




Reporting of Demographics & Subgroup Analyses in Premarketing Studies of FDA Approved High-Risk Cardiovascular Devices, 2014–2022

Matthew J Swanson ^{1,2}, Colin L Uyeki¹, Sarah R Yoder¹, Sanket S Dhruva ³, Jennifer E Miller⁴, Joseph S Ross ^{4–6}

¹Frank H. Netter MD School of Medicine, Quinnipiac University, North Haven, CT, USA; ²Leonard N. Stern School of Business, New York University, New York, NY, USA; ³Department of Medicine, University of California, San Francisco School of Medicine, San Francisco, CA, USA; ⁴Department of Medicine, Yale School of Medicine, New Haven, CT, USA; ⁵Department of Health Policy and Management, Yale School of Public Health, New Haven, CT, USA; ⁶Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, CT, USA

Correspondence: Matthew J Swanson, Frank H. Netter MD School of Medicine, Quinnipiac University, 370 Bassett Road, North Haven, CT, 06473-1908, USA, Email Matthew.Swanson@stern.nyu.edu

Background: Representation of diverse study populations in pivotal clinical trials for medical devices and subgroup analyses for demographic groups to explore differences in safety and effectiveness are essential to understanding the benefits and risks in diverse populations. The US Food and Drug Administration (FDA) has taken many steps to improve transparency and subgroup analyses over the past decade, but there has not been a recent evaluation of demographic reporting and subgroup analyses.

Methods: We reviewed all FDA Premarket Approvals for high-risk cardiovascular devices from 2014 to 2022, focusing on pivotal studies supporting device approval. We abstracted detailed demographic data about the age, sex, race, ethnicity, and socioeconomic position of study participants. We also assessed the presence and results of subgroup analyses to understand the safety and effectiveness of devices across trial populations.

Results: Analysis of 92 pivotal studies revealed that age and sex were reported in 96.7% of the studies, while race and ethnicity were reported in 71.7% and 58.7%, respectively. However, only 7.9% of studies explicitly detailed the participation of older adults (≥ 65 years) and no studies reported patients' socioeconomic position. Subgroup analyses by sex were conducted in 70.7% of studies, with 12.3% reporting significant differences. In contrast, analyses by race and ethnicity were performed in only 12.0% of the studies, with 9.1% reporting significant differences.

Conclusion: Approximately one-third of pivotal studies for high-risk cardiovascular devices approved by the FDA from 2014 to 2022 did not report the race of study participants, nearly 40% did not report ethnicity, and more than 90% did not report the participation of older adults (≥ 65 years). Subgroup analyses were infrequently conducted by age or race and ethnicity. There is a need for better trial demographic reporting and conduct of subgroup analyses in premarketing studies to ensure the safety and effectiveness of medical devices for all patients.

Keywords: FDA, clinical trial, cardiovascular device, diversity, inclusion, equity

Introduction

Clinical trial diversity has long been an area of concern, with significant underrepresentation of key patient demographic groups such as older adults, women, and racial and ethnic minority patients.^{1–5} This underrepresentation has great clinical significance, impeding the generalizability of trial results. Policymakers, recognizing the criticality of this issue, have taken substantial steps toward improvement. The Food and Drug Omnibus Reform Act (FDORA) in 2022 and the Food and Drug Administration (FDA) Center for Devices and Radiological Health's 2022 strategic plan underscore legislative and regulatory commitments to enhancing trial diversity, including mandates for sex and gender analyses in device development.^{6,7}

Efforts to promote inclusive representation in clinical trials have a history of legislative support. The Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012 and the subsequent FDA action plan in 2014 to enhance demographic data collection highlight a commitment to diversity and the accurate assessment of medical interventions across all population segments.^{8,9} Recognizing the unique challenges and opportunities presented by medical devices and drugs is crucial for designing inclusive trials. Medical devices, due to their specific applications and complexities, and drugs, benefiting from a wider application context, face distinct barriers to achieving diverse recruitment. Yet, the goal remains the same: to ensure trials reflect the broad population for reliable generalizability.

