Modeling Shear Stress-Mediated Endothelial Barrier Properties of Cerebral Cavernous Malformations
(Technical project)

Cultural Biases in the Definition of Informed Consent for Experimental Treatment
(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
Maia C. Jenckes

November 1, 2021

Technical Team Members:
Elise Carey and Madison Myott

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

MC Forelle, Department of Engineering and Society
Brian Helmke, Department of Biomedical Engineering
Chris Highley, Department of Biomedical Engineering

Introduction

On a six-hour airplane flight this past summer, I was seated next to a psychiatric physician who worked for the US government. He told me about a medical research study he had helped supervise outside the United States. In order to participate, the patients were required to meet a certain score requirement on a survey intended to prove that they adequately understood the study and could give informed consent. However, the participants' educational and cultural background influenced their understanding of the information provided, and program supervisors became concerned that patients were being turned away from receiving a beneficial treatment simply because they did not meet a foreign doctor's arbitrary definition of understanding. This concern led to a revision of how the survey results were used and interpreted, a decision this physician agreed with. I do not have most of the details of this research study, but it raises an interesting question. How should this type of criteria be decided, and who should decide it?

The Nuremberg Code Directives for Human Experimentation state "The voluntary consent of the human subject is essential…The duty and responsibility for ascertaining the quality of consent rests upon each individual who initiates, directs, or engages in the experiment…a personal duty and responsibility that may not be delegated to another with impunity (Trials of War, 1949, p. 181). The Nuremberg Code, widely regarded as a standard for medical ethics in human experimentation, was developed during the Nuremberg trials following WWII in response to the crimes against humanity perpetuated by Nazi scientists who tortured and killed the people they made unwilling subjects of their medical research. How these directives have been carried out and enforced has always depended on political and cultural context. The decisions in Nuremberg trials themselves, in which eight of twenty-three defendants were acquitted, were based almost entirely on the evaluations of British, French, and US medical investigators (Weindling, 2001). The acquittals, as Paul Weindling remarks, indicate

"how complex it was to discriminate between war crimes and politically sanctioned racial atrocities, on one hand, and legitimate scientific inquiry, on the other" (2001, p. 38). These distinctions were ultimately made by experts and officials with their own national histories of "politically sanctioned racial atrocities."

The United States has an especially rocky history with medical research involving minority or otherwise marginalized social groups. These social groups have generally been subject to one of two extremes: either complete exclusion from the data pools of research studies, or violent exploitation. The former scenario implies research being done to benefit the majority or otherwise culturally dominant social group, with other social groups sidelined as negligible. The latter scenario–exploitation–has most often involved sacrificing the individuals in non-dominant social groups for the benefit of the dominant social group. In both cases, the research has been performed without regard for the interests of the neglected or exploited patient population. High profile examples from relatively recent history include the infamous Tuskagee Syphilis study and the case of Henrietta Lacks, a black woman whose cervical cancer cells were harvested and cultured without her knowledge or consent (Tuskegee, 2022; Skloot, 2010). For the men involved in the Tuskegee study as well as Henrietta Lacks, it was not only their position as a racial minority that was exploited, but also their socioeconomic status; they had few other options for medical care. Both are part of a long history of events that have destroyed Black Americans' trust in the medical community even as other aspects of medical research become more reliable and widely accepted.

Many of these obscene violations of medical responsibility have not even been swept under the rug, they have been publicly defended as appropriate ethical decisions. Following the Tuskagee study's publication in 1972, an advisory panel concluded that while its long-term

continuation was unethical, “scientific justification” for the study “could not be ruled out” in the short-term (Butler, 1973). Heavy bias and lack of protection from ethical policy and decision-makers has further contributed to black communities' distrust of medical scientists, and has increased their reluctance to voluntarily participate in research, which unfortunately exacerbates their exclusion from sample populations, reinforcing the dominant social group as the primary target and beneficiary of medical research (Freimuth et al., 2001). The exclusion of certain social groups from research population–as a result of both researcher neglect and justified individual reluctance–results in disparities such as inadequate study of how diseases present on darker skin, product design for safety or functionality based on average size and physicality of white men, and failure to account for genetic and lifestyle factors prevalent in certain populations (Ebede and Papier 2006; Villarosa, 2018).

