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Race and ethnicity reporting and representation in hemophilia clinical trials

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Key Points

- Despite increases in the reporting of race/ethnicity, Black and Hispanic persons were consistently underrepresented in hemophilia trials.
- Strategies must be developed to overcome the underrepresentation of historically marginalized populations in interventional trials.

Racial and ethnic representativeness in clinical trials is crucial to mitigate disparities in outcomes; however, diversity among hemophilia trials is unknown. The aim of this study is to examine the reporting and representation of race and ethnicity in trials of people with hemophilia (PwH). In this cross-sectional study, the ClinicalTrials.gov database was queried in April 2023 for interventional clinical trials involving PwH between 2007 and 2022. The distribution of participants (observed) was compared with expected proportions based on US Hemophilia Treatment Center (HTC) and country-specific census data with observed-to-expected ratios (OERs). Of 129 trials included, 94.6% were industry sponsored, with a mean of 62 participants and mean age of 26.8 years. Overall, 52.0% (n = 66) of trials reported data on race and ethnicity, increasing from 13.9% in 2007-2012 to 22.5% in 2013-2016 to 100% in 2017-2022 (P = .001). Among these 66 trials, 65.8%, 22.8%, 5.1%, 3.9% of participants were White, Asian, Hispanic, and Black, respectively. OERs were 10% to 20% lower for White participants vs US HTC, and US, UK, and Canadian census populations and ~75% lower for Black or Hispanic participants when compared with US HTC and US census population. OERs for Asian participants were 1.6 to 3 times higher than Canada, US, and UK census populations. The reporting of race and ethnicity in hemophilia trials has drastically improved; however, Black and Hispanic PwH remain especially underrepresented. To address these disparities, stakeholders across the clinical trial enterprise need to implement strategies to ensure equitable participation.

Introduction

Significant advances in preventing, diagnosing, and treating disease have been realized for some populations; however, many who experience the greatest health challenges do not benefit because of inadequate representation in the clinical trial enterprise.[1] The lack of representation limits the generalizability of results and may preclude widespread implementation. Furthermore, lack of clinical trial diversity limits access to life-saving treatments, potentially costing the health care systems unnecessary expense and hinders further innovation. Lack of representation also undermines the medical establishment, furthers already-prevalent distrust in marginalized communities, and widens health care disparities.[1]

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ClinicalTrials.gov is publicly available at: https://ClinicalTrials.gov/; US HTC data are available from: https://www.cdc.gov/ncbddd/hemophilia/communitycounts/data-viz.html; census data are available from: https://www.cia.gov/the-world-factbook/.

To address racial and ethnic disparities in clinical trials, the US Food and Drug Administration (FDA) issued a final ruling requiring clinical trial sponsors to report participants' racial and ethnic data to the ClinicalTrials.gov registry in 2017.[2] Since this ruling, the reporting of race and ethnicity has increased by 13.5% annually according to a study of all registered interventional trials conducted in the United States between 2000 and 2020.[3] However, across several common chronic diseases including cancer, cardiovascular disease, and diabetes, Black and Hispanic persons remain underrepresented in interventional trials.[4-7]

Despite the growing number of studies documenting the underrepresentation of Black and Hispanic individuals in interventional trials for common chronic diseases, the reporting of racial and ethnic data and representativeness for rarer chronic diseases is lacking. Understanding diversity in clinical trial participation for rarer conditions is important because there may be distinct barriers and facilitators for diseases with smaller patient populations. For example, in 2020, the FDA issued industry guidance on improving racial and ethnic participation in interventional trials and acknowledged the unique challenges for interventional clinical trials of rarer conditions.[2] However, data to quantify the problem is lacking, and there is a dearth of information on what might account for potential racial and ethnic disparities in clinical trial participation for those with rare diseases, including nonmalignant hematologic conditions.

This study aims to examine the reporting and representativeness of race and ethnicity among interventional clinical trials enrolling people with hemophilia (PwH) as participants. Congenital hemophilia is a rare, X-linked genetic disorder leading to a deficiency in coagulation factor protein VIII or factor IX. In the past 50 years, the life expectancy for PwH has improved due to the development and use of robust therapies, which are the result of trials that have demonstrated the efficacy of factor concentrates to prevent and treat bleeding events.[8] Thus, it is a model of a rare disease population that has benefited from the discovery and implementation of new therapies. However, it is unknown whether there is adequate racial and ethnic reporting or representation in interventional trials that led to these discoveries.

