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Minority recruitment trends in phase III prostate cancer clinical trials (2003-2014): progress and critical areas for improvement

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Abstract

Purpose: U.S. minority groups have been historically underrepresented in phase III prostate cancer clinical trials despite often having higher risk disease. This study analyzes enrollment trends of major U.S. racial/ethnic groups in phase III prostate cancer trials between 2003-2014 compared to Surveillance, Epidemiology, and End Results (SEER) incidence data.

Materials and Methods: Phase III prostate cancer trials primarily enrolling patients from the U.S. were identified in the ClinicalTrials.gov database. Enrollment trends were analyzed for major racial/ethnic groups. Prostate cancer incidence data from the SEER registry was used to identify enrollment targets. The enrollment difference was determined by calculating the absolute difference between the percentage of a racial/ethnic subgroup in the SEER registry population and the percentage of that subgroup in the phase III prostate cancer trial population.

Results: Among 39 studies identified, African American enrollment in therapeutic trials increased across the study period ($p<0.001$). The enrollment difference for African Americans was -9.0% (95% CI, -7.6 to -10.5; $p<0.001$) in 2003-05 and 1.4% (95% CI, 0.2 to 2.6; $p = 0.020$) in 2012-14. However, African American men were under-enrolled in metastatic disease trials (enrollment difference = -5.8%; 95% CI, -4.8 to -6.8; $p<0.001$). Latino and Asian American men were consistently under-enrolled in all trial types.

Conclusions: U.S. minority groups were largely under-enrolled in phase III prostate cancer trials between 2003-2014. While recruitment efforts may have had an impact, as demonstrated by increased enrollment of African American men, there remains a need to expand recruitment efforts to achieve diversity in trials.

Introduction:

Racial and ethnic disparities in prostate cancer persist. Compared to White men, African American men experience 60% higher incidence of disease, are more likely to be diagnosed at a younger age, have more aggressive disease, are more likely to be undertreated for high-risk disease, and have more than twice the mortality due to prostate cancer.[1–3] Hispanic/Latino men with prostate cancer are more likely to be diagnosed with advanced stage prostate cancer and have higher tumor grades compared to non-Hispanic White men.[4] Filipinos, Asian Indians/Pakistanis, and Pacific Islanders in the United States (U.S.) are also more likely to present with advanced prostate cancer compared with White men.[5,6] Numerous factors likely interact and contribute to these disparities, including socioeconomics, access to care, quality of care, environmental factors, genetics, and systematic under-representation in clinical trials.[7,8]

U.S. minority groups have been historically underrepresented in phase III prostate cancer clinical trials.[9] With low enrollment of minorities, trials often lack statistical power to reveal potential racial and ethnic differences in response to therapy. Acknowledging the need for increased minority inclusion, the Health Revitalization Act of 1993 mandated guidelines for minority inclusion in National Institutes of Health (NIH) funded research.[10] The Act was amended in 2001 to define minimum standards for collecting and reporting data by sex/gender and race/ethnicity, and again amended in 2017 with a requirement for phase III clinical trials to submit results by sex/gender and race/ethnicity to ClinicalTrials.gov.[11] Since the enactment in 1993, efforts have been made to increase the enrollment of minorities in prostate cancer trials, but it is unclear if they are having a meaningful impact.[12]

This study aims to analyze enrollment trends of major U.S. racial/ethnic groups in phase III prostate cancer clinical trials. We compare clinical trial enrollment of each group to prostate cancer incidence data from the Surveillance, Epidemiology, and End Results (SEER) registry, as a suggested enrollment target for racial/ethnic groups. We chose to use the SEER registry because it accounts for cancer diagnoses in a large proportion of the U.S population and is designed to mirror the sociodemographics of the U.S. census.[13] We hypothesize that the proportion of each U.S. minority subgroup in the clinical trial population will increase across the study period, but will not exceed the proportion of each subgroup in the SEER prostate cancer population.

Methods:

Data Collection

We identified phase III prostate cancer clinical trials completed between 2003-2014 from the U.S. National Library of Medicine (NLM) ClinicalTrials.gov database. The ClinicalTrials.gov database defines a clinical trial (therapeutic or behavioral) as a clinical study where participants are assigned to treatment or control groups and researchers evaluate the effects of an intervention on health-related outcomes.[14] We define a therapeutic clinical trial as an investigation of a drug, biologic agent, dietary supplement, surgical procedure, radiotherapy, device or implant. A behavioral clinical trial was defined as a clinical study that evaluates the effects of an intervention on a behavioral outcome.

Although the ClinicalTrials.gov database was created in February 2000, only two prostate cancer clinical trials were registered from 2000-2002; therefore, we chose to begin the study period in 2003. Trials completed after 2014 were not included because SEER population data on incidence was not yet available after 2014. Trials enrolling participants outside of the U.S. and Canada were excluded. Included trials primarily enrolled patients from the U.S., but eight trials enrolled some patients from Canada. Of these eight trials, only 7.9% of the enrollment locations were in Canada.

Trials with incomplete reporting of participant race/ethnicity were included if they at a minimum reported the White population. If a study did not publish any enrollment results by race or ethnicity within their publication(s) or on ClinicalTrials.gov, corresponding authors were contacted electronically with a request for enrollment data. If results were not found in publication(s), on ClinicalTrials.gov, or by email request, the trial was excluded (Fig. 1).

We utilized prostate cancer incidence data from the SEER registry to calculate the proportion of disease burden and to identify enrollment targets by race/ethnicity and time period. SEER registry locations are strategically chosen to represent the racial/ethnic demographics of the U.S. census.[13] For example, based on the 2010 U.S. Census and SEER data, African Americans account for 12.6% and 10.9% of the population, respectively.

We analyzed incidence data for 688,266 patients diagnosed with prostate cancer between 2003 and 2014 using the SEER*Stat software (version 8.3.4).[15] SEER records were categorized by

race and ethnicity into: non-Hispanic White (hereafter: White), non-Hispanic Black/African American (hereafter: African American), Asian American or Pacific Islander (hereafter: Asian American), and Hispanic/Latino (hereafter: Latino). Other categories of interest in the SEER records included time period (2003-05, 2006-08, 2009-11, 2012-14) and disease stage.