It is not only medical ignorance that affects the quality of information and care that researchers and physicians can provide; it is also socio-cultural ignorance that contributes to this inadequacy. Without understanding certain perspectives of subject populations, researchers and physicians can not take into account how the information they provide will be understood and interpreted. Other such examples are pointed out by Meador and Zazove (2005) in a journal article discussing aspects of Deaf culture that influence communication between medical providers and Deaf patients, such as how grammatical differences between English and ASL can affect how even written communication is interpreted, and how different etiquette values can lead to inefficient communication.

Existing infrastructure for ensuring informed consent in experimental treatments does not address these factors that contribute to medical inequity, and in fact reinforces them in certain situations. The existing systems of medical ethics–like much medical technology–are designed

for the Western colonial majority, and are too often inadequate when applied outside that demographic. This bias affects the ability of these groups to benefit from experimental treatments, such as the treatments that will hopefully result from research on Cerebral Cavernous Malformations, the disease that my technical project is trying to model and better understand.

Technical Topic

Cerebral cavernous malformations (CCM) is a genetic vascular disease that results in leaky, malformed blood vessels (lesions) in the brain. These lesions are characterized by impaired blood-brain barrier function, which can lead to major neurological problems and cerebral hemorrhage (Awad and Polster, 2019). There is no therapeutic treatment currently available; the only existing treatment is surgical removal of the lesions, an invasive procedure that does not prevent new lesions from forming as a result of the same genetic cause (Cerebral Cavernous Malformation, n.d.). KRIT-1 (or CCM-1) is one of three genes responsible for the disease (Pagenstecher et al., 2009).

While KRIT-1 has been confidently linked to CCM, its role in the cell signaling pathways that regulate endothelial behavior and morphology is not well understood. The established involvement of KRIT-1 in shear stress regulated signaling pathways and the localization of CCM lesions to mostly low shear stress (usually venous) blood vessels provokes the hypothesis that lesion formation may be a result of abnormal shear stress response of the endothelial layer (Li et al., 2019).

The goal of this technical project is to design an in vitro design model to aid in studying the mechanism behind the formation of CCM lesions. Current attempts at modeling the physiological conditions of CCM pathology omit characteristics such as blood vessel anatomy, vessel-specific levels of shear stress, and blood brain barrier permeability, or look at these

characteristics only in isolation (Macek Jilkova et al., 2014). Targeted siRNA will be used to knock down KRIT-1 protein expression and mimic the loss-of-function mutation responsible for the disease (Li et al., 2020). Exposing these cells to shear stress with a parallel-plate flow chamber will help establish the effects of the simulated KRIT-1 gene mutation on shear stress response and cell-cell junctions that, if compromised, could contribute to blood-brain barrier leakiness. A perfusable hydrogel model of the affected vasculature will be designed to incorporate the specific architecture of cerebral microvasculature and identify how the dimensional aspects of cerebral blood vessels play into lesion formation and characteristic leakiness.

Several assays will then be used to investigate shear stress adaptation and endothelial barrier permeability within the physiological mimic conditions of the model. Flourescent staining of cytoskeletal filaments will create a picture of the affected cells' structural adaptation to fluid flow conditions, and staining for junctional proteins will provide a quantitative indicator of endothelial barrier effectiveness (Ranadewa et al. 2021). Barrier effectiveness will also be measured by the amount of fluorescently-tagged dextran (a sugar molecule) able to penetrate the endothelial layer into the hydrogel (Choi et al., 2010).

Understanding the abnormalities in endothelial barrier properties and shear stress adaptation as a result of KRIT-1 mutations will provide insight into the signaling pathways involved in CCM lesion formation. Mapping these signaling pathways is a step towards the development of non-surgical treatments that target or compensate for faulty signaling pathways and treat CCM at its source.

STS Topic

When a new non-surgical, therapeutic treatment is eventually developed, it will require human trials, and will become an experimental treatment for people with genetic CCMs. The design of the human trials will be subject to the infrastructure and standards around informed consent as

well as to the decisions of the researchers in charge of the trials. Understanding bias and in the way that informed consent is acquired is essential to designing research studies so that they do not exacerbate existing medical inequities and to ensuring that access to experimental treatments is distributed fairly and in a way that prioritizes patient well-being.

Bias and stereotyping, or the assumed correlation between a trait and an identity, is central to feminist STS theory and has implications in how research studies are typically designed. Often stereotyping becomes a binary analysis: someone displays this characteristic and therefore is part of this identity group, or they do not display the characteristic and therefore are excluded from the group. This binary analysis creates deeply ingrained social perceptions of links between trait and identity that are not inherently true (Suchman, 2007). This type of analysis also easily applies as a description of the informed consent process: demonstrate this measure of understanding and you can provide informed consent, fail to demonstrate and you will be excluded from the research study. This distinction is important and not inherently problematic, because informed consent is absolutely necessary, and thus must be demonstrated in some way. Therefore, critical examination of the processes for obtaining informed consent should be approached carefully, without disregarding the importance of somehow making a distinction. However, the problem arises in how the deciding criterion might be selected, sometimes somewhat arbitrarily, by whoever is given that authority.

Often the goal of scientific researchers is to be as objective as possible, but objectivity can be complicated to pin down when it involves social and cultural differences. In describing her research project on perspectives of indigenous bioscientists, Sisseton Wahpeton Oyate professor and sociopolitical scholar Kim Tallbear writes, “For feminist epistemologists, more ‘strongly objective’ inquiry does not only not require ‘point of viewlessness,’ (Harding, 1991 as cited in Tallbear, 2014) it actively incorporates knowledge from multiple locations” (TallBear, 2014, p. 176). Instead of striving for objectivity in the form of “point-of-viewlessness”--which

in practice is easily biased towards the point of view of the deciding actor–researchers should incorporate the perspectives of everyone they plan to involve in their research, and everyone their research is intended to serve. Tallbear continues that "the views from such lives can produce empirically more accurate and theoretically richer explanations than conventional research that treats the views from some lives and not others as bias" (2014, p. 176). Conventional research methods treat the researcher as an objective authority, so that their viewpoint is sometimes the only one not treated as biased.

Crucially, the onus of informed consent should be on researchers and physicians to provide information in a way that is designed for participants, instead of making it the responsibility of the participants to understand information not designed for their consumption and meet criteria that does not account for their individual backgrounds. Incorporating diverse viewpoints into research design will also ensure that "a wider variety of people access a fairer share of the benefits of scientific knowledge production" instead of current research vaguely intended for "the good of all" that falls short of that goal and only benefits those whose viewpoints were involved in its design (TallBear 2014, p. 177).

Research Question and Methods

How is the predominant definition of informed consent in experimental treatment biased towards Western colonial cultural understandings, and how can the infrastructure around its implementation be designed in a way that mitigates bias that favors dominant social groups?

I will try to answer this question using a feminist STS framework, in order to look at ideas of bias, objectivity, and stereotyping. Most of my research will fall into two categories: patient perspectives and provider perspectives. On the patient side, I will conduct a literature review of case studies, patient surveys, and published perspectives of diverse patient participants in medical research. I will focus on both patient outcomes and patient experiences, the latter

involving aspects such as comfort, ease of communication, and provider clarity. I will also incorporate statistical analyses of outcomes for minority patients compared to their systemically privileged counterparts.

On the provider side, I will focus on the criteria involved in organizing experimental research, from the perspectives of those in charge of making both ethical and organizational decisions. I will pay attention to specific efforts to include underrepresented patient populations, and make note of factors that may function as barriers to participation, intentionally or otherwise, particularly for cases in which accessibility was established as an issue. Cases in which diversity and accessibility were successfully prioritized will also be taken into account.