Methods

In this cross-sectional study, the ClinicalTrials.gov database was queried in April 2023. The US National Institutes of Health launched the ClinicalTrials.gov database in 2000 to collect data on trials with new drug applications, though its purpose has expanded over time.[9] Sponsors and investigators submit data to the repository because they are required to by laws/regulations or they do so voluntarily. Beginning in 2005, the International Committee of Medical Journal Editors required authors to submit clinical data to ClinicalTrials.gov, and in 2006, the World Health Organization indicated that interventional trials should enter data to ClinicalTrials.gov or similar databases.[9] In 2007, the FDA expanded the types of studies that needed to submit data to ClinicalTrials.gov. In 2017, investigators were required to report data on race and ethnicity to ClinicalTrials.gov as part of the data submission process.[10] ClinicalTrials.gov is the largest database of clinical trials in the world, and it contains trials conducted outside of the United States given the International Committee of Medical Journal Editor's requirement and World Health Organization recommendation for sponsors to submit information to the registry.[11]

For our study, we searched the ClinicalTrials.gov database for trials with "hemophilia" as the condition, coded as "interventional" and with "results." There was a total of 157 trials identified. Each trial record contained information on the trial sponsor, site, completion date, phase, intervention type, inclusion criteria, and participant information, including the number of participants according to race and ethnicity. Trial information was entered into a standardized REDCap database, then exported to the SAS software for data analyses.

There were 2 main outcomes as follows: (1) the proportion of trials reporting data on at least 1 racial or ethnic group (yes or no), and (2) the distribution of race and ethnicity. Race and ethnicity was based on the US Office of Budget Management Categories, as required by FDA. These categories included Hispanic/non-Hispanic, White, Black, Asian, Native Hawaiian/Pacific Islander, and American Indian/Alaska Native.[12] Outcomes were compared according to several trial and participant characteristics that reflected the trial characteristics to determine if certain features, including trial size, phase, etc. were associated with outcomes. Trial characteristics included the country, trial phase, the year of study completion, sponsor type, and trial length, which was computed based on the start and completion dates. Participant characteristics included sex, mean age, the type of hemophilia (A and/or B), severity (mild, moderate, severe), and whether people with inhibitors were included. Participant characteristics were derived from the trials' inclusion criteria. Hemophilia severity corresponds to baseline factor levels and bleeding risk. Inhibitors are alloantibodies that develop against factor VIII or IX activity and are a complication of hemophilia that render factor-replacement therapy ineffective. The ClinicalTrials.gov database records participant characteristics in aggregate (per trial), and thus, the mean age was computed as a weighted average. Trial and participant characteristics were computed according to the 2 outcomes (reporting of race and ethnicity and the distribution of race and ethnicity) and compared with χ^2, t, and analysis of variance tests. χ^2 tests were used to test differences across categorical variables and analysis of variance tests were used to test differences across numerical variables.

The racial and ethnic distribution of trial participants (observed) was also compared with external populations to determine if the observed proportions aligned with what would be expected, based on 5 different populations. For these analyses, we used observed-to-expected ratios (OERs) and 95% confidence intervals (CIs), which were computed using the delta method.[13] The first expected population was from US Hemophilia Treatment Center (HTC) data. The Centers for Disease Prevention Community Counts Registry data was used to estimate the US HTC hemophilia population.[14] The Community Counts Registry is a public health monitoring program that aims to gather and share information about common health issues, medical complications, and causes of death that affect people with bleeding disorders cared for over 140 US HTCs. There were 4 countries with census data (Brazil, Canada, the United States, and the United Kingdom). These 4 countries were selected based on the availability of data on race and ethnicity, as

many countries do not routinely collect data on race or ethnicity or in a manner that generally aligns with the US Office of Budget Management Categories race and ethnicity categories.[15] All analyses were conducted in SAS version 9.4.

Results

Reporting of race and ethnicity

Of the 157 trials identified in the initial search, 28 were excluded because they were prematurely terminated. Of the 129 trials analyzed, the completion year ranged from 2007 to 2022 and the average study length was ~3 years (Figure 1). The majority were industry-sponsored (122/129; 94.6%), and on average, 62 participants were included, and the average age of participants was 26.8 years. Most trials included those with severe (79/129; 61.2%) or moderate and severe (18/129; 14%) disease though 10/129; 7.8% of trials included participants of all severities, including people with mild hemophilia. Each trial was conducted in an average across 7.4 countries (standard deviation = 6) (Table 1). Approximately 42/129; 32.6%, 90/129; 70.0%, and 111/129; 86.1% of trials included at least 1 site in lower-middle, upper-middle, and higher-income countries, respectively, and none were conducted in low-income countries.