Understanding the distinctions between medical device and drug trials is key to addressing population diversity. Drug trials, organized into four phases, assess safety and efficacy, whereas device trials, typically conducted in feasibility and pivotal stages, focus on safety and performance, as well as effectiveness. The scale and global reach of drug trials often exceed those of device trials, affecting the diversity and applicability of results. This contrast highlights the necessity of targeted recruitment and inclusion strategies to cultivate representative and diverse study populations.

Effective representation requires consistent demographic reporting, a point underscored by the FDA in 2020 with an effort to support greater consideration of a wide range of demographic factors in clinical trial design.¹⁰ Adding to this, the inclusion of socioeconomic status, although not currently mandated, could provide valuable insights into inclusivity and identify socio-demographic barriers to participation. While these recommendations aimed at expanding clinical trial diversity through more inclusive eligibility criteria and recruitment practices, translating these policies into practice, particularly for high-risk cardiovascular devices that are most common among FDA Premarket Approvals (PMA),¹¹ remains inadequately documented. This gap is particularly concerning given the high stakes of these devices, where demographic-specific responses can significantly impact patient outcomes.^{12–15} For medical devices, the FDA also has specific guidance about the evaluation and reporting of sex⁷ as well as age-, race-, and ethnicity-specific data in clinical studies.¹⁶

One notable example highlighting the importance of representative study populations is seen with left atrial appendage occlusion (LAAO) devices, such as the WatchmanTM device, approved by the FDA in 2015. These devices are used to occlude the part of the left atrium where clots commonly form in patients with atrial fibrillation with the goal of reducing stroke risk. However, the study populations in the two key comparative trials that supported FDA approval were comprised of approximately 70% men,^{17,18} leaving a gap in understanding the device's safety and effectiveness in women. An independent study later revealed that women had two-fold higher odds of major adverse events (MAE) and a two-fold higher risk of death in-hospital post-procedure.¹⁹ About six weeks after publication of this study, in September 2021, the FDA sent a letter alerting healthcare providers about these risks.²⁰ This example underscores the consequences of under-enrolling women in clinical trials and highlights the risks that patients may face due to incomplete data on device safety and effectiveness in diverse populations.

This study endeavors to fill this critical knowledge gap. The recent legislative and policy efforts have aimed to address the disparities in clinical trial participation, but challenges persist in implementing these policies, especially in the context of high-risk medical devices. By analyzing demographic data from pivotal premarketing studies that supported FDA approvals of original high-risk therapeutic cardiovascular devices between 2014 and 2022, we aim to shed light on FDA transparency and the real-world implications of its diversity initiatives. We specifically focused on pivotal clinical studies, as they are the foundational clinical evidence for the FDA's approval decisions. Although the FDA's "Clinical Trial Snapshots" program provides clinical trial data for pharmaceuticals and biologics, focusing on the demographic composition of trial participants and highlighting how well the drug worked in various demographic groups, such reporting is unavailable for medical device approvals.²¹ Therefore, this study is poised to offer a comprehensive overview of the progress made and challenges that persist in ensuring diversity in clinical trials for medical devices. Doing so will provide valuable insights into the effectiveness of policy interventions and identify areas where further efforts are needed to achieve truly inclusive and representative clinical research.

Materials and Methods

We comprehensively reviewed all original high-risk therapeutic cardiovascular devices approved from 2014 to 2022, utilizing the FDA's publicly accessible PMA database.²² One author (MJS) selected devices using the following filters: "Cardiovascular" under advisory committee and "Originals Only" under supplement type. We excluded feasibility