In analyzing research from the scientists' perspective, I will also look into how cultural diversity among researchers influences scientific and ethical approaches. For example, Kim Tallbear's indigenous standpoint research, cited earlier, includes perspectives from several indigenous bioscientists who spoke about how their cultural values prompted experimental outlooks that differed from those of their peers (Tallbear, 2014).

Finally, I work in a research laboratory associated with UVA Health, and I have connections to several researchers, some of whom do clinical work. If they are willing to share some of their experiences, I will incorporate their thoughts on organizing clinical research, interacting with patients, and interacting with their clinical and academic peers.

Conclusion

When is it ethical to offer an experimental treatment in place of an established one? One of the most important factors in answering this question is informed consent. By nature of how legal and medical systems work, it usually comes down to someone–an individual or a group–to decide what information will be provided to participants, how that information will be communicated, and what criteria should be met to demonstrate sufficient understanding. The

educational, cultural, and social backgrounds of potential research participants affect how they receive and interpret the information given. A goal of objectivity often results in experimental design that is not actually objective, but biased towards the viewpoint of the designer, and in the modern United States, this viewpoint is most commonly a Western colonial one. This bias affects the opportunity of some social groups to participate and benefit from research and experimental treatments. Active efforts to account for diverse backgrounds and perspectives in the design of informed consent processes would help to close this gap and create a more equitable and ethical approach to experimental medicine.

References

Anon. 1949. “Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law.”

Anon. 2022. “Tuskegee Study - Timeline - CDC - NCHHSTP.” Retrieved November 25, 2022 (https://www.cdc.gov/tuskegee/timeline.htm).

Anon. n.d. “Cerebral Cavernous Malformation | National Institute of Neurological Disorders and Stroke.” Retrieved November 25, 2022 (https://www.ninds.nih.gov/health-information/disorders/cerebral-cavernous-malformation).

Awad, Issam A., and Sean P. Polster. 2019. “Cavernous Angiomas: Deconstructing a Neurosurgical Disease: JNSPG 75th Anniversary Invited Review Article.” *Journal of Neurosurgery* 131(1):1–13. doi: 10.3171/2019.3.JNS181724.

Butler, Broadus N. 1973. “Final Report of the Tuskegee Syphilis Study Ad Hoc Advisory Panel.” *U.S. Department of Health, Education, and Welfare.*

Choi, James J., Shougang Wang, Yao-Sheng Tung, Barclay Morrison, and Elisa E. Konofagou. 2010. “Molecules of Various Pharmacologically-Relevant Sizes Can Cross the Ultrasound-Induced Blood-Brain Barrier Opening in Vivo.” *Ultrasound in Medicine & Biology* 36(1):58–67. doi: 10.1016/j.ultrasmedbio.2009.08.006.

Freimuth, Vicki S., Sandra Crouse Quinn, Stephen B. Thomas, Galen Cole, Eric Zook, and Ted Duncan. 2001. “African Americans’ Views on Research and the Tuskegee Syphilis Study.” *Social Science & Medicine* 52(5):797–808. doi: 10.1016/S0277-9536(00)00178-7.

Ebede, Tobechi, and Art Papier. 2006. “Disparities in Dermatology Educational Resources.” *Journal of the American Academy of Dermatology* 55(4):687–90. doi:

10.1016/j.jaad.2005.10.068.

Harding, Sandra. 1991. *Whose Science? Whose Knowledge?: Thinking from Women's Lives*. Cornell University Press.

Li, Jia, Yang Zhao, Paul Coleman, Jinbiao Chen, Ka Ka Ting, Jaesung Peter Choi, Xiangjian Zheng, Mathew A. Vadas, and Jennifer R. Gamble. 2019. "Low Fluid Shear Stress Conditions Contribute to Activation of Cerebral Cavernous Malformation Signalling Pathways." *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* 1865(11):165519. doi: 10.1016/j.bbadis.2019.07.013.

Li, Jia, Yang Zhao, Choi Jaesung, Ka Ka Ting, Paul Coleman, Jinbiao Chen, Victoria C. Cogger, Li Wan, Zhongsong Shi, Thorleif Moller, Xiangjian Zheng, Mathew A. Vadas, and Jennifer R. Gamble. 2020. "Targeting MiR-27a/VE-Cadherin Interactions Rescues Cerebral Cavernous Malformations in Mice | PLOS Biology." Retrieved November 25, 2022 (https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3000734).

Macek Jilkova, Zuzana, Justyna Lisowska, Sandra Manet, Claude Verdier, Valerie Deplano, Christian Geindreau, Eva Faurobert, Corinne Albigès-Rizo, and Alain Duperray. 2014. "CCM Proteins Control Endothelial B1 Integrin Dependent Response to Shear Stress." *Biology Open* 3(12):1228–35. doi: 10.1242/bio.201410132.

Meador, Helen E., and Philip Zazove. 2005. "Health Care Interactions with Deaf Culture." *The Journal of the American Board of Family Practice* 18(3):218–22. doi: 10.3122/jabfm.18.3.218.

Pagenstecher, Axel, Sonja Stahl, Ulrich Sure, and Ute Felbor. 2009. "A Two-Hit Mechanism Causes Cerebral Cavernous Malformations: Complete Inactivation of CCM1, CCM2 or CCM3 in Affected Endothelial Cells." *Human Molecular Genetics* 18(5):911–18. doi:

10.1093/hmg/ddn420.

Ranadewa, D., J. Wu, V. A. Subramanianbalachandar, and R. L. Steward. 2021. “Variable Fluid Flow Regimes Alter Human Brain Microvascular Endothelial Cell-Cell Junctions and Cytoskeletal Structure.” *Cytoskeleton (Hoboken, N.J.)* 78(6):323–34. doi: 10.1002/cm.21687.

Skloot, Rebecca. 2010. *The Immortal Life of Henrietta Lacks*. Crown Publishers.

Suchman, Lucy. 2007. “Feminist STS and the Sciences of the Artificial.” P. 26 in *The Handbook of Science and Technology Studies*, edited by E. J. Hackett. MIT Press.

TallBear, Kim. 2014. “Indigenous Bioscientists Constitute Knowledge across Cultures of Expertise and Tradition : An Indigenous Standpoint Research Project.” Pp. 173–91 in. The Hugo Valentin Centre, Uppsala University.

Villarosa, Linda. 2018. “Why America’s Black Mothers and Babies Are in a Life-or-Death Crisis.” *The New York Times*, April 11.

Weindling, Paul. 2001. “The Origins of Informed Consent: The International Scientific Commission on Medical War Crimes, and the Nuremberg Code.” *Bulletin of the History of Medicine* 75(1):37–71.

Section	Requirements	Notes	S
Title page (10)	- Follows template		1
Intro (50)	- Clear problem definition - Useful background info - Closes with thesis statement	Immensely too long, and as such, somewhat redundant. Cut it down	4
Tech Topic (30)	- Describes current tech - Describes proposed solution		3

	- Compelling argument for usefulness and appropriateness of solution - Relationship to STS problem		
STS Topic (50)	- Discusses connection between human, social, and technical elements - Explains relationship between STS and technical component - Describes relevant / applied STS theories	Minor tweaks	4
Research Q & Methods (30)	- States research question - Justifies importance of research question - Describes how topic will be analyzed - Details how data will be gathered and analyzed	Interview & survey methods still a little underbaked See my notes for more details	2
Conclusion (10)	- Re-states problem - Explains how solution will impact society - States expected results	Minor tweaks	1
References (20)	- 20 sources - APA 6th edition + - Sources used well to support content and analysis	Frequent errors with un-initialed first names Other minor errors	1

Total score: 180/200