Overall, 52.0% (n = 67) of trials reported data on at least race and/or ethnicity, this proportion increased from 13.9% in 2007-2012 to 22.5% in 2013-2016 to 100% in 2017-2022 ($P = .001$) (Table 1). Reporting of racial and ethnic data was also significantly greater among trials with more participants, but not other trial characteristics (eg, trial length, phase, number of countries, hemophilia type, and severity).

Distribution of race and ethnicity

Of the 67 trials that collected data on race or ethnicity, only 1 trial reported ethnic data as "Hispanic/non-Hispanic" and was excluded from further analyses as racial distribution could not be determined. Of the remaining 66 trials, a total of 4573 total participants were included, with a mean of 71 participants per trial (standard deviation = 67.9), ranging from 5 to 292 participants. Most trials were conducted within multiple countries, with an average of 7.5 countries in each trial. The most common country sites were the United States (n = 42) followed by Italy (n = 26), Australia (n = 25), Poland (n = 24), Germany (n = 22), and France (n = 22).

In terms of race, 65.8% (3010/4573) of trial participants were White, 22.8% (1043/4573) were Asian, 3.9% (179/4573) were Black, 2.3% (105/4573) were other races, and 3.8% (174/4573) were missing data. Fewer than 1% of participants were of multiple races or American Indian/Alaska Native. Overall, 5.1% (233/4573) of participants were Hispanic (Table 2). Thirty (45.6%) trials reported having no Black participants and 35 (53.0%) trials reported no Hispanic participants. Between the earliest study period (2007-2012) and the most recent (2017-2022), there was a significant increase in the proportion of participants who were Asian (from 1.7%-24.7%, $P < .001$) and a significant decrease in the Hispanic participants (from 17.1%-5.2%, $P = .015$). There was a nonsignificant decline in the proportion of participants who were White. The proportion of Black participants insignificantly increased from <1% to 4.2% and remained low (Figure 2).

Phase 1/2/3 trials had a greater number of White participants, whereas phase 4 trials tended to have proportionately more Asian participants. Trials that included people with inhibitors had a greater proportion of Black and Hispanic participants vs trials that did not

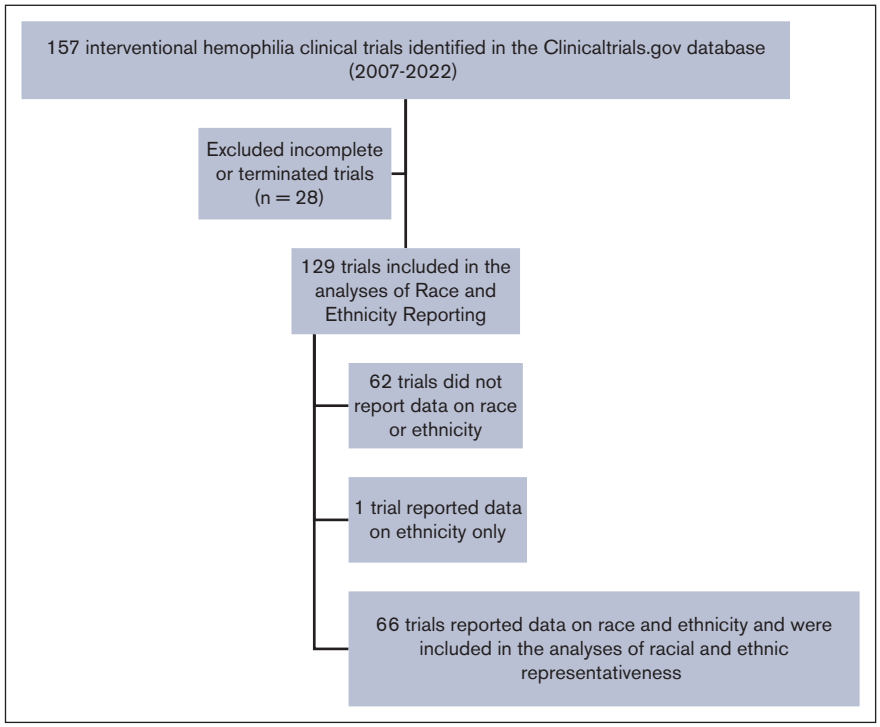

Figure 1. Study selection criteria of hemophilia interventional clinical trials.

