Lack of Regulation of Minority Data Inclusion in FDA Clinical Trials

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Introduction

At the beginning of this year, I was tasked with my Capstone project: creating a skin tone inclusive, non-invasive bilirubinometer for infants. I was confused as to why was there a need for a skin tone inclusive bilirubinometer. Shouldn't this medical device work on all patients? I soon began to understand that the non-invasive bilirubinometer produced inaccurate readings for dark skin tone patients, causing these patients to be subjected to unnecessary treatments. I was perplexed: how could a medical device come to market, not work on all patient populations, and still pass all regulatory processes? My Capstone project alluded to a larger, more systematic problem, one concerned with the regulatory processes of medical devices and the inclusion of minority demographic data.

The Federal Drug Administration (FDA) upholds standards and regulatory processes for bringing medical products to the market for hospitals, private practices, and healthcare systems to purchase. The most recent effort put forth by the FDA to address the lack of inclusion of minority data in clinical trials was the Safety and Innovation Act (SIA) of 2012. The SIA was enacted by the FDA to restructure approval fees and provide medical product manufacturers with recommendations of including minority data (Sen. Harkin, 2012). At first glance, the FDA SIA seems like a step towards eradicating racial healthcare disparities that have long been ignored by the United States government (Matthew, 2018). However, this legislation does not provide strict regulations on the inclusion of minority demographic data in medical device clinical trials, only providing a loose set of recommendations that are virtually unenforceable. This form of governance over medical products is extremely inefficient, does not meet a benchmark of safety, and perpetuates racial disparities in the healthcare setting. To create safe medical products for all societal groups, it is important for regulatory agencies like the FDA to promote values of

inclusion, uphold inclusion metrics for clinical trials, and offer strict regulations that hold legal enforcement mechanisms. Without these principles, medical products can become ineffective for societal groups excluded from clinical trials and cost billions of dollars in poor health outcomes and treatment strategies (Goldman et al., 2022). Simultaneously, manufacturers expenditures will increase to address technologies that only perform well on a particular societal group, creating a wildly inefficient system for medical product creation and validation.

In this paper, I argue that poor healthcare polices and an imbalanced power dynamic between the FDA and manufacturers perpetuate racial disparities by a lack of inclusion of minority demographic data in medical product clinical trials. First, I will provide an overview of the literature on the current state of inclusion of minority demographic data and the effects this has on patient populations. Then, I will analyze FDA and related agencies legislation to understand what political artifacts these generate in concert with the current healthcare system. Through this analysis, I find that there is a distinct correlation between healthcare policy and an unwillingness to offer strict regulations on the inclusion of minority data in medical product clinical trials. Finally, I will end with a discussion on mistrust between minority patients and healthcare providers and the ways in which this research can benefit the healthcare system holistically.

Literature Review

Without a rigorous form of sustaining patient diversification in medical device clinical trials, devices can become either overtly ineffective or produce harmful side effects for darker-skinned patients. In particular, three devices were shown to disproportionately affect the quality of healthcare for darker-skinned patients: pulse oximeters, bilirubinometers, and X-Rays. Firstly, during the height of the COVID-19 pandemic, it became apparent that pulse oximeters

overestimated oxygen levels in dark-skinned patients, causing these patients to eventually be hospitalized because of extremely low oxygen levels (Elahi, 2021). A paper published in the *Federation of American Scientists* asserts, "Studies show, for instance, that Black COVID-19 patients have been 29% less likely to receive supplemental oxygen on time and three times as likely to suffer occult hypoxemia during the pandemic," (Wickerson, 2022). Hypoxia, if left untreated, can produce irreversible damage to tissue function by altering biochemical balances vital for cellular processes (Rocca et al., 2022). Dark-skinned patients who were hospitalized from dangerously low oxygen levels are subjected to long-term adverse side effects of untreated hypoxia at a much higher rate than white patients. Secondly, bilirubinometers are a non-invasive measurement device that seek to measure bilirubin levels in infants and assess the precedence of jaundice. However, this form of screening presents a significant discrepancy for infants with darker skin tones, potentially resulting in unnecessary phototherapy prescriptions with side effects such as imbalances in the neonatal thermal environment, reduction of early-stage maternal-infant interactions, and melanocytic nevi and skin cancer (Xiong et al., 2012). Lastly, among medical imaging modalities, X-Rays prove to be less effective for dark-skinned patients, delaying critical diagnoses and access to medication (Ray, 2022). All three devices underscore a much broader concern: an unmotivated nature held by medical device manufacturers and the FDA in creating inclusive medical device clinical trials, ones that prioritize thorough subgroup analyses while promoting safety.

Racial biases extend further than FDA regulation of medical devices, often infiltrating into other sectors of FDA product jurisdiction. The FDA is responsible for the regulatory oversight of food, drugs, biologics, medical devices, and products associated with veterinary applications. Drugs, certain medical devices, and combinatory products are required to complete

clinical trial testing, which is broken up into multiple phases. A study conducted at Duke University found that of the 32,000 subjects that participated in new drugs trials in the United States in 2020, 8% were Black, 6% were Asian, and 11% were Hispanic. Researchers in the Department of Medicine at Duke University also addressed how counterintuitive this approach is by stating, "In contrast to these low trial participation statistics, underrepresented racial and ethnic minority groups carry a disproportionately high burden of chronic diseases that garner the most investment in drug research and development," (Kelsey et al., 2022). Demographic statistics for subjects enrolled in clinical trials are progressively decreasing, illustrating a deep-rooted disconnect between the purpose of clinical trials and the prevalence of chronic diseases within minority groups.

Current FDA inclusion recommendations for medical device clinical trials do not improve the inclusion of minority demographics within private stakeholders. Funders of medical device trials develop parameters of clinical studies, including inclusion metrics with relevant test groups, and submit the methodology and results of clinical studies to the FDA for approval. A study conducted by the Rothman Orthopedic Institute at Thomas Jefferson University Hospital on orthopedic medical device clinical trials from January 2003 to January 2020 found that only 49% reported on race and 37.3% reported on ethnicity (Issa et al., 2023). Similarly, a study conducted by the Yale School of Medicine found that of the studies conducted on premarket approval devices in 2015, 51% reported race and 33% reported on ethnicity. Fewer than 20% of these trials met all demographic criterion set forth by the FDA SIA (Dhruva et al., 2017). Premarket approval devices are also known as high-risk devices and present substantial, if not life-threatening, side effects with device failure or malpractice, and require the most regulation from the FDA. Without legal repercussions, it has been shown that submittals produced by

private third parties to the FDA for medical device clinical trials lack proper inclusion of minority demographics. Overall, this establishes that private stakeholders, without regulatory ramifications, will not put extraneous effort into the diversification of medical device clinical trials. This produces a positive feedback loop, meaning that the FDA and private stakeholders enable one another to allow for the repetition and consistent lack of adequate subgroup analyses within medical device clinical trials. From these findings two issues are established: the FDA, by offering no enforcement mechanisms for diversification in medical device clinical trials, allows and perpetuates minimal effort put forth by private stakeholders to comply with recommendations.

With the aim of understanding the evolution of demographic inclusion in medical device clinical trials, I have chosen to employ Winner's "Do Artifacts Have Politics?" framework. In this framework, politics are defined as the arrangement of power and authority in human associations as well as the activities that take place within those arrangements. Winner identifies two fundamentally political artifacts: those that comply with a political value or question, and those that are inherently political and are compatible with a particular sociotechnical system (Winner, 1980). Technologies contain deeply embedded political and historical biases, and it is important to understand the context in which they were produced. Holistically, this allows for an understanding of how technologies impact different social groups, aspects of sociotechnical systems, and the distribution of power between differing social groups. Healthcare itself is one of the most ingrained sociotechnical systems in the United States. In the American healthcare system, racial and ethnic minorities receive lower quality care, are less likely to receive routine healthcare, and therefore, have poorer health outcomes than white patients (Ray, 2022). While these disparities relate to a broad distribution of racial inequalities in the United States, they also

allude to a foundational problem within institutions regulating and monitoring healthcare. By using this framework, I will analyze how historical and political situations have allowed for leniency of inclusion of minority data in medical device clinical trials regulated by the FDA. This approach allows for a causal analysis of how the biases inherent in certain medical devices propagate throughout the system, how regulatory institutions such as the FDA reinforce these biases by lack of inclusion regulation, and how these biases were constructed in the first place.

Methods

The approach to gathering data involves integrating quantitative information on demographic inclusion post-policy implementation with an analysis of the historical and political context influencing FDA actions and advancements in inclusion efforts. First, I considered the historical context of the FDA SIA in articles analyzing policy efficacy and implementation, and what political factors influenced these goals and actions. I utilized a multitude of primary sources, including the FDA SIA Congressional enrolled bill and public law documents, FDA SIA Section 907 Action Plan materials, and Congressional hearings of the Prescription Drug User Fee Act of 1992 and NIH Revitalization Act of 1993. Second, I gathered secondary sources, mostly from research studies considering the impact of the FDA's SIA since its adoption in 2012. These studies consider the efficacy of these recommendations in including more social groups in medical device clinical trials. In the review of this literature, I examined specific social and political factors that have prevented the adoption of regulations that promote inclusion of varying demographics in medical device clinical studies, backed by quantitative data of inclusion metrics since 2012.

Analysis

To begin with, the Prescription Drug User Fee Act (PDUFA) of 1992 restructured the power dynamic between the FDA and third-party manufacturers. As stated by the House of Representatives, the PDUFA "amends the Federal Food, Drug, and Cosmetic Act to provide authority for the Secretary of Health and Human Services to assess and collect fees from manufacturers of prescription drugs beginning in FY 1993," (Rep. Dingell, 1992). Prior to the PDUFA, the FDA was an entity that solely ran off taxpayer dollars. The installation of this legislation incentivized, if not forced, the FDA to collect fees from drug companies for pursuit of clinical trials and placed a substantial portion of the financial burden on drug manufacturers. Overtime, manufacturers seeking to produce medical devices, generic, biosimilar, and animal drugs were subjected to the same fees prescription drug manufacturers were required to pay (FDA Commissioner, 2023). The goal of the PDUFA was to expedite the speed of the drug approval process, failing to consider the offset effects this act would have on safety metrics. Demographic inclusion metrics are a subset of overall clinical trial safety and were disregarded to align with manufacturer goals. The PDUFA required the FDA to seek resources from third party manufacturers, diminishing regulatory power that was previously held over manufacturers. Currently, 45% of the FDA's budget comes from fees collected by applications to produce and market medical devices and drugs (Breen, 2021). Drugs and medical devices produced by third party manufacturers are strongly compatible with the PDUFA, and in their nature, require a sociotechnical system that allows for quick approval times and a lack of attention towards safety. Corresponding with Winner's framework, medical devices, drugs, and/or biologics produced after the implementation of the PDUFA are representative of a complacency with the inherent sociotechnical system, one that favors profit over safety.

Furthermore, the National Institute of Health (NIH) Revitalization Act of 1993 encouraged the FDA to disregard inclusion metrics of various demographic subgroups. The NIH Revitalization Act of 1993 required the NIH to include women and minority demographic groups in all research projects and clinical studies. As stated in the public law document, section 492B, "In conducting or supporting clinical research for purposes of this title, the Director of NIH shall, subject to subsection (b), ensure that- (A) women are included as subjects in each project of such research; and (B) members of minority groups are included as subjects in such research," (Sen. Kennedy, 1993, p. 12). This meant that the NIH has grounds for enforcing strict regulations on inclusion of demographic data in all forms of research and clinical studies. However, there is no mention of the FDA in any of the public law sections and supplemental clauses (Sen. Kennedy, 1993). Granted, the act specifically inquires about the proceedings of the NIH, and this is because the NIH is an entity fully supplied by taxpayer dollars. Since the PDUFA was passed in 1992, the FDA had already shifted from strict taxpayer dollar funding to partial manufacturer funding. Entities reliant on industry-sponsored or privately funded research, including the FDA, were exempt from abiding by new demographic inclusion metrics (Issa et al., 2023). This perpetuated the groundwork laid by the PDUFA, meaning that the FDA was to continue to prioritize efficiency over safety and had no incentive to regulate the inclusion of demographic subgroup analyses. The combination of both the PDUFA and the NIH Revitalization Act of 1993 produced drugs and medical devices under FDA guidance that symbolically reinforce the prescribed sociotechnical system, one that alludes to a political artifact of a power dynamic between the FDA and medical manufacturers.

Finally, the FDA SIA of 2012 further established no regulatory power of the FDA over inclusion of demographic subgroups. The FDA SIA mostly sought to reform fee programs

governing biological products, medical devices, prescription, pediatric, and generic drugs established by the FDA. The law states, “Food and Drug Administration Safety and Innovation Act - Amends the Federal Food, Drug, and Cosmetic Act (FFDCA) to reauthorize and establish new Food and Drug Administration (FDA) prescription drug user-fee programs...” (Sen. Harkin, 2012). However, section 907 of the SIA specifically mandates the FDA to report to Congress on the status of inclusion of subgroup analyses and propose an action plan that puts forth inclusion recommendations. Demonstrated in section 907b of the public law document, “…recommendations, as appropriate, to improve completeness and quality of analyses of data on demographic subgroups in summaries of product safety and effectiveness data and in labeling,” (Sen. Harkin, 2012). Simultaneously, this section offers manufacturers a loophole for including minority subgroups, by putting forth recommendations that allow for a lack of availability of such demographic data. Regardless, recommendations are not enforceable by law and supplied the FDA with no enforcement metrics for ensuring that manufacturers are in accordance with such recommendations. The FDA SIA Section 907 Action Plan outlined simple data presentation of demographic inclusion to Congress and minimal effort towards producing sufficient recommendations for manufacturers (Commissioner, 2019). Prior to the installation of the SIA, 44.4% of orthopedic medical device trials reported race demographic, compared to a 54.2% reporting of race post-SIA installment. The percent change of race reporting before and after the adoption of SIA was not found to be statistically significant, indicating that the SIA was not involved in the improvement of reporting demographic data (Issa et al., 2023). This data displays the weak enforcement nature of the FDA SIA and further demonstrates the power dynamic between manufacturers and the FDA. Pressure to bring drugs, biologics, and medical devices to market cause the FDA to promote unenforceable recommendations that manufacturers have no

intention in following. Politically, this consistent cycle of failed healthcare policies continuously perpetuates the existing sociotechnical system, one that prioritizes quick routes to market over thorough examination of safety through multiple subgroup analyses.

The FDA itself argues that the action plans proposed by the agency in 2012 through the SIA represent a change in focus towards safety metrics (Commissioner, 2019). The agency consistently tries to present a narrative of safety and effectiveness for diverse populations through action plans and marketing materials of the SIA. I argue that it is impossible for the FDA to uphold these values with the current power imbalance between manufacturers and the agency. Medical products that are brought to market strengthen past legislation and indicate no need for revision, further cementing the existing sociotechnical system in place. This offers little incentive for political innovation and continues to endorse the current power distribution. These products figuratively portray the value of quick approval times rather than safety and inclusion of minority demographic data. Until actual regulations are put forth by the FDA governing inclusion metrics of minority data, the regard of safety is not apparent or upheld by the agency.

Conclusion

Through the analysis I have presented, it is evident that the policies put in place by both the FDA and NIH have created a longstanding standard for the lack of inclusion of minority data in medical product clinical trials. This standard has been maintained by the power imbalance between FDA and medical product manufacturers, granted by the PDUFA, the NIH Revitalization Act of 1993, and the FDA SIA of 2012. All three policies benefit the established sociotechnical system relating to healthcare that is not concerned with the inclusion of all societal groups, specifically minority demographics.

This research offers one limitation, in that I did not explore the relationship between patient and provider, and minority groups willingness to participate in medical product clinical trials. Cases like the Tuskegee syphilis experiments have been shown to increase medical mistrust between minority groups and medical providers, diminishing minority groups resolve to participate in any medical trials and research studies (Duff-Brown, 2017). While this limitation presents substantial concerns in the recruitment of a diverse patient population for medical product trials, it should not be ignored and should be further investigated. With further investigation, there is a potential for the restoration of trust between minority groups and medical providers that could help aid in diversification of medical product trials.

By presenting this information, I hope this propels solutions in restructuring medical product clinical trials to serve and benefit all consumers of the American healthcare system, while still producing effective and novel medical products. Specifically, I hope this discussion motivates FDA policymakers to provide strict regulations on the inclusion of minority data in medical device clinical trials. This topic portrays that racial disparities in the healthcare systems are still prevalent and there is much work to be done to eradicate these barriers. I hope this research incites meaningful and open conversations in ways to which the healthcare system can be reformed to include better inclusivity and diversity standards while upholding the fundamental duties of healthcare.

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