the STEADY-PD III steering committee, the clinical research sites' coordinators and investigators were informed about the importance of

Table Overall Design and Enrollment of Participants Belonging to Marginalized Racial and Ethnic Groups Comparison Between STEADY-PD III and SURE-PD3

	STEADY-PD III	SURE-PD3
Minority recruitment strategies	• Translated study and recruitment materials. • Recruitment toolkit • Minority Recruitment Application with extra funding available • Local initiatives with events in collaboration with organizations • Participation in RECRUIT • Mandatory 10% minority inclusion by the NINDS	• Translated study materials • Recruitment toolkit • Encouraged 10% minority inclusion by the NINDS • Supplemental site funding offered for local initiatives to enhance minority enrollment
Consented participants	413	585[a]
No. of clinical sites	57	61
No. of sites requesting additional funds for minority recruitment	6	0
Total racial and ethnic minorities consented, % (N)	10.4 (43)	6.5 (38)
Hispanic or Latino, % (N)	2.91 (12)	2.91 (17)
Black or African American, % (N)	3.15 (13)	1.03 (6)
Asian, % (N)	2.91 (12)	1.54 (9)
Native Hawaiian or other Pacific Islander, % (N)	0.24 (1)	0.34 (2)
American Indian or Alaska Native, % (N)	1.21 (5)	0.68 (4)
Randomized participants	336	298
Total racial and ethnic minorities randomized, % (N)	10.1 (34)	5.4 (16)

Abbreviations: NINDS = National Institute of Neurological Disorders and Stroke; STEADY-PD III = Safety, Tolerability, and Efficacy Assessment of Isradipine for PD; SURE-PD3 = Study of Urate Elevation in Parkinson Disease.
[a] Two additional participants were consented but lacked data on race or ethnicity and were excluded from analysis.

marginalized racial and ethnic group enrollment, and informed that the study completion was dependent on reaching the specific goal previously defined by the NINDS. Therefore, it is possible that the condition to meet the milestones could have motivated additional focus on the recruitment of participants belonging to marginalized groups by site staff.

Both trials selected centers serving populations belonging to marginalized racial and ethnic groups and provided translated trial materials to support the enrollment of such participants. Strategies included the identification of potential participants from sites' broader health care network databases and dedicated funding for translation of trial-related documents. Nevertheless, STEADY-PD III encouraged the translation of recruitment and advertisement materials, whereas SURE-PD3 mostly focused on consent forms and scales. Only STEADY-PD III used a program for funding additional minority outreach at sites, and only STEADY-PD III sites participated in the RECRUIT initiative. In their Health Care Provider Outreach Letter, STEADY-PD III investigators also included a sentence encouraging the enrollment of participants from marginalized racial and ethnic groups, whereas SURE-PD3 did not (eFigures 1–4, links.lww.com/CPJ/A395). Nevertheless, it appears that the effect of the intervention did not fully explain the recruitment differences. Of interest, the RECRUIT trial group also acknowledges the possibility that differences in NINDS guidance and policies could have played a role in the overall recruitment of participants belonging to marginalized racial and ethnic groups.[11]

Although both trials were large phase 3 NINDS-funded trials, the number of consented or randomized participants belonging to marginalized racial and ethnic groups was small and the estimates were imprecise. Given that the difference was seen only for racial and not ethnic marginalized groups and the analysis was not prespecified prior to first consent, chance cannot confidently be ruled out as the cause.

Previous studies identify underrepresentation of participants belonging to marginalized racial and ethnic groups in PD trials or even missing data regarding racial and ethnic information in most clinical trials in the United States.[7,15] Many reasons for these deficiencies have been hypothesized. As large PD trials are mostly performed in subspecialized movement disorders clinics, persons from marginalized racial and ethnic groups might have lower enrollment rates as they are less likely to be followed by general neurologists or movement disorders specialists.[16–18]

Most of the difference in recruitment of participants from marginalized racial and ethnic groups resulted from differences in enrollment of African American patients. Hesitancy and lack of trust in the health system and in clinical research by African American participants have been reported.[19,20] The contribution of negative experiences, such as in the Tuskegee Study of Untreated Syphilis, has been reported as a historical factor underlying such distrust. In that study, which ran from 1932 to 1972, treatment was unethically withheld from African American patients to allow investigators to observe the natural history of syphilis.[21,22]

Previous studies have also reported that patients belonging to marginalized racial and ethnic groups may be less well informed about or aware of clinical trials.[23,24] For instance, a recent study evaluating the willingness of Hispanic individuals with PD to participate in clinical trials revealed that the lack of awareness regarding PD research remained a significant obstacle. Additional reasons limiting recruitment also included language barriers and potential financial burden.[24] Similar evidence has also been descried in other subspecialties. Non-White participants in 2 oncology clinics were less likely to gather clinical trial information from physicians or from the internet when compared with White individuals and more likely to believe that they had been treated in clinical trials without their knowledge,[25] reflecting the true experience of marginalized racial and ethnic groups in recent times.[22]

Strategies to increase the number of participants belonging to marginalized racial and ethnic groups in PD research have been tested. In 2012, Tilley et al. performed an ancillary study of a recruitment intervention to increase diversity in enrollment. The increase in community physicians' engagement in clinical trials and the selection of coordinators strongly connected to the community did not result in higher enrollment of patients from marginalized racial and ethnic groups.[26] The RECRUIT trial reported that promoting trust-based approaches between physician-investigators and minority-serving physicians and their patients might be a successful strategy.[27] This intervention was implemented in the STEADY-PD III trial at selected sites. Other initiatives focusing on recruitment of marginalized racial and ethnic groups into PD trials have been developed. The Fostering Inclusivity in Research Engagement for Underrepresented Populations in Parkinson's Disease supported by the Michael J. Fox Foundation was created with a goal of developing specific interventions to educate and engage participants belonging to marginalized racial and ethnic groups in PD research.[28] Of note, only 6 clinical sites requested additional funds to enhance racial and ethnic diversity in enrollment in STEADY-PD III, and none did in SURE-PD3. Although the underlying reasons are unclear, the lack of clear guidelines and knowledge of how funds may be better used to directly promote the recruitment of such groups might have contributed to the low number of applications.

TAKE-HOME POINTS

- Although both studies had similar eligibility criteria and targeted similar PD subpopulations, STEADY-PD III enrolled a higher percentage of persons belonging to marginalized racial and ethnic groups when compared with SURE-PD 3.
- Differential incentives for achieving minority recruitment goals by funding agencies might be a contributing factor for the observed difference.
- Additional research should identify factors associated with differential recruitment of marginalized racial and ethnic groups in Parkinson disease trials and investigate the role of trial sponsors and funding agencies.

Our descriptive comparison has several limitations. First, our study involved only 2 trials and small numbers of participants belonging to marginalized racial and ethnic groups, which may limit the generalization of and confidence in our results. Differences in eligibility criteria between the 2 trials might have partially contributed to the observed differences. In addition, we do not have detailed information on the racial and ethnic background of the study research coordinators and investigators, which might have played a role in the enrollment of minorities. A detailed comparison between the enrollment of patients belonging to marginalized racial and ethnic groups and the baseline demographic distribution in the catchment areas of the study recruitment sites was not performed. Finally, most strategies implemented in both trials had a goal to increase the overall enrollment of participants from racial and ethnic marginalized groups, with no specific targeted programs to different subpopulations.

STEADY-PD III enrolled a larger percentage of participants belonging to marginalized racial and ethnic groups compared with SURE-PD3, although both trials targeted similar PD subpopulations and recruited from overlapping clinical sites. Differential incentives for achieving recruitment of patients from marginalized racial and ethnic groups and differential implementation of targeted recruitment efforts at selected sites may explain the difference. Strong incentives for the recruitment of patients belonging to marginalized racial and ethnic groups (e.g., tying it to continued study funding) may be warranted.

Future research should identify factors affecting recruitment of this population and strategies for improving participation of historically marginalized racial and ethnic groups in PD trials. The inclusion of diverse racial and ethnic populations in clinical trials is urgently needed to advance our understanding of PD across all races and ethnicities.

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Disclosure

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