Table 1. Characteristics of interventional hemophilia trials reporting race and ethnicity data

	Total	Race or ethnicity Not reported	Race or ethnicity Reported	
	N (%)	N (%)	N (%)	*P* value*
Total	129 (100.0)	62 (48.0)	67 (52.0)	
Phase				.31
1	13 (10.1)	6 (46.2)	7 (53.8)	
2	23 (17.8)	13 (56.5)	10 (43.5)	
3	68 (52.7)	29 (42.6)	39 (57.4)	
4	22 (17.1)	11 (50)	11 (50)	
Missing	3 (2.3)	3 (100)	0 (0)	
Trial length (y)				.07
<2	48 (37.2)	24 (50)	24 (50)	
2-5	56 (43.4)	31 (55.4)	25 (44.6)	
≥5	25 (19.4)	7 (28)	18 (72)	
Study completion date				.001
2007-2012	36 (27.9)	31 (86.1)	5 (13.9)	
2013-2016	40 (31)	31 (77.5)	9 (22.5)	
2017-2022	53 (41.1)	0 (0)	53 (100)	
Sponsor type				.20
Industry	122 (94.6)	57 (46.7)	65 (53.3)	
Academic	7 (5.4)	5 (71.4)	2 (28.6)	
Hemophilia type				
Hem A	76 (58.9)	35 (46.1)	41 (53.9)	.36
Hem B	29 (22.5)	17 (58.6)	12 (41.4)	
Hem A and B	23 (17.8)	9 (39.1)	14 (60.9)	
Missing	1			
Severity†				.87
All severities	10 (7.8)	4 (40)	6 (60)	
Moderate and severe	18 (14)	9 (50)	9 (50)	
Severe	79 (61.2)	37 (46.8)	42 (53.2)	
Missing	22 (17.1)	12 (54.5)	10 (45.5)	
Included inhibitor patients	36 (22.9)	12 (33.3)	24 (66.7)	.07
Number of participants				.65
<30	48 (37.2)	25 (52.1)	23 (47.9)	
30-59	30 (23.3)	15 (50)	15 (50)	
60+	51 (39.5)	22 (43.1)	29 (56.9)	
Number of countries				.48
1-3	21 (37.5)	11 (52.4)	10 (47.6)	
4-10	13 (23.2)	8 (61.5)	5 (38.5)	
>10	22 (39.3)	9 (40.9)	13 (59.1)	
Site location(s)‡				
United States	84 (65.1)	41 (48.8)	43 (51.2)	.82
North America	89 (69)	44 (49.4)	45 (50.6)	.64
South America	27 (20.9)	11 (40.7)	16 (59.3)	.39
Europe	95 (73.6)	45 (47.4)	50 (52.6)	.79

Hem, hemophilia.
*χ^2 tests were used to measure differences across categorical variables and *t* tests were used to measure differences across continuous variables (age, number of participants).
†There were no trials recorded as having only mild or mild and moderate participants.
‡Includes at least 1 site in the region listed.
§Trials were counted if they had at least 1 site income category listed. Incomes are based on World Bank income classification, there were no sites in low-income countries.

Table 1 (continued)

	Total	Race or ethnicity Not reported	Race or ethnicity Reported	
	N (%)	N (%)	N (%)	*P* value*
Africa	27 (20.9)	12 (44.4)	15 (55.6)	.67
Asia	92 (71.3)	43 (46.7)	49 (53.3)	.64
World Bank income classification§				
Low-middle income	42 (32.6)	18 (42.9)	24 (57.1)	.41
Upper-middle income	90 (70.0)	44 (49.0)	46 (51.1)	.78
High income	111 (86.1)	55 (49.6)	56 (50.5)	.40
Mean (standard deviation)				
Number of participants analyzed	62.3 (58.25)	51.9 (43.42)	71.9 (68.14)	.005
Mean age	26.8 (13.18)	27.5 (13.51)	26.1 (12.97)	.777
Number of countries	7.4 (6.58)	7.3 (6.63)	7.5 (6.58)	.844

Hem, hemophilia.
*χ^2 tests were used to measure differences across categorical variables and *t* tests were used to measure differences across continuous variables (age, number of participants).
†There were no trials recorded as having only mild or mild and moderate participants.
‡Includes at least 1 site in the region listed.
§Trials were counted if they had at least 1 site income category listed. Incomes are based on World Bank income classification, there were no sites in low-income countries.

include those with inhibitors (Table 2). The average age of participants, number of countries, and states were not strongly correlated ($r < 0.6$) with the proportion of Black, Hispanic, and Asian participants.