studies, studies missing data, summaries using a meta-analysis for the pivotal study, and automated external defibrillators (AEDs). We excluded AEDs because the FDA approves these devices leveraging existing clinical data. Two authors (CLU and SRY) abstracted data from pivotal studies listed in the FDA's Summary of Safety and Effectiveness Data about patients historically underrepresented in clinical trials: older age (age ≥ 65 years), female sex, from racial and ethnic minority groups, and of low socioeconomic position. We exclusively extracted this data because these groups are often underrepresented in clinical trials, aiming to ensure medical equity and understand device impacts across diverse populations. The inclusion of socioeconomic status addresses an important yet underexplored characteristic of patients historically underrepresented in clinical trials. To complement data from the FDA's PMA database when pivotal study details were insufficient, we sought additional information from ClinicalTrials.gov and PubMed's listing of MEDLINE-indexed journals. For the studies that reported race information, we noted the specific races included. Additionally, we determined whether these studies conducted subgroup analyses to identify significant demographic differences. We documented the presence of subgroup analyses focusing on age, sex, race, and ethnicity within each pivotal study. Furthermore, we identified any instances where these subgroup analyses yielded significant findings, highlighting differences in device safety or effectiveness across diverse patient groups. Where significant subgroup findings were reported, we carefully extracted direct quotes from the FDA's Summary of Safety and Effectiveness Data, capturing the essence of the significant results and the precise language used, thereby shedding light on the implications of these findings. We used descriptive statistics to analyze the data. We prepared this study in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies.

Results

From 2014 to 2022, 92 pivotal studies supported FDA approval of 92 original high-risk therapeutic cardiovascular devices. Age was reported in 89 studies (96.7%; Table 1), but only 7 (7.9%) explicitly reported the proportion of older age patients ≥ 65 years. Sex was reported in 89 studies (96.7%). Race was reported in 66 studies (71.7%), although 2 of these studies reported only the percentage of white patients. Additionally, of studies that reported specific racial minority groups, 3 (5.0%) reported zero Asian patients, 19 (41.3%) reported zero American Indian or Alaska Native patients, 18 (46.2%) reported zero Native Hawaiian or Other Pacific Islander patients, and 7 (13.5%) reported zero patients from other races. Ethnicity was reported in 54 studies (58.7%) as Hispanic or Latino and non-Hispanic or Latino, although race

Table 1 Pivotal Studies Supporting the FDA Approval of 92 High-Risk Therapeutic Cardiovascular Devices that Reported Characteristics of Patients Historically Underrepresented in Clinical Trials and Subgroup Analyses, 2014–2022

	Reported Characteristics, No. (%), N=92	Reported Subgroup Analyses, No. (%)
Age	89 (96.7)	27 (29.3)
Advanced Age (>65) Eligible	78 (84.8)	–
Advanced Age (>65)	7 (7.9)	–
Sex	89 (96.7)	65 (70.7)
Race	66 (71.7)	11 (12.0)
White	66 (100)	
Black	63 (95.5)	
Asian	60 (90.9) ^A	
American Indian or Alaska Native	46 (69.7) ^B	
Native Hawaiian or Other Pacific Islander	39 (59.1) ^C	
Other	52 (78.8) ^D	
Ethnicity	54 (58.7)	
Socioeconomic Status	0 (0)	–

Notes: ^A3 studies (5.0%) reported zero Asian patients enrolled. ^B19 studies (41.3%) reported zero American Indian or Alaska Native patients enrolled. ^C18 studies (46.2%) reported zero Native Hawaiian or Other Pacific Islander patients enrolled. ^D7 studies (13.5%) reported zero patients enrolled from other races.

and ethnicity were often combined (eg, listing “Hispanic” as race or “First Nations/White”), and the categories were at times not inclusive or all-encompassing. No studies reported patients’ socioeconomic position.

Subgroup analyses by age were performed for 27 studies (29.3%), among which 2 (7.4%) reported any statistically significant difference in device safety or effectiveness. Subgroup analyses by sex were performed for 65 studies (70.7%), among which 8 (12.3%) reported statistically significant differences. Subgroup analyses by race and ethnicity were performed for 11 studies (12.0%), among which 1 (9.1%) reported a statistically significant difference. In total, 10 studies (10.9%) had statistically significant subgroup findings, including 2 for age, 8 for sex, and 1 for race and ethnicity (Table 2). For example, for BIOTRONIK Inc’s Astron Pulsar Stent System, a notable instance was observed where the reported data showed a statistically significant increase in MAE between genders after 12 months: 9.6% of male subjects experienced an MAE compared to 19.8% of female subjects. However, a common issue with these subgroup analyses was the lack of specificity, often resulting in broad conclusions, such as reports of “lower efficacy for women” without clarity whether further investigation was pursued to understand these sex-based differences in outcomes. No approvals were restricted or specified to a particular patient population based on demographic factors.