Data Analyses

We calculated an enrollment difference using the difference between the percentage of a subgroup in the trial population and the percentage of that subgroup in the SEER population. The enrollment difference was a positive value if the trial enrollment percentage exceeded the SEER population percentage, and a negative value if the SEER population percentage exceeded the trial enrollment percentage. If a study did not report enrollment data for a certain race/ethnicity, its total population was not included in the calculation of the proportion of trial population represented by that race/ethnicity.

We conducted a two-sample test of proportions comparing the percentage of each racial/ethnic subgroup in the trial population to that of the U.S. prostate cancer population for the four time periods in the study (2003-05, 2006-08, 2009-11, 2012-14). The null hypothesis was that the proportions of a given race/ethnicity in the clinical trial and prostate cancer populations were equal. In order to observe changes in enrollment proportions over time, a chi-squared test for trend was used. We focused the trends analyses on therapeutic trials, and excluded behavioral trials because these two trial types are considerably different in their size, methods of enrollment, and enrollment settings. Additionally, there were not enough behavioral trials in our study to

perform a separate trend analysis. Sub-analyses of trend and enrollment difference were also done for therapeutic trials enrolling patients with metastatic disease. All p-values were 2-sided and the statistical significance threshold was defined as $p<0.05$. All analyses were performed using STATA version 15 (College Station, Texas).

Results:

Seventy-seven phase III prostate cancer clinical trials with enrollment locations in the U.S. were completed between 2003 and 2014 and registered with the NLM ClinicalTrials.gov database. Twenty-six trials did not meet eligibility criteria (Fig. 1). Of the remaining 51 trials, 12 did not have available data on participant race or ethnicity within the study's publications, on ClinicalTrials.gov, or by emailing a data request to the corresponding authors.

Thirty-nine phase III prostate cancer clinical trials were included with a total clinical trial population of 20,820 (Table 1). Of the 35 therapeutic trials, 27 were drug trials, two were dietary supplement trials, two tested biologic agents, two were surgical trials, one tested a medical device, and one was a radiation therapy trial (Data Supplement). Seventeen trials enrolled patients with localized and/or regional disease (43.6%) and 11 trials enrolled patients with metastatic disease (28.2%). Five trials enrolled patients without prostate cancer, and accounted for 30.7% of the total trial population of the study (Table 1). Three of the five trials enrolling patients without prostate cancer were behavioral interventions and two studied preventative drug therapies.

Of the 35 trials resulting in publication, five trials (14.3%) published enrollment data only for White patients and categorized non-White patients as “other” or “unknown”, 28 (80.0%) published enrollment data on African Americans, 18 (51.4%) on Latinos, and 18 (51.4%) on Asian Americans. Of all trials in this study, only three (7.7%) reported enrollment results stratified by both race and ethnicity within the ClinicalTrials.gov database.

Comparison of SEER and trial populations (2003-2014)

White patients accounted for 69.5% of prostate cancer incidence in the SEER registry, and represented 77.8% of the total trial population, 82.0% of the therapeutic trial population, and 63.1% of the behavioral trial population ($p<0.001$, Fig. 2). African American patients represented 14.2% of prostate cancer incidence in the SEER registry, 17.9% of the total trial population ($p<0.001$), 14.3% of therapeutic trial population ($p=0.72$), and 30.4% of the behavioral trial population ($p<0.001$). Latino patients accounted for 8.8% of prostate cancer incidence in the SEER registry, 4.2% of the total trial population, 3.7% of the therapeutic trial population, and 5.9% of the behavioral trial population ($p<0.001$). Asian American patients accounted for 4.6% of prostate cancer incidence in the SEER registry, 1.0% of the total trial population, and 0.8% of the therapeutic trial population ($p<0.001$).

Trends in enrollment (by 3-year intervals)

The proportion of White patients was consistently above SEER-based target enrollment in therapeutic trials across the four study intervals; however, this proportion decreased over time

with a significant test for trend (p<0.001; Fig. 3, A). The proportion of African American men in the therapeutic trial population progressively increased across the study period (p<0.001; Fig. 3, B). The proportion of Latinos did not significantly change (p<0.46; Fig. 3, C), and the proportion of Asian Americans modestly increased (p=0.035; Fig. 3, D).

The White enrollment difference decreased across the study period, from 20.4% (95% CI, 18.8 to 22.1; p<0.001) in 2003-05 to 13.0% (95% CI, 11.7 to 14.4; p<0.001) in 2012-14 (Fig. 4, A). The African American enrollment difference was -9.0% (95% CI, -7.6 to -10.5; p<0.001) in 2003-05 and 1.4% % (95% CI, 0.2 to 2.6; p=0.020) in 2012-14 (Fig. 4, B). Latino and Asian American men were consistently below SEER-based target enrollment. The Latino enrollment difference ranged from -3.9% to -5.7% (Fig. 4, C), and the Asian American enrollment difference ranged from -3.4% to -3.9% (Fig. 4, D).

In the sub-analysis of therapeutic trials enrolling patients with metastatic disease, White patients represented 65.0% of the SEER population with distant disease, and 84.7% of the metastatic trial population from 2003 to 2014. Across all years, African American men accounted for 17.5% of the SEER population with distant disease, and 11.7% of the metastatic trial population. The proportion of White enrollment decreased over time with a significant test for trend (p<0.001; Fig. 5, A). African American enrollment trended towards increased enrollment (p=0.014; Fig. 5, B). The African American enrollment difference was -13.1% (95% CI, -10.4 to -15.7; p<0.001) in 2003-05 and -2.9% (95% CI, -1.1 to -4.7; p=0.004) in 2012-14 (Data Supplement). Latino and Asian American patients were consistently below enrollment targets in metastatic trials (Fig. 5, C

and D). Latino enrollment decreased (p=0.026; Fig. 5, C), while Asian American enrollment modestly increased (p=0.027; Fig. 5, D).

Discussion:

It has been 25 years since the Health Revitalization Act of 1993 mandated the inclusion of minorities in NIH funded research. The NIH amended the act in 2001 to include guidelines for stratifying study results by sex/gender and race/ethnicity, and has recently mandated reporting of baseline enrollment data by race/ethnicity for publication on ClinicalTrials.gov.[11] The Food and Drug Administration designated 2016 the "Year of Diversity in Clinical Trials" to encourage minority inclusion.[16] In spite of these efforts, our findings suggest that African American men are under-enrolled in advanced disease trials, and Latino and Asian American men are under-enrolled in all types of trials. However, government mandates and support for diversity may have impacted enrollment, as demonstrated by significantly increased enrollment of African Americans in therapeutic trials.

Our results demonstrate that investigators are not sufficiently reporting data by race/ethnicity. Only three studies in this analysis reported enrollment results stratified by race and ethnicity in ClinicalTrials.gov. Over 14% of studies resulting in publication did not report African American enrollment, and simply categorized patients as "White" and "other". It has long been established that African American men have a higher incidence and risk of death from prostate cancer, so it is concerning that a significant percentage of trials do not report African American enrollment. Additionally, only half of the trials published data on Latino and/or Asian American enrollment,

which are the fastest growing racial/ethnic groups in the U.S.[17] Future trials should oversample racial/ethnic minority groups, above SEER incidence rates, to allow for statistically powered race-stratified or sub-group analyses.[18] Additionally, funding agencies – such as the NIH, should identify ways to enforce enrollment and publication mandates.

In order to optimize minority enrollment, researchers must address limited access to care at academic centers, patient mistrust of healthcare systems, researcher biases, and cultural and linguistic barriers to enrollment. Therapeutic cancer trials at large cancer centers may be less accessible to minority communities.[19] Studies have also shown minorities are more likely to participate in trials when research personnel are from the same racial, cultural or linguistic background, or when they are enrolled through trusted institutions such as places of worship and community-based organizations.[20–23] Biases amongst clinical research teams must also be addressed. For example, some researchers believe minorities have little interest in research participation and therefore don't recruit, despite the fact that studies report minorities are willing to participate in clinical trials at the same rate as their White counterparts.[24–26] Our finding that behavioral trials have had more success in recruiting minorities compared to therapeutic trials may reflect differences in investigator beliefs, study design, and enrollment location.

This study has some limitations. First, SEER incidence data as enrollment targets for clinical trials may underestimate the burden of disease among minorities, as there are areas that do not participate in the SEER program (e.g., Detroit) and SEER data covers only 34.6% of the total U.S. population.[27–29] Second, we excluded twelve trials because they did not publish any

enrollment data by race/ethnicity or provide data when it was requested via email correspondence, and many of the included trials had incomplete reporting. There is potential for selection bias since studies not reporting enrollment data may have inadequate inclusion of minorities. Therefore, our study findings may overestimate minority enrollment. Third, this study did not account for substantial diversity within racial/ethnic categories by disaggregating data among Asian American or Latino patients. Lastly, we did not utilize individual patient data but rather relied on summary statistics.

Despite these limitations, this study has several strengths. It is the first investigation of prostate cancer clinical trial enrollment utilizing SEER incidence data and trial enrollment data to evaluate enrollment disparities. It provides researchers with a suggested framework to establish clinical trial enrollment targets. It also evaluates reporting on race/ethnicity within publications and on ClinicalTrials.gov, which is a valuable database for providers, patients, and researchers to access trial results and information.

Conclusions:

Much work remains in order to improve the enrollment of U.S. minority groups in phase III prostate cancer clinical trials. Efforts to improve enrollment may have led to increased inclusion of African American men in therapeutic trials as a whole; however, they face under-enrollment in advanced disease trials. Asian American and Latino patients also face persistent under-enrollment across all trial types. Investigators should work to improve recruitment and

enrollment efforts, and report enrollment data by race and ethnicity so that patients, providers, and researchers can better grasp the generalizability and applicability of study results.

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Figure Legends:

Figure 1. Flow diagram showing study identification, eligibility, and inclusion process.

Figure 2. Phase III prostate cancer clinical trial enrollment by race/ethnicity and trial type in comparison to proportion of prostate cancer in Surveillance, Epidemiology, and End Results (SEER) registry population by race/ethnicity from 2003-2014.

* indicates significant *P* value (<0.05) from two sample test of proportion comparing proportion of trial enrollment by race/ethnicity and trial type to proportion of prostate cancer in SEER by race/ethnicity.

†Asian American enrollment results not reported in the four behavioral trials.

Figure 3. Percentage of White, African American (AA), Hispanic/Latino (HL), and Asian American (Asian) patients amongst phase III prostate cancer therapeutic trial population and the Surveillance, Epidemiology, and End Results (SEER) prostate cancer population, 2003 to 2014. (A) White. (B) AA. (C) HL (D) Asian. *P* trend value corresponds to chi-square test for trend of proportion in trial enrollment. *P* value for two sample test of proportion comparing proportion of trial enrollment by race/ethnicity to proportion of prostate cancer in SEER by race/ethnicity was significant (<0.05) for all comparisons.

Figure 4. Enrollment difference between phase III prostate cancer therapeutic trials and the Surveillance, Epidemiology, and End Results (SEER) prostate cancer population with 95% confidence intervals, 2003 to 2014. (A) White patients. (B) African American patients. (C) Hispanic/Latino patients. (D) Asian American patients. The enrollment difference is the absolute difference between the percentage of a racial/ethnic group in the trial population and the percentage of that racial/ethnic group in the SEER population.