The proportion of all trial participants who were White was ~20% lower than the US HTC population (OER, 0.83; 95% CI, 0.80-0.86) and 10% to 20% lower than the general population of the United States (OER, 0.85; 95% CI, 0.82-0.87), United Kingdom (OER, 0.80; 95% CI, 0.78-0.82), and Canada (OER, 0.91; 95% CI, 0.88-0.94) (Table 3). The proportion of trial participants who were Black or Hispanic was ~75% lower than the US HTC and the US general population, but it was not significantly different when compared with the general population in Canada or the United Kingdom. The percentages of trial participants who were Asian were 60% to 300% higher than general population in Canada (OER, 1.64; 95% CI, 1.43-1.88), the United Kingdom (OER, 2.43; 95% CI, 2.10-2.82) and the United States (OER, 3.65; 95% CI, 3.08-4.32) (Table 3).

Discussion

Our study found that <25% of interventional hemophilia trials conducted before the 2017 FDA requirement to collect data on race and ethnicity did so, whereas all trials conducted on or after 2017, reported data on race and ethnicity. Despite increases in the reporting of race and ethnicity, Black and Hispanic persons were consistently and especially underrepresented in hemophilia interventional trials where observed proportions, which included all study participants and not just those in the United States, were less than a third of what was expected when compared with the US HTC and general population throughout the study period. Our finding that about half of the trials reported having no Black participants or Hispanic participants is stunning, especially when considering the diverse US HTC population and the global hemophilia population.[16]

In our study of 129 interventional trials for hemophilia treatments, the reporting of race and ethnicity improved dramatically and was universal in studies conducted in 2017 and later, and calendar year was the most prominent determinant of reporting. These trends are in line with the 2017 FDA reporting mandate, indicating the effectiveness of standards.[2] The universal reporting of race and ethnicity is somewhat unique in our study, given that trials of other diseases have high but incomplete compliance.[3,17] In a study that examined 20 000 interventional trials across multiple diseases, 42% of trials in the period before 2017 reported data on race and/or ethnicity compared with 91% in the 2017 period.[3,17] In a similar study of pediatric trials, the proportion reporting race and ethnicity tripled between 2000 and after 2017, but only 87% of trials conducted in 2018 reported data on race and ethnicity.[18]

Despite the dramatic increase in the reporting of race and ethnicity in hemophilia interventional trials, we found that the proportion of participants who were Hispanic and Black did not increase over time and these 2 groups remain especially underrepresented. The increase in reporting of race and ethnicity contrasted with the lack of increase in Hispanic and Black participants in hemophilia interventional trials over time. This indicates that collecting racial and ethnic data may be helpful to identify gaps in recruitment, but it is not enough to close them. Structured diversity plans have been proposed to mitigate racial and ethnic disparities in clinical trial participation.[19] These plans include an overview of disease occurrence, drug development strategy, targeted enrollment of members of racial and ethnic minorities, and measures to enroll a diverse population.[19] Diversity plans may be especially needed for trials of hemophilia given that it is a rare disease, and accruing an adequate sample size overall, without even considering race and ethnicity, is challenging. Establishing a precise goal of racial and ethnic representation has been proposed,[20] though setting targets would require careful consideration given that the number of expected White, Black, Hispanic, Asian and other participants would vary depending on target population definitions (ie, within a

Table 2. Hemophilia interventional trial participants' race and ethnicity according to trial characteristics

	No. of participants	White N (%)	Black N (%)	Asian N (%)	Other N (%)	Unknown N (%)	Multiple race N (%)	AI/AN N (%)	Hispanic N (%)	*P* value*
Phase										<.001
1	109	76 (69.7)	2 (1.8)	29 (26.6)	1 (0.9)	0 (0)	0 (0)	1 (0.9)	0 (0)	
2	509	418 (82.1)	27 (5.3)	33 (6.5)	21 (4.1)	0 (0)	1 (0.2)	1 (0.2)	18 (3.5)	
3	3351	2300 (68.6)	139 (4.1)	694 (20.7)	78 (2.3)	95 (2.8)	8 (0.2)	23 (0.7)	204 (6.1)	
4	604	216 (35.8)	11 (1.8)	287 (47.5)	6 (1.0)	78 (12.9)	1 (0.2)	5 (0.8)	11 (1.8)	
Completion year										<.001
2007-2011	111	97 (87.4)	1 (0.9)	3 (2.7)	5 (4.5)	0	0	5 (4.5)	19 (17.1)	
2012-2016	895	608 (67.9)	27 (3.0)	160 (17.9)	10 (1.1)	80 (8.9)	0	2 (0.2)	29 (3.2)	
2017-2022	3567	2305 (64.6)	151 (4.2)	880 (24.7)	91 (2.6)	93 (2.6)	10 (0.3)	23 (0.6)	185 (5.2)	
Trial length										<.001
<2 y	951	550 (57.8)	34 (3.6)	345 (36.3)	4 (0.4)	14 (1.5)	0 (0)	2 (0.2)	62 (6.5)	
2-5 y	1733	1157 (66.8)	67 (3.9)	370 (21.7)	65 (3.8)	28 (1.6)	8 (0.5)	20 (1.2)	96 (5.5)	
>5 y	1889	1303 (69.0)	78 (4.1)	328 (17.4)	37 (2.0)	131 (6.9)	2 (0.1)	8 (0.4)	75 (4.0)	
Sponsor type										<.001
Industry	4500	2950 (65.6)	178 (4.0)	1041 (23.2)	101 (2.2)	173 (3.8)	10 (0.2)	25 (0.6)	229 (5.1)	
Academic	73	60 (82.2)	1 (1.4)	2 (2.7)	5 (6.8)	0	0	5 (6.8)	4 (5.5)	
Hemophilia category										<.001
Hem A	3318	2153 (64.9)	119 (3.6)	753 (22.7)	81 (2.4)	164 (4.9)	5 (0.2)	29 (0.9)	198 (6.0)	
Hem B	536	370 (69.0)	26 (4.9)	124 (23.1)	5 (0.9)	6 (1.)	2 (0.4)	0 (0)	17 (3.2)	
Hem A and B	719	487 (67.7)	34 (4.7)	166 (23.1)	20 (2.8)	3 (0.4)	3 (0.4)	1 (0.1)	18 (2.5)	
Severity†										<.001
Severe	3030	2025 (66.8)	116 (3.8)	691 (22.8)	51 (1.7)	118 (3.9)	6 (0.2)	9 (0.3)	145 (4.8)	
Moderate and severe	374	204 (54.5)	2 (0.5)	157 (42.0)	0 (0)	11 (2.9)	0 (0)	0 (0)	0 (0)	
All severities	306	196 (64.1)	35 (11.4)	52 (17.0)	8 (2.6)	11 (3.6)	2 (0.7)	1 (0.3)	32 (10.5)	
Missing	863	585 (67.8)	26 (3.0)	143 (16.6)	47 (5.4)	33 (3.8)	2 (0.2)	20 (2.3)	56 (6.5)	
Included participants with inhibitor										<.001
No	3490	2326 (66.6)	95 (2.7)	825 (23.6)	62 (1.8)	145 (4.2)	7 (0.2)	10 (0.3)	138 (4.0)	
Yes	1083	684 (63.2)	84 (7.8)	218 (20.1)	44 (4.1)	28 (2.6)	3 (0.3)	20 (1.8)	95 (8.8)	

Number of trial participants across 66 trials that reported data on race and ethnicity.
Race is reported separately from ethnicity (non-Hispanic vs Hispanic), thus the sum of percentages across race and ethnicity will be ≥100.
AI/AN, American Indian/Alaska Native; Hem, hemophilia.
**P* values were computed with χ^2 tests that compare differences in the racial distribution across trial characteristics.
†There were no trials recorded as having only mild or mild and moderate participants.

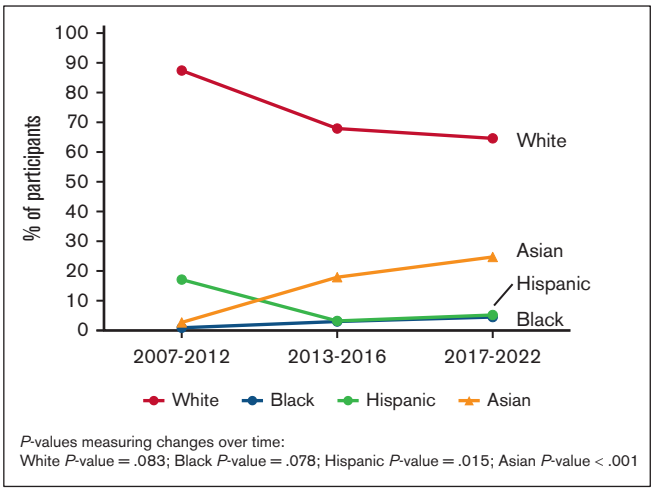

Figure 2. Proportion of hemophilia trial participants according to race and ethnicity between 2007 and 2022.