Discussion

Among the 92 pivotal studies supporting FDA approval of 92 original high-risk therapeutic cardiovascular devices between 2014 and 2022, patient age and sex were nearly always reported, although few studies reported the explicit participation of older adults (≥ 65 years). In contrast, only three-quarters and three-fifths of studies reported patient race and ethnicity, respectively. And no studies reported patients’ socioeconomic position. The inconsistency in reporting is further underscored by substantial disparities in the enrollment of racial minority groups, where the degree of underrepresentation varied widely. For example, while 3 studies (5.0%) reported no Asian patients, as many as 18 studies (46.2%) lacked any Native Hawaiian or Other Pacific Islander patients, revealing a striking range of underrepresentation from 5% to nearly 50% in the studies. Similar findings have been shown in orthopedic²³ and neurosurgical²⁴ medical devices, highlighting the need for stronger federal mandates and enforcement of study inclusivity.

Moreover, demographic subgroup analyses, which are crucial for understanding the safety and effectiveness of devices across trial populations and a key component of the FDA’s action plan to enhance the collection and availability of demographic subgroup data, was conducted in fewer than 30% of all studies by age and just 12% by race and ethnicity, consistent with prior research.²⁵ This contrasts with analysis by sex, which was done by more than 70% of studies. These findings highlight that while reporting of and subgroup analyses by sex have improved,²⁶ there are still gaps in multiple other key demographic categories. Additionally, the ambiguity in subgroup differences reported raises concerns about the depth and power of analysis conducted.²⁷ Furthermore, the lack of targeted approvals raises questions about if and how subgroup analyses are used in regulatory decision-making.

Our findings illustrate a lack of uniformity in demographic reporting across studies, suggesting that the FDA’s Summary of Safety and Effectiveness Data template could include comprehensive race and ethnicity categories. This change would ensure structured and complete demographic reporting, with explicit documentation of zero participants in specific categories, thereby enhancing transparency and the utility of these data for regulatory and public health analyses.

The FDORA represents a meaningful stride towards diverse inclusivity by requiring sponsors to submit diversity action plans (DAPs) alongside their study protocols or Investigational Device Exemption (IDE) applications for pivotal drug studies and device trials.¹ These DAPs are designed to set clear target goals for participant diversity, reflecting the population’s demographics most likely to use the medical device or drug being tested.²⁸ Moreover, the FDORA mandates include detailed strategies for achieving these goals, such as outreach efforts to underrepresented communities, collaborations with community organizations, and using culturally tailored recruitment materials.

In response to these challenges, legislative measures like FDORA represent a crucial step toward rectifying these disparities. However, the journey from policy to practice in clinical trial diversity, particularly in medical device research, requires a concerted effort from all stakeholders in the medical device ecosystem. The effectiveness of these regulatory efforts hinge on rigorous enforcement and careful monitoring. As such, continued vigilance and assessment of these policies in clinical trials and post-marketing studies are essential to gauge their impact and identify areas for further improvement.

Table 2 Descriptions of Statistically Significant Subgroup Findings in Pivotal Studies for FDA Approved High-Risk Cardiovascular Devices, 2014–2022