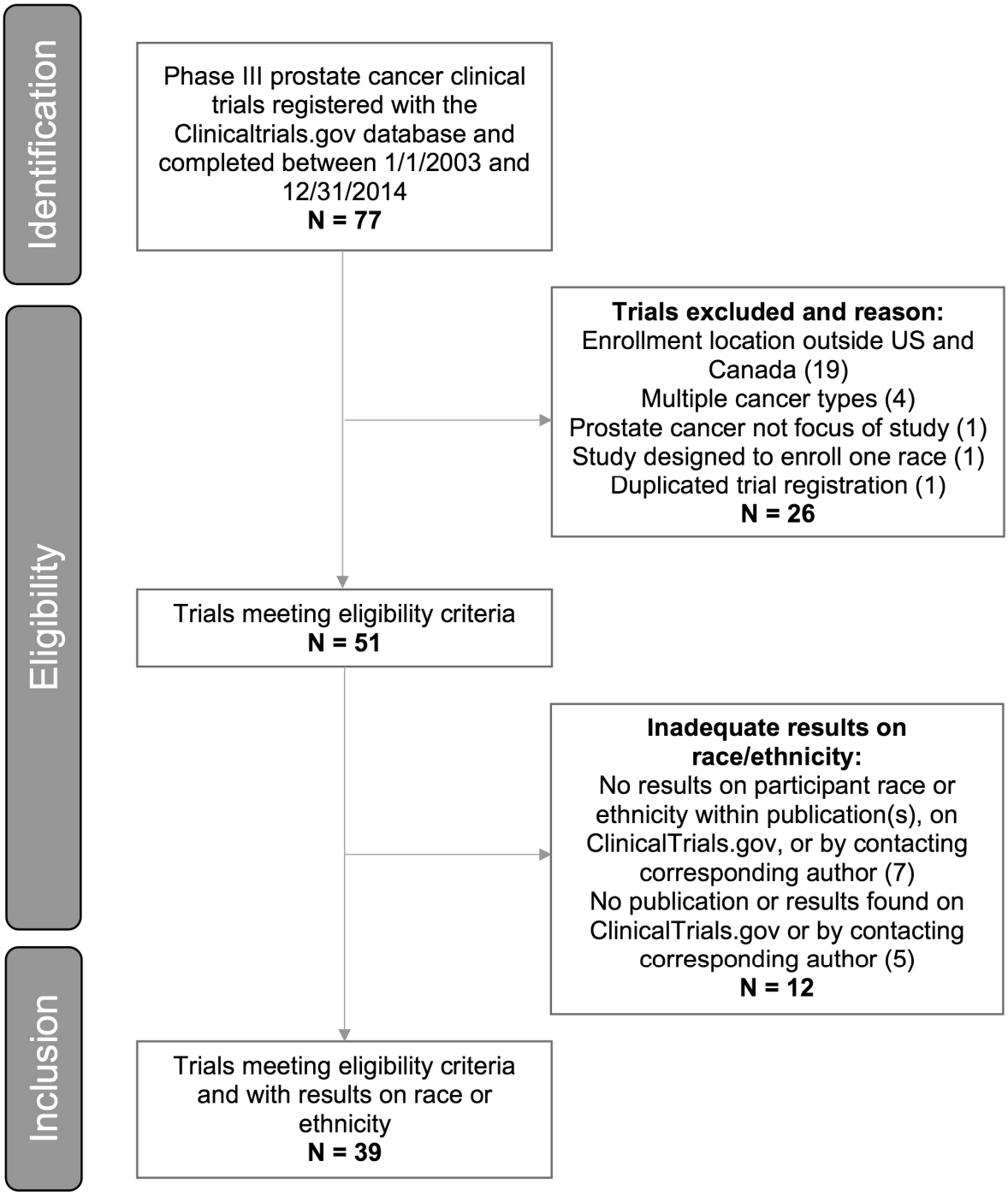
Figure 5. Percentage of White, African American (AA), Hispanic/Latino (HL), and Asian American (Asian) patients in phase III prostate cancer clinical trials enrolling patients with metastatic disease and the in Surveillance, Epidemiology, and End Results (SEER) metastatic prostate cancer population, 2003 to 2014. (A) White. (B) AA. (C) HL. (D) Asian. *P* trend value corresponds to the chi-square test for trend of proportion in trial enrollment.
P value for two sample test of proportion comparing proportion of trial enrollment by race/ethnicity to proportion of prostate cancer in SEER by race/ethnicity was significant (<0.05) for all comparisons except for HL in 2003-05.

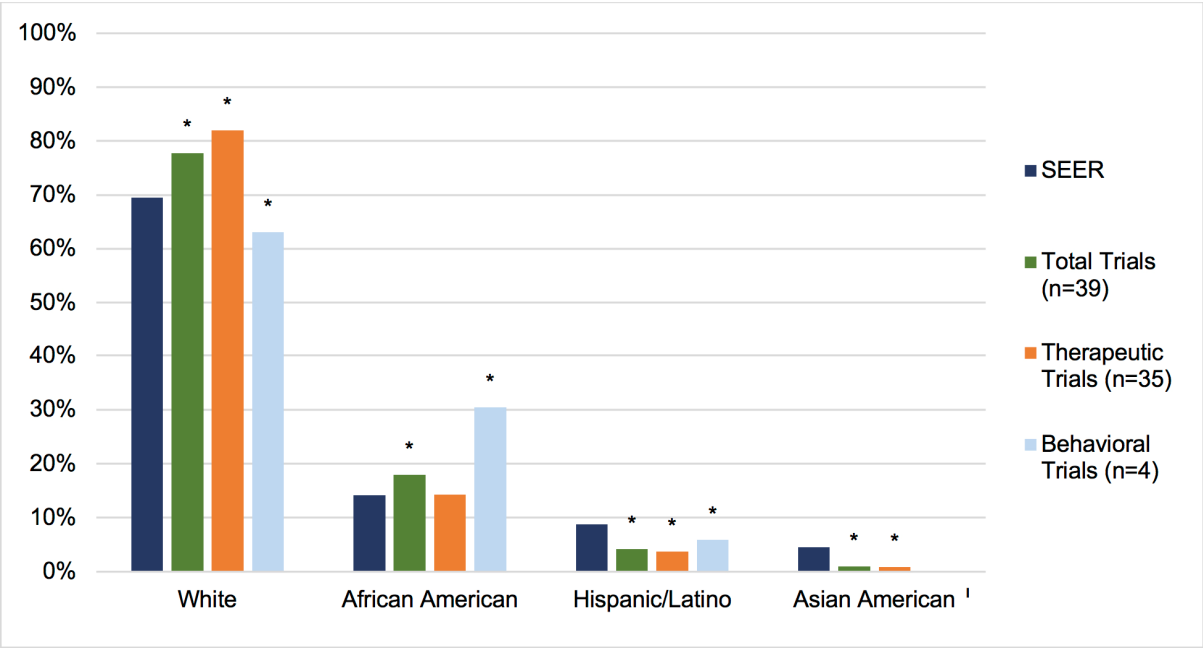
†Hispanic/Latino enrollment in metastatic trials not reported in 2009-11.

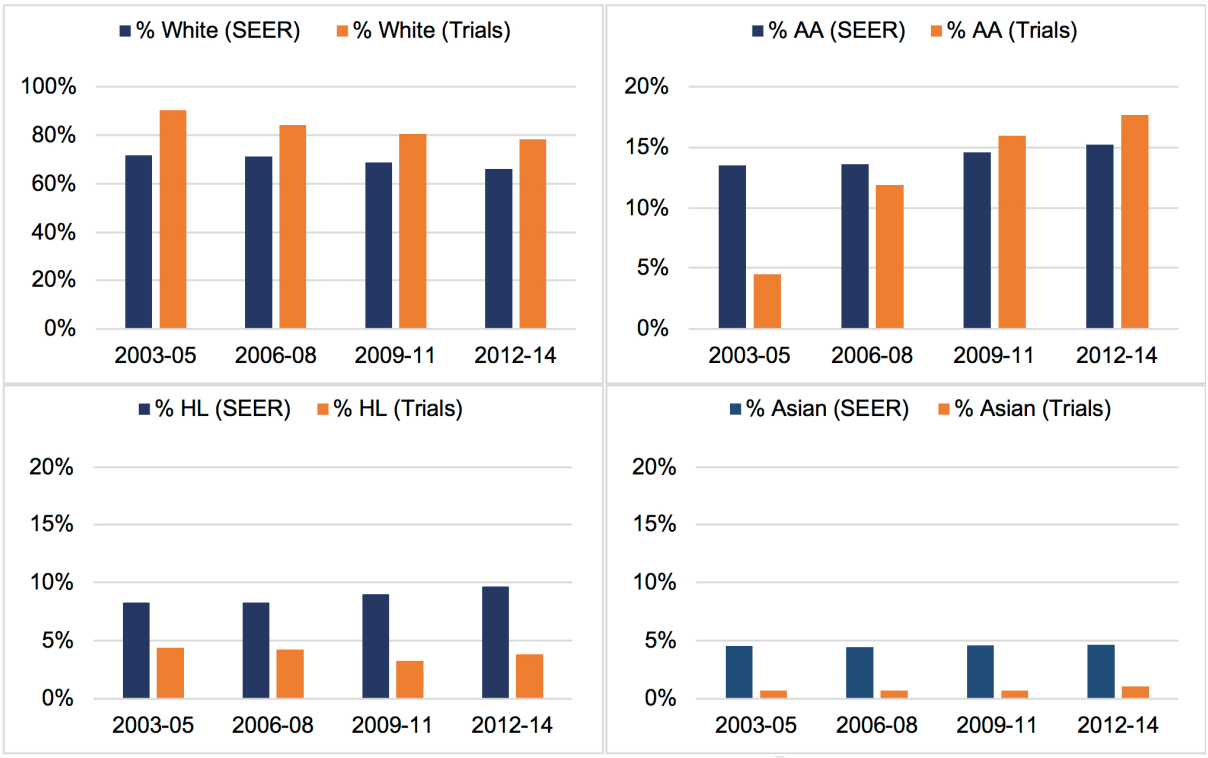
Table 1. Characteristics of phase III clinical trials included in this analysis

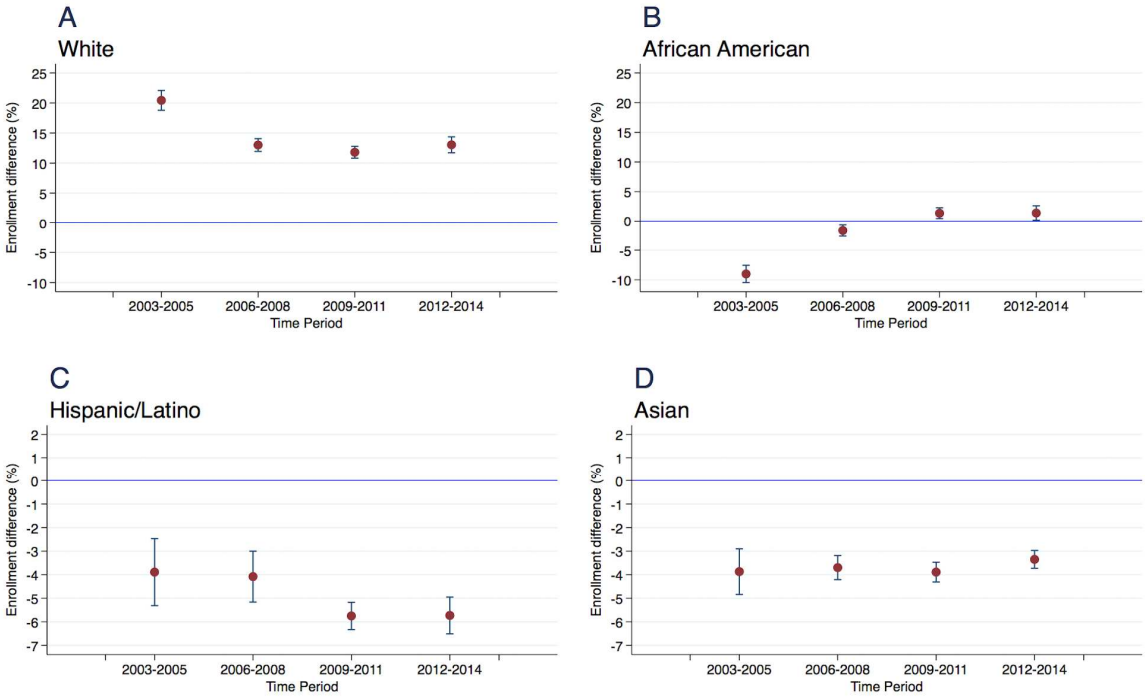
	Number of Trials (%)	Trial Population (%)
Total Trials	39	20,820
Trial Intervention		
Therapeutic	35 (89.7)	16,177 (77.7)
Behavioral	4 (10.3)	4,643 (22.3)
Year of Study Completion		
2003-2005	8 (20.5)	3,627 (17.4)
2006-2008	8 (20.5)	6,668 (32.0)
2009-2011	12 (30.8)	6,815 (32.7)
2012-2014	11 (28.2)	3,710 (17.8)
Clinical Stage of Trial Population		
Localized and/or regional	17 (43.6)	8,467 (40.7)
Distant	11 (28.2)	5,058 (24.3)
Failure after localized treatment	6 (15.4)	911 (4.4)
No cancer	5 (12.8)	6,384 (30.7)
Primary Funding Source		
NIH or other U.S. government	25 (64.1)	13,840 (66.5)
Industry	11 (28.2)	6,657 (32.0)
University	3 (7.7)	323 (1.5)
Enrollment Location		
United States	31 (79.5)	12,677 (60.9)
United States and Canada	8 (20.5)	8,143 (39.1)

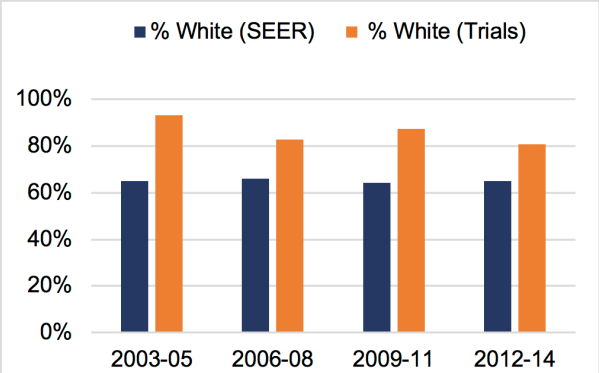
Abbreviation: NIH, National Institute of Health; U.S., United States.

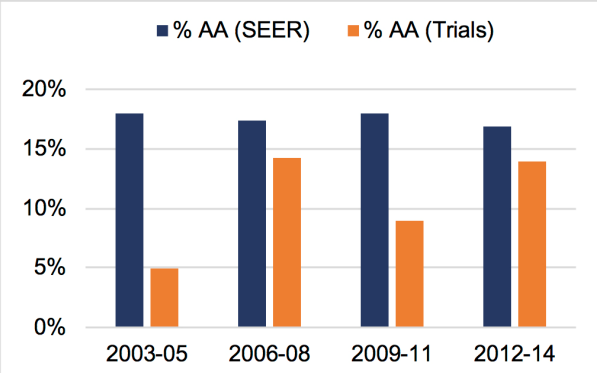

Identification
Eligibility
Inclusion
Phase III prostate cancer clinical trials registered with the Clinicaltrials.gov database and completed between 1/1/2003 and 12/31/2014
N = 77
Trials excluded and reason:
Enrollment location outside US and Canada (19)
Multiple cancer types (4)
Prostate cancer not focus of study (1)
Study designed to enroll one race (1)
Duplicated trial registration (1)
N = 26
Trials meeting eligibility criteria
N = 51
Inadequate results on race/ethnicity:
No results on participant race or ethnicity within publication(s), on ClinicalTrials.gov, or by contacting corresponding author (7)
No publication or results found on ClinicalTrials.gov or by contacting corresponding author (5)
N = 12
Trials meeting eligibility criteria and with results on race or ethnicity
N = 39

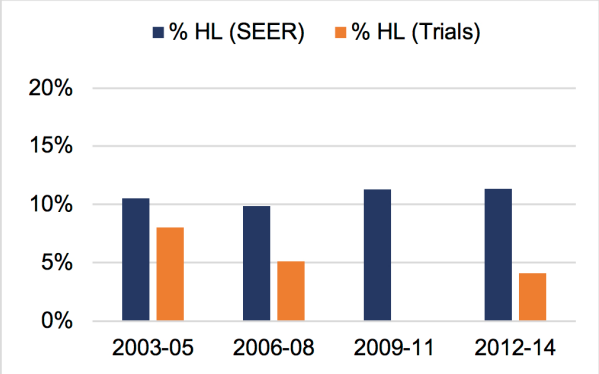


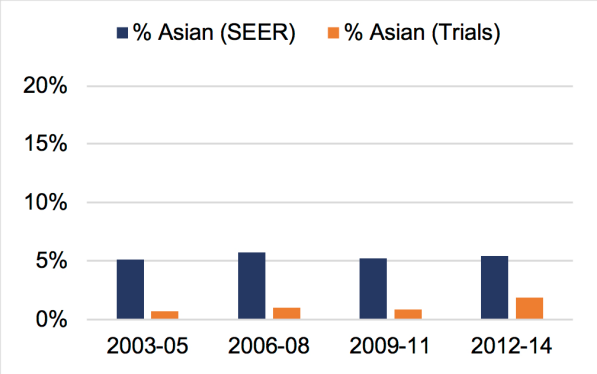












Abbreviation Key:

AA: African American

HL: Hispanic/Latino

NIH: National Institutes of Health

SEER: Surveillance, Epidemiology, and End Results registry

Supplementary Tables and Figures:

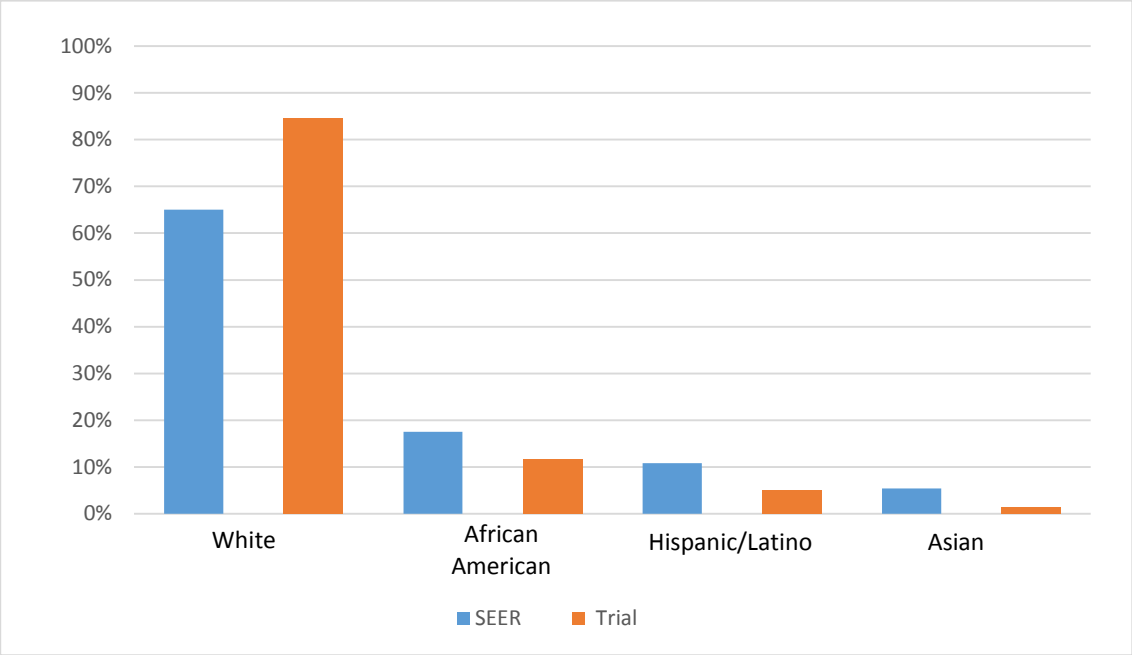
eTable 1. Phase III prostate cancer clinical trial enrollment in comparison to SEER incidence (2003-2014)

	2003-2005		2006-2008		2009-2011		2012-2014	
	SEER	**Trial**	**SEER**	**Trial**	**SEER**	**Trial**	**SEER**	**Trial**
All Trials (n=39)								
White	115,725 (71.7%)	2766 (76.3%)	128,665 (71.1%)	5085 (76.3%)	122,817 (68.7%)	5,409 (79.4%)	97,160 66.0%	3,710 (79.1%)
African American	21,794 (13.5%)	565 (11.4%)	24,640 (13.6%)	1,321 (19.8%)	26,115 (14.6%)	1,114 (17.0%)	22,428 (15.2%)	617 (16.6%)
Hispanic/Latino	13,349 (8.3%)	180 (5.5%)	15,012 (8.3%)	57 (4.1%)	16,109 (9.0%)	124 (3.3%)	14,237 (9.7%)	98 (4.0%)
Asian American	7,372 (4.6%)	2 (0.3%)	8,002 (4.4%)	8 (0.7%)	8,201 (4.6%)	9 (0.6%)	6,872 (4.7%)	49 (1.3%)
Therapeutic Trials (n=35)								
White	115,725 (71.7%)	957 (92.1%)	128,665 (71.1%)	4,030 (84.1%)	122,817 (68.7%)	5,344 (80.5%)	97,160 66.0%	2,934 (79.1%)
African American	21,794 (13.5%)	36 (4.5%)	24,640 (13.6%)	571 (11.9%)	26,115 (14.6%)	1,019 (15.9%)	22,428 (15.2%)	617 (16.6%)
Hispanic/Latino	13,349 (8.3%)	35 (4.4%)	15,012 (8.3%)	57 (4.2%)	16,109 (9.0%)	124 (3.3%)	14,237 (9.7%)	49 (4.0%)
Asian American	7,372 (4.6%)	2 (0.7%)	8,002 (4.4%)	8 (0.7%)	8,201 (4.6%)	11 (0.7%)	6,872 (4.7%)	29 (1.3%)
Metastatic Disease Trials (n=11)								
White	4,500 (65%)	385 (93.2%)	4,847 (65.9%)	877 (82.8%)	5,073 (64.3%)	1,323 (87.2%)	6,091 (65.0%)	517 (80.7%)
African American	1,245 (18.0%)	14 (4.9%)	1,277 (17.4%)	151 (14.3%)	1,419 (18.0%)	152 (9.0%)	1,581 (16.9%)	229 (14.0%)
Hispanic/Latino	726 (10.5%)	23 (8.0%)	725 (9.9%)	54 (5.1%)	890 (11.3%)	na	1,062 (11.3%)	41 (4.1%)
Asian American	356 (5.1%)	2 (0.7%)	422 (5.7%)	7 (1.0%)	411 (5.2%)	10 (0.9%)	509 (5.4%)	31 (1.9%)

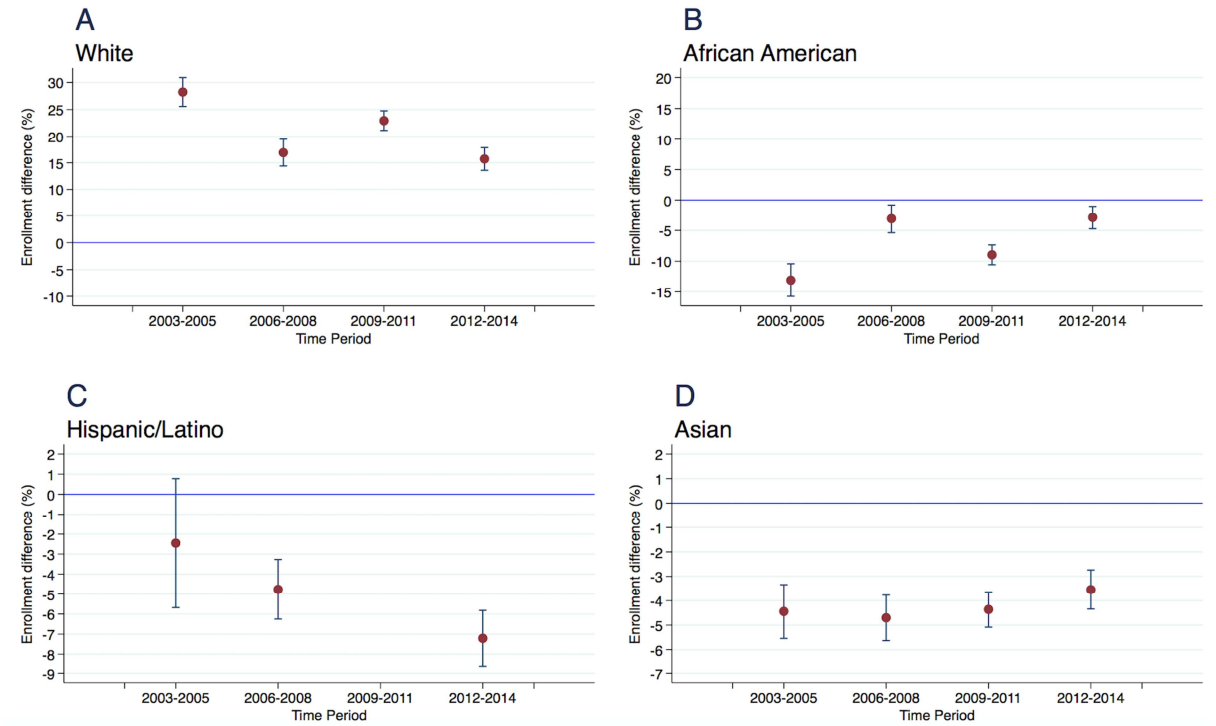
Abbreviation: SEER, Surveillance, Epidemiology, and End Results Registry.

eTable 2. Phase III prostate cancer clinical trials analyzed in the current study[1-39]

National Clinical Trial Identifier	Primary Author (publication year)	Intervention Type
NCT00182052	Smith, MR (2004)	Therapeutic (drug)
NCT00164437	No publication	Behavioral
NCT00005947	Small, EJ (2006)	Therapeutic (biologic)
NCT00027859	Walczak, JR (2003)	Therapeutic (drug)
NCT00002855	Millikan, RE (2008)	Therapeutic (drug)
NCT00002703	Zietman, AL (2005)	Therapeutic (radiation)
NCT00196781	Taylor, KL (2010)	Behavioral
NCT00177619	Greenspan, SL (2007)	Therapeutic (drug)
NCT00244309	Elshaikh, MA (2005)	Therapeutic (drug)
NCT00136487	Smith, MR (2006)	Therapeutic (drug)
NCT00196807	Taylor, KL (2013)	Behavioral
NCT00004001	Petrylak, DP (2004)	Therapeutic (drug)
NCT00171639	Campbell, SC (2010)	Therapeutic (drug)
NCT00028574	Loprinzi, CL (2009)	Therapeutic (drug)
NCT00002723	Ahles, TA (2004)	Therapeutic (drug)
NCT00657904	Iversen, P (2010)	Therapeutic (drug)
NCT00065442	Kantoff, PW (2010)	Therapeutic (biologic)
NCT00002760	Small, EJ (2004)	Therapeutic (drug)
NCT00626431	Spitz, A (2012)	Therapeutic (drug)
NCT00255125	Hamilton-Reeves, JM (2013)	Therapeutic (dietary supplement)
NCT00117286	No publication	Therapeutic (drug)
NCT00043069	Kearns, AE (2010)	Therapeutic (drug)
NCT00007644	Wilt, TJ (2012)	Therapeutic (surgery)
NCT00106691	Taneja, SS (2013)	Therapeutic (drug)
NCT00004635	Figg, WD (2009)	Therapeutic (drug)
NCT00002597	Jones, CU (2011)	Therapeutic (drug)
NCT00623090	Dorfman, CS (2010)	Behavioral
NCT00110214	Kelly, WK (2012)	Therapeutic (drug)
NCT00928434	No publication	Therapeutic (drug)
NCT00398281	Halpern, EJ (2012)	Therapeutic (drug)
NCT01825642	Gilbert, SM (2017)	Therapeutic (surgery)
NCT00765479	Bosland, MC (2013)	Therapeutic (dietary supplement)
NCT00134056	Quinn, DI (2013)	Therapeutic (drug)
NCT00004054	Rosenthal, SA (2015)	Therapeutic (drug)
NCT01415960	No publication	Therapeutic (drug)
NCT01538628	Mariados, N (2015)	Therapeutic (device)
NCT00079001	Smith, MR (2014)	Therapeutic (drug)
NCT00329797	Kachnic, LA (2013)	Therapeutic (drug)
NCT00931528	Pisansky, TM (2014)	Therapeutic (drug)



eFigure 1. Proportion of enrollment in phase III prostate cancer metastatic disease trials in comparison to proportion of metastatic prostate cancer in Surveillance, Epidemiology, and End Results (SEER) population by race, 2003-2014.



eFigure 2. Enrollment difference between phase III prostate cancer interventional trials enrolling only patients with metastatic disease and the Surveillance, Epidemiology, and End Results (SEER) metastatic prostate cancer population with 95% confidence intervals, 2003 to 2014. (A) White patients. (B) African American patients. (C) Hispanic/Latino patients. (D) Asian American patients. The enrollment difference is the absolute difference between the percentage of a racial/ethnic group in the trial population and the percentage of that racial/ethnic group in the SEER population.

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