specific country, the world) or the disease subgroup for whom the drug is being developed for (eg, those with inhibitors). For example, we observed that the proportion of Asian participants compared with the US and UK populations was greater than expected but would likely be far lower than what would be expected compared with countries in Asia. We also found that the proportion of Black and Hispanic clinical trial participants was not significantly different than what would be expected, when compared with the Canadian and UK general population. While recognizing the careful consideration of establishing goal definitions, disease agnostic industry guidelines have been developed to set target goals based on US census, surveillance, and real-world evidence incorporating disease occurrence and severity.[20] Similar to what was used in our study, US-based enrollment goals could be based on general population/census data and the Center for Disease Control and Prevention's Community Counts registry of HTCs, while taking into account that 80% of PwH in the United States receive care at these centers, and that racial and ethnic differences in HTC access may exist.[21,22]

In addition to establishing goals, there are multilevel barriers that need to be assessed and addressed to diversify hemophilia interventional trial participation. In studies of other diseases, there are system (geographical access, lack of infrastructure/support, restrictive eligibility criteria, and financial limitations), physician (lack of awareness, time or bias), and patient (beliefs, willingness to participate, financial reasons) level barriers to clinical trial participation.[23-25] The contribution of these barriers to hemophilia interventional trial participation is not yet known, though there are unique features of hemophilia and its care to consider. In terms of system-level factors, the US HTC Network, which treats ~80% of PwH in the United States,[26] and the European Hemophilia Network,[27] are existing infrastructures that could be more deliberately utilized. For example, although most US clinical trial recruitment is already occurring at HTCs, those that serve a more diverse population could be targeted for clinical trial recruitment. In addition, engagement of hematologists in the community and outside of the HTC network could also facilitate enrollment of a more diverse population of participants. The American Society of Hematology has developed diversity equity and inclusion-focused toolkits and resources to guide clinical trial sponsors, health care professionals, and advocates toward a more equitable and inclusive clinical trial ecosystem.[28] Furthermore, while hemophilia care is limited in sub-Saharan Africa, capacity building efforts in this region may lend itself to future clinical trial recruitment as well.[29] Involving lived experience experts (those living with hemophilia) in the trial design process may also improve diverse trial recruitment.[30]

Additional information on physician and patient-level factors within HTCs that influence hemophilia clinical trial participation is needed. For example, it is not known what proportion of eligible hemophilia patients are offered and ultimately decide to enroll in hemophilia clinical trials, and whether this varies according to race and ethnicity. For example, our data demonstrated that more White participants were included in phase 1/2 trials than other racial groups. It is unknown if a bias exists on the part of the investigator, wanting to ensure a more adherent participant, or quite possibly, at the participant level, possibly due to mistrust, precluding more equitable enrollment into these early-stage trials. In studies of other diseases, there are mixed findings on whether Black and Hispanic persons are more or less likely to be invited to participate in a clinical trial.[31] At least 1 study suggests that physicians may be less likely to consider Hispanic persons as eligible and another study found that Black persons were more likely to be deemed ineligible due to perceived noncompliance.[32,33] A meta-analyses of oncology clinical trials suggests that when patients are invited to enroll in a clinical trial, participation rates are similar in Black and White patients and another study reported that patient trust in their physician is a predictor of enrollment.[34] The underrepresentation of Black and Hispanic persons in clinical trials may also stem from the quality of patient-provider communication and trust,[35] as well as patient-level barriers that include mistrust, logistical constraints, lack of understanding, financial barriers, and cultural congruence.[36] Medical mistrust has contributed to Hispanic and Black persons' lower clinical trial participation in preventive interventional trials and those of other diseases; however, trust in physicians is 1 factor that may mitigate mistrust in clinical trials.[37,38] For the hemophilia population, patients' long-standing relationships with their HTC

Table 3. Observed to expected ratios of clinical trial enrollment compared to hemophilia and general census populations

	White	Black	Hispanic	Asian
	OER ratio (95% CI)	OER ratio (95% CI)	OER ratio (95% CI)	OER ratio (95% CI)
US HTCs	0.83 (0.80-0.86)	0.34 (0.15-0.78)	0.29 (0.16-0.54)	–
US census	0.85 (0.82-0.87)	0.24 (0.11-0.50)	0.27 (0.15-0.48)	3.65 (3.08-4.32)
UK census	0.80 (0.78-0.82)	0.97 (0.43-2.20)	–	2.43 (2.10-2.82)
Canada census	0.91 (0.88-0.94)	0.90 (0.40-2.03)	–	1.64 (1.43-1.88)
Brazil census	1.37 (1.33-1.41)	0.51 (0.24-1.11)	–	–

medical providers could be leveraged, especially given findings that trust in medical providers has been shown to improve adherence to prophylaxis in PwH, outside the trial setting.[39] Other special considerations for hemophilia clinical trial participation is participant burden and the need for laboratory and in-person follow-up. One of the FDA's proposed solutions is to use mobile phlebotomist and/or local laboratories to reduce participant burden that includes transportation, childcare, and lack of paid-sick leave, all of which have been noted barriers to clinical trial participation among Black and other racial and ethnic minorities.[40,41] For hemophilia, the need for special coagulation laboratory processing and storage could complicate this proposed solution. The aforementioned American Society of Hematology project seeks to identify opportunities to improve diversity in classical hematology clinical trials; the results of their analysis will be published soon.

A general rationale for enrolling an adequate number of people across race and ethnicities is to measure the responsiveness of new therapies across a diverse population, in stratified analyses.[19] While race and ethnicity is a sociopolitical construct and not reflection of biological structure, racial and ethnic differences in the response to other treatments and devices for other diseases have been documented.[42] There is known variability in the pharmacokinetics of factor-replacing therapies for PwH,[43] but it is not known if drug response varies specifically according to race or ethnicity. In the 2017 HAVEN-1 clinical trial of emicizumab among 35 participants with severe hemophilia A and inhibitors who were in the emicizumab vs prophylaxis groups, annualized bleeding rate ratios were similar in Asian, Black, and White participants.[44] Studies of other hematologic and cardiovascular diseases showed that Hispanic, African American, and Asian persons with atrial fibrillation may have a higher risk of intracranial hemorrhage than White persons, and African Americans may require higher doses to prevent thrombotic events compared to White persons.[45]

There are several limitations in our study. First, the ClinicalTrials.gov database does not contain site- or country-specific data on race and ethnicity, so we were not able to precisely examine regional, state, etc. disparities. Furthermore, it is possible that the ClinicalTrials.gov database may not capture all interventional trials during our study period, though given the reporting requirements, it is assumed that most practice-changing interventional trials are reasonably represented. In audits of the ClinicalTrials.gov registry (that included all diseases), there was imperfect reporting compliance, though >65% of industry-led trials reported results to ClinicalTrials.gov and nearly 100% of all trials led by larger pharmaceutical companies, which is common in hemophilia drug development, reported data.[11] Further investigations using the European Clinical Trial Registry could be helpful to identify general characteristics of hemophilia clinical trials, though the European registry does not contain information on race nor ethnicity. An additional limitation of our study is that the US Office and Budget and Management race and ethnicity groups are reported in the ClinicalTrials.gov registry, and other countries' census may define race and ethnicity differently. Additionally, many countries do not report data on race and ethnicity in their census data, thus an adequate denominator is lacking. Furthermore, our study used cross-sectional data, which limits causal inferences that can be made regarding changes in FDA reporting guidelines and the reporting of racial and ethnic data, though cross-sectional data collected over multiple years is often used to measure associations between policy change and outcomes. Despite these limitations, our study is the first to examine racial and ethnic differences in hemophilia clinical trial participation, informing diversity equity and inclusion efforts within the classical hematology community and beyond.

In conclusion, we observed that the reporting of race and ethnicity in hemophilia interventional trials has drastically improved following the 2017 FDA mandate to do so. However, Black and Hispanic people remain especially underrepresented in hemophilia interventional trials, which likely stem from multilevel barriers along the recruitment process including individual, community, organizational and institutional barriers. Further investigations into the role of HTCs, physician and patient-level barriers are needed to better understand and address racial and ethnic disparities in hemophilia interventional trial participation. With this understanding, strategies must be developed that focus on all stakeholders in the clinical trial enterprise to overcome the underrepresentation of historically marginalized populations in hemophilia interventional trials.

Authorship

Contribution: S.A.F., L.A.V., and C.L.K. designed the research; S.A.F. and A.K. performed the research; S.A.F. analyzed data; and all authors assisted in drafting and revising the manuscript.

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