Volumetric Assessment of Pulmonary Artery Thrombus Burden
(Technical project)

The Analysis of Relevant Social Groups Dynamics:
Influences on the Development of AI/ML based Medical Device Regulations
(STS project)

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By
Yeongju Lee

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Technical Team Members: Rohey Colley, Nyota Patel

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. Luke Wilkins, Division of Vascular and Interventional Radiology

Introduction

Artificial intelligence (AI) and machine learning (ML) can potentially transform the scientific landscape, including many medical domains, by learning from vast data and improving performance. Over the past few decades, AI/ML software has been incorporated into integral components of medical devices, facilitating earlier disease detection, more precise diagnosis, and more targeted therapies. For instance, many studies have proved that AI/ML-based medical imaging devices can detect and analyze tumors on medical images accurately and effectively (Benjamens et al., 2020; Yuba & Iwasaki, 2022). Furthermore, some of these devices have been used in clinical settings to significantly improve treatment outcomes and mortality (Muehlematter et al., 2021; Tang, 2019). As AI/ML-based technologies continue to evolve, we can expect even more profound advancements in healthcare.

Despite the promises of AI/ML software as a medical device (SaMD), these advanced technologies bring new challenges. Developing accurate and effective AI/ML-based medical devices is still challenging due to the quantity and quality of datasets (Liu et al., 2022). AI/ML learns by analyzing training data and predicting based on new input data. When the dataset is vast, AI/ML algorithms may take longer to decide, which is impractical in fast-paced clinical settings. Sometimes, the diverse datasets required for training AI/ML algorithms are limited. When AI/ML algorithms train based on insufficient and biased data, they may produce inaccurate evaluations and recommendations, potentially harming patient safety. Therefore, more research is needed to develop precise and effective AI/ML-based medical devices.

AI/ML technologies also raise concerns about privacy issues, malpractice, and a lack of safety checks. The governmental agency can resolve these issues under adequate regulations. In the United States (US), the US Food and Drug Administration (FDA) regulates the safety and

effectiveness of medical devices. Similar to other medical devices, the FDA reviews novel and modified AI/ML-based SaMD through an appropriate premarket pathway based on the significance or risk posed to patients. However, with the emergence of continuous learning algorithm-based medical devices, the FDA recognizes that their traditional AI/ML-based SaMD regulatory paradigms do not sufficiently supervise AI/ML technologies (FDA, 2019). Thus, a new regulatory framework is needed to address the adaptability of these advanced technologies.

My thesis addresses the concerns associated with AI/ML-based SaMD through a technical and STS topic. In my technical project, I will discuss the development of advanced AI/ML-based SaMD to recognize complex patterns in medical imaging data and provide quantitative assessments to improve the treatment of cardiovascular disease. In my STS project, I will focus on the FDA and stakeholders' involvement in developing a new regulatory framework for AI/ML-based SaMD.

Technical Topic

A pulmonary embolism (PE) is the third most common cause of cardiovascular death among adults in the US (Bělohlávek et al., 2013; Rivera-Lebron et al., 2019). It occurs when a blood clot blocks blood flow in an artery that carries blood from the right side of the heart to the lungs. Most PEs originate as blood clots called thrombi in the veins of the lower extremities. The consequences of PE vary, ranging from asymptomatic to cardiovascular instability and death. Depending on the degree of blockage and its effects on blood circulation, a treatment for PE can be different. Blood thinners or anticoagulants are the most common treatment for low-risk PE. Those with massive and submissive PE may remove thrombi via catheter-directed thrombectomy or surgical intervention. Physicians conduct catheter-directed thrombectomy by inserting a catheter into a large vein and either delivering clot-dissolving medications (thrombolytics) or

physically removing the thrombus once the catheter is in place. This novel PE intervention allows for rapid relief of heart strain.

Despite the promising benefits, catheter-directed thrombectomy is associated with a risk of complication due to insufficient clinical endpoints. Healthcare providers determine the success of catheter-directed thrombectomy based on improvement in blood pressure and visualization of the thrombus burden in the pulmonary artery using computed tomography (CT) angiography. However, blood pressure can only be obtained at the end of postoperative intervention, restricting physicians' discretion in deciding the termination point for treatment. Additionally, the manual analysis of CT images is very time-consuming and prone to misdiagnosis. These inadequate clinical endpoints leave physicians without clear criteria for appropriately concluding thrombus removal procedures, potentially leading to complications such as bleeding in the pulmonary artery. According to a systematic review and meta-analysis of patients with high-risk PE, in-hospital mortality and major bleeding after catheter-directed thrombectomy were 8.7% and 5.4%, respectively (Chandra et al., 2022). Although these rates are substantially lower than other PE treatments, further improvement in the safety and efficacy of catheter-directed thrombectomy is necessary (Milioglou et al., 2023).

One potential sufficient endpoint is the volume of retrieved thrombus compared to the presenting thrombus burden. Such an endpoint can be obtained during catheter-directed thrombectomy using an automated volumetric analyzer of intraoperative CT images. To this day, radiologists and cardiologists do not use the automated method to measure the volume of the pulmonary artery thrombus on a CT image (Liu et al., 2022). Therefore, developing an efficient, automated-based volumetric analyzer is urgently demanded in diagnosing and treating PE.

With the booming growth of AI, especially the recent advancements in deep learning (DL), utilizing advanced DL-based methods for automated and effective medical image analysis has become possible. DL neural network is made of multiple layers of algorithms that recognize and extract features from the input data patterns in the image. Inputting a CT data set into this convoluted neural network allows the computer to automatically classify, detect, and segment an object in the image.

For our technical project, we plan to develop a computational framework in Python using a type of DL neural network called U-Net. We will design this computational framework to classify CT images with PE (classification), then localize (detection) and delineate the borders (segmentation) of thrombus burden in the CT scans. From this, we can quantify the volume of the thrombus burden by multiplying the sum of cross-sectional areas of the thrombus by the scale factor, which is the ratio of pixel dimensions to real-world measurements. Furthermore, statistical testing will be determined to validate the computational framework's accuracy and efficacy. One possible method to validate the precision and efficacy is conducting a comparative analysis of the thrombus burden output volume compared to the expected output.

Adopting more advanced AI algorithms can address the difficulty of segmenting PE on CT images and develop reliable AI-based volumetric analyzing software. With our technology, we can enhance the precision and efficacy of catheter-directed interventions, ultimately fostