Advancing Skin-Tone Inclusive Bilirubin Assessment: Refinement and Design of a Non-Invasive Measurement Device

(Technical project)

Lack of Regulation of Minority Data Inclusion in FDA Clinical Trials

(STS project)

A Thesis Prospectus
In STS 4500
Presented to
The Faculty of the
School of Engineering and Applied Science
University of Virginia
In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science in Biomedical Engineering

By

Gabriella Haiz

October 27, 2023

William Adu-Jamfi, Kaitlyn Hixson, Mark Provost

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

ADVISORS

Dr. MC Forelle, Department of Engineering and Society

Dr. Brian Helmke, Department of Biomedical Engineering

Dr. William Guilford, Department of Biomedical Engineering

Introduction:

Racial health disparities in the United States begin at birth, with an infant mortality rate (IMR) for the non-Hispanic black population being 10.8 for every 1000 live births versus an IMR of 4.6 for every 1000 births for the non-Hispanic white population (Jang & Lee, 2022). In order to address racial disparities in the health setting, it is important to understand the decades of poor policy making, systematic racism, and the construction of socioeconomic barriers have upheld this benchmark of healthcare quality for minority groups (Matthew, 2018). The Federal Drug Administration (FDA) upholds standards and regulatory processes for bringing medical devices to the market for hospitals, private practices, and healthcare systems to purchase. Currently, the FDA does not provide strict regulations to include minority demographic data in medical device clinical trials, providing a loose set of recommendations that are virtually unenforceable.

Neonatal (newborn) jaundice, resulting from the accumulation of yellowish pigment, bilirubin, presents substantial health risks to both term and preterm infants in their first week of life. Approximately 50% of term and 80% of preterm infants develop jaundice during this critical period (Woodgate & Jardine, 2015). If left untreated or undetected, jaundice can lead to severe complications such as encephalopathy, hearing loss, and kernicterus—a debilitating and long-lasting neurological disorder (Kemper et al., 2022). To manage this condition, up to 10% of term neonates and 25% of preterm neonates require phototherapy, which employs blue light to reduce bilirubin levels in the blood by converting it into the easily excretable lumirubin (Queensland Clinical Guidelines, 2022).

Monitoring and diagnosing hyperbilirubinemia (the presence of too much bilirubin in the blood) currently rely on two methods: the invasive measurement of total serum bilirubin (TSB) through venous or heel stick blood samples and non-invasive transcutaneous bilirubinometry (TcB) using a handheld bilirubinometer. However, TcB screening presents a significant discrepancy for neonates 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). The inaccurate measurements of bilirubin in neonates with darker skin tones not only exposes the shortcomings of existing bilirubin measurement techniques but also underscores a broader concern- an unmistakable racial bias in healthcare. This bias disproportionately affects neonates with darker skin tones, leading to unequal access to care and exacerbating racial health disparities (Chokemungmeepisarn et al., 2020). FDA approved medical devices that have not been tested on all minority subgroups have been shown to be ineffective, and at times, harmful in practice, with the aforementioned bilirubinometer being a prime example.

In my technical project, I will consider a specific example in which tolerance to systemic healthcare racism produced a device, the bilirubinometer, that only served one specific group of people: light-skinned neonates. In my STS project, I aim to understand why there is such leniency in FDA recommendations for inclusion of minority data in medical device clinical trials and how these recommendations can become enforceable.

Technical Topic:

Jaundice, a common condition in infants, occurs due to the excessive breakdown and replacement of red blood cells, which releases bilirubin into the bloodstream (NHS UK, 2022). In a fully developed human body, bilirubin is then transported via bloodstream to the liver for excretion. However, infants possessing underdeveloped livers cannot excrete bilirubin in an efficient manner, causing the buildup of bilirubin in fat tissue. While the pathology of neonatal jaundice cannot be remedied, the tools used for diagnosis and treatment quantification can be improved upon. A study conducted in South India concluded that TcB and TSB levels, two major indicators of hyperbilirubinemia, have a stronger linear relationship in lighter-skinned patients, making bilirubinometer measurements more accurate for this group of patients (Varughese et al., 2018). The inaccurate bilirubinometer readings for darker-skinned neonates is due to the substantial overlap in absorption spectra between bilirubin and melanin (Onks et al., 1993). This overlap can lead to TcB overestimation, and an unnecessary prescription of phototherapy, potentially resulting in adverse side effects for dark-skinned neonates.

Last year's Capstone group developed a novel measurement method involving continuous photoconversion of bilirubin, akin to phototherapy. Transmittance of 460 nm light through the skin is measured at specific intervals. By computationally analyzing the decay curve and identifying the point where the transmittance curve reaches a horizontal asymptote as bilirubin fully converts to lumirubin, the initial cutaneous concentration of bilirubin (TcB) can be determined. This year's goal is to refine the computational model for more accurate bilirubin assessment from absorbance measurements and establish an *in vitro* model that replicates bilirubin flow and diffusion into the skin, facilitating realistic testing.

Currently, there is no way to computationally account for the overlap of absorbance spectra between bilirubin and melanin. To remedy this, we will integrate existing absorbance

data to differentiate between melanin and bilirubin absorbance spectra through an Exponential Moving Average (EMA) model. We will then employ mass balance equations to develop a time-dependent mathematical model for neonatal bilirubin concentration, that will help asymptotically inform the EMA model. Finally, we will optimize parameters within the computational model, validated by an *in vitro* model and the mass-balance model.

The mechanism behind the movement of bilirubin from the bloodstream into tissues remains poorly understood. This creates a limited knowledge base for constructing a multi-compartmental computational model to simulate bilirubin flow and photoconversion, potentially leading to inaccuracies in bilirubin quantification. To address this knowledge gap, an *in vitro* flow dialysis model will be created that includes a bilirubin solution dialyzing into a hydrophobic gel, to simulate fat tissue. Initially, we will work on creating stable solutions, mimicking blood, by incorporating varying physiological concentrations of bilirubin and albumin. Additionally, we will create a hydrophobic material that replicates *in vivo* skin properties, including the skin chromophores melanin and oxyhemoglobin. *In vitro* continuous flow dialysis will then be used to assess the diffusive properties of bilirubin as it moves from the solution into the tissue replica. Using the *in vitro* model, spectrophotometry (the measurement of absorbance wavelengths) will be employed to measure the photoconversion of bilirubin under 460 nm light, providing a more robust proof of concept for this method of quantifying bilirubin levels. This model will not only validate the computational model but also assist in refining computational model parameters and enhancing our understanding of bilirubin movement and photoconversion.

The combination of the computational model, enriched by insights from the *in vitro* model, will enable accurate prediction of bilirubin levels in skin with varying melanin concentrations and deepen our understanding of the mechanisms of bilirubin transport within the

body. This integrated approach ensures a holistic understanding that neither model can achieve in isolation and strengthens the proof-of-concept for the novel method developed by last year's Capstone group, potentially paving the way for the future development of a prototype medical device. A prototype medical device that is inclusive to all skin-tones is a small victory in ensuring equitable healthcare to consumers and raises awareness of the underlying biases that are ever present in the American healthcare system.

STS Topic:

Among actors in the healthcare setting, medical devices oftentimes contain discriminatory biases that, when implemented in practice, produce harmful effects to groups targeted by these biases. Bilirubinometers are not the only medical device exhibiting racial biases, with another example being pulse oximeters. 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). The fact that the biases included in the pulse oximeter design were only found during a global pandemic, one that took millions of lives, exhibits the lack of inclusion of minority data in medical device clinical trials. The technological mechanisms employed in these medical devices are almost identical, and as described, led to cascading health and financial adversities due to their integrated biases. Biases, whether implicit or explicit, are not just affecting the ability of a singular device, bilirubinometers; it is a wide-scale problem that includes other medical devices, practices, and information.

The FDA, the United States agency that controls the approval and distribution of medical devices, provides a weak framework for inclusion of minority data. When considering the FDA

recommendations put forth in 2022 for inclusion of minority data, the recommendations presented are up for broad interpretation and only offer a mechanism of identifying race/ethnicity for candidates of medical clinical trials (FDA, 2022). A study investigating diversity in medical trails found that around 14% of the devices submitted to the FDA for approval provided subgroup analyses that included data on effectiveness, safety, sensitivity and selectivity for gender, race, and age. Concurrently, the number of patients included in these subgroups analyses were also found to be too small to draw meaningful conclusions on device safety and effectiveness (Fox-Rawlings et al., 2018). Under these pretenses, the FDA cannot continuously maintain inclusion of minority data with recommendations that are unenforceable, convoluted, and vague in nature.

Without a rigorous form of sustaining patient diversification in medical device clinical trials, devices can become either overtly ineffective or produce harmful side effects. Considering the pulse oximeter case, "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). Among medical imaging modalities, X-Rays prove to be less effective for dark-skinned patients, delaying critical diagnoses and access to medication (Ray, 2022). These disparities in medical devices stem from inadequate testing on a diverse group of patients prior to market launch, with the FDA the sole supervisor for monitoring the processes and methods for clinical trial testing.

Medical devices are not a singular issue when considering racial disparities in the American healthcare system. Research shows, that 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). To contend FDA

recommendations, it is important to evaluate the environment in which these medical devices were constructed. In his *Do Artifacts Have Politics?* piece, Winner asserts, "To understand which technologies and which contexts are important to us, and why, is an enterprise that must involve both the study of specific technical systems and their history as well as a thorough grasp of the concepts and controversies of political theory," (Winner, p. 135). Medical devices containing discriminatory biases are not an isolated problem, it is a symptom of a larger, institutionalized form of inequity. By understanding the policy that regulates and outputs biased medical devices, the inequities that are implemented systematically throughout the entirety of the American healthcare system will become clearer, and remedies to these issues will follow.

Research question and methods:

The research question I will be investigating is: Why are there no strict regulations governing inclusion of minority data in FDA clinical medical device trials? To answer this question, I will be doing a thorough policy analysis of FDA diversity efforts since its installation as a government agency in 1906. This will include an examination of Congressional hearings, white papers, FDA conducted studies on diversity efforts, and the repository of official recommendation papers. Simultaneously, I will be conducting a literature review of UVA anthropologic resources on minority health data. This part of the research approach will consider how anthropologic information, whether scientifically or socially constructed, informed FDA recommendations for inclusion of minority data. Specifically, this holistic research approach reflects on the biases that instruct implementation of policies, or lack thereof, in the medical setting, and how efforts can be allocated to reduce predisposition in the creation of medical devices.

Conclusion:

In my technical project, I will be combining the information acquired from the flow dialysis model, *in vitro* model, and mass-balance computational model to not only improve the efficacy of bilirubinometers on dark-skinned patients, but to create a deeper understanding of the physiological mechanisms of bilirubin and lumirubin throughout the human body. The STS portion of my thesis will consider microscale effects of systematic racism in the American healthcare system, specifically how FDA recommendations of medical device clinical trials perpetuate inequitable access to quality healthcare across minority demographics. By combining these two deliverables, I will display the ways in which FDA medical device clinical trials can be re-structured to serve and benefit all consumers of the American healthcare system, while still producing effective and novel medical devices.

Citations:

Chokemungmeepisarn, P., Tantiprabha, W., Kosarat, S., & Manopunya, S. (2020). Accuracy of the Bilicare™ transcutaneous bilirubinometer as the predischarge screening tool for significant hyperbilirubinemia in healthy term and late preterm neonates. *The Journal of Maternal-Fetal & Neonatal Medicine*, *33*(1), 57–61. https://doi.org/10.1080/14767058.2018.1484098

Elahi, Amara. (2021). Covid: Pulse oxygen monitors work less well on darker skin, experts say. *BBC News*. https://www.bbc.com/news/health-58032842

Food Drug Administration (FDA) (2022). Collection of Race and Ethnicity Data in Clinical Trials: Guidance for Industry and Food and Drug Administration Staff. FDA, 1-16. https://doi.org/ FDA-2016-D-3561

Fox-Rawlings, S. R., Gottschalk, L. B., Doamekpor, L. A., & Zuckerman, D. M. (2018). Diversity in Medical Device Clinical Trials: Do We Know What Works for Which Patients? *The Milbank Quarterly, 96*(3), 499–529. https://doi.org/10.1111/1468-0009.12344

Jang, C. J., & Lee, H. C. (2022). A Review of Racial Disparities in Infant Mortality in the US. *Children*, *9*(2), 257. https://doi.org/10.3390/children9020257

Kemper, A. R., Newman, T. B., Slaughter, J. L., Maisels, M. J., Watchko, J. F., Downs, S. M., Grout, R. W., Bundy, D. G., Stark, A. R., Bogen, D. L., Holmes, A. V., Feldman-Winter, L. B., Bhutani, V. K., Brown, S. R., Maradiaga Panayotti, G. M., Okechukwu, K., Rappo, P. D., & Russell, T. L. (2022). Clinical Practice Guideline Revision: Management of

Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. *Pediatrics, 150*(3), e2022058859. https://doi.org/10.1542/peds.2022-058859

Matthew, Dayna Bowen. (2018*). Just Medicine: A Cure for Racial Inequality in the American Healthcare System*. New York University Press.

National Health Services of the United Kingdom (NHS UK). (2022). Newborn jaundice—Causes. *NHS UK*. https://www.nhs.uk/conditions/jaundice-newborn/causes/

Onks, D., Silverman, L., & Robertson, A. (1993). Effect of melanin, oxyhemoglobin and bilirubin on transcutaneous bilirubinometry. *Acta Paediatrica*, *82*(1), 19–21. https://doi.org/10.1111/j.1651-2227.1993.tb12507.x

Queensland Clinical Guidelines. (2022). Neonatal Jaundice. *Queensland Clinical Guidelines, 9*(22), 3-31. http://www.health.qld.gov.au/qcg

Ray, Roger. (2022).Racial Bias Deeply Rooted in Healthcare Technology and Medical Devices | *Chartis.* https://www.chartis.com/insights/racial-bias-deeply-rooted-healthcare-technology-and-medical-devices

Varughese, P. M., Krishnan, L., & Ravichandran. (2018). Does Color Really Matter? Reliability of Transcutaneous Bilirubinometry in Different Skin-Colored Babies. *Indian Journal of Paediatric Dermatology*, *19*(4), 315. https://doi.org/10.4103/ijpd.IJPD_3_18

Winner, L. (1980). Do Artifacts Have Politics? *Daedalus*, 109(1), 121-136. http://www.jstor.org/stable/20024652

Wickerson, Grace. (2022). An Overdue Fix: Racial Bias and Pulse Oximeters. *Federation of American Scientists*. https://fas.tghp.co.uk/publication/an-overdue-fix-racial-bias-and-pulse-oximeters/

Woodgate, P., & Jardine, L. A. (2015). Neonatal jaundice: Phototherapy. *BMJ Clinical Evidence*, 0319.

Xiong, T., Tang, J., & Mu, D.-Z. (2012). Side effects of phototherapy for neonatal hyperbilirubinemia. *Chinese Journal of Contemporary Pediatrics, 14*(5), 396–400. https://pubmed.ncbi.nlm.nih.gov/22613117/#:~:text=The%20short%2Dterm%20side%20effects,syndrome%20and%20circadian%20rhythm%20disorder.