Applicant	Device Name	No. Subgroup Analyses Reported	No. Significant Subgroup Analyses	Type of Significant Subgroup Analyses	Significant Findings
St. Jude Medical	CardioMEMS™ HF Pressure Measurement System	1	1	Sex	“Benefit/risk profile for the device in women is not as favorable as that in men because of the apparently diminished effectiveness in women.”
Edwards Lifesciences, LLC.	Edwards SAPIEN XT™ Transcatheter Heart Valve, model 9300TFX and Accessories	1	1	Sex	“The non-inferiority primary endpoint was met in males as well as in patients with or without atrial fibrillation, but not met in females.”
Lutonix	LUTONIX® Drug Coated Balloon PTA Catheter	1	1	Sex	“Primary effectiveness data from this study suggest a reduced treatment effect in women, as compared with observed outcomes in men.”
Medtronic Inc.	Medtronic Model 5071 Lead	2	1	Age	“Leads implanted in patients in the age group of 19–65 year of age experienced better complication free survival (93.9% at 5 years), comparing to either younger or older patient group (75.5% and 79.0% at 5 years, respectively).”
BIOTRONIK, INC.	Astron Pulsar Stent System, Pulsar-18 Stent System	2	1	Sex	“The only secondary endpoint that reached a statistically significant difference was the MAE [Major Adverse Event] rate at 12 months ($p = 0.031$), with a MAE rate observed for male subjects of 9.6% (19/197) and a MAE rate for female subjects of 19.8% (17/86).”
ABIOMED Inc.	Impella RP® System	1	1	Sex	“A trend towards higher mortality was observed in female patients.”
Essential Medical, Inc.	MANTA™ Vascular Closure Device	3	2	Age, Sex	“There was a statistically significant difference for safety outcomes for gender and age. Major Complications, Minor Complications and Valve Academic Research Consortium-2 Major Vascular Complications occurred more frequently in female subjects and in older adults (> 80 years) than in male and younger subjects.”
Bard Peripheral Vascular, Inc.	VENOVO Venous Stent System	3	1	Race, Ethnicity	“The small differences based on race and ethnicity are likely due to the small sample size.”
CVRx, Inc.	BAROSTIM NEO® System	1	1	Sex	“Females had a statistically larger benefit in quality-of-life and NT-proBNP.”
Medtronic Vascular, Inc.	Abre Venous Self-expanding Stent System	1	1	Sex	“Primary patency at 12 months was lower in female subjects compared to male subjects, $p = 0.052$.”

Our findings also highlight the critical role of post-marketing real-world studies. Essential for broadening our understanding of device performance across diverse populations, these studies complement pre-marketing efforts and align with FDA initiatives to increase clinical trial inclusivity. These post-marketing evaluations are crucial for capturing longitudinal data on safety and efficacy among underrepresented groups, potentially uncovering adverse reactions or efficacy differences not apparent in the controlled environments of pre-marketing trials. Emphasizing rigorous methodologies and multidisciplinary collaboration is key to generating reliable evidence and adapting regulatory practices to better protect and serve all population segments.²⁹

It is important to note that our study's focus on high-risk therapeutic cardiovascular devices may limit the generalizability of our findings. We relied on pivotal trial identification and demographic data from FDA Summaries, acknowledging that additional details might be accessible via ClinicalTrials.gov or related publications. Furthermore, the retrospective nature of our analysis, while informative, does not allow for real-time assessment of ongoing trials and may not fully capture the dynamic changes in trial demographics and policies that occur after our review period.

Conclusions

The lack of sufficient representation in clinical trial populations severely hampers the possibility of conducting robust subgroup analyses crucial for assessing population-specific risks and benefits.³⁰ This shortfall is especially critical in medical devices, where demographic-specific responses are inadequately documented and can have significant implications for safety and effectiveness. Our findings reveal a large gap in the reporting of race and ethnicity in pivotal studies, with approximately 30% not reporting race and 40% not reporting ethnicity, as well as more than 90% not reporting participation of older adults (≥ 65 years). Additionally, subgroup analyses were infrequently conducted, especially by age, race, and ethnicity. To overcome these challenges, it is critical to adopt practices that involve consistent reporting of patient demographics and comprehensive subgroup analyses. Implementing such practices, aligned with the directives of FDORA, is not only a regulatory requirement but also a step towards meaningful change in medical research. By prioritizing the collection and analysis of detailed demographic data and performing rigorous subgroup analyses, we can enhance the integrity and fairness of healthcare, ensuring that medical devices are effectively and safely applicable to all segments of the US population.³¹ Ensuring that clinical trials accurately reflect the populations they intend to serve is essential for developing medical interventions that are both effective and equitable.

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the Greene Law Firm, in a qui tam suit alleging violations of the False Claims Act and Anti-Kickback Statute against Biogen Inc that was settled in September 2022. The authors report no other conflicts of interest in this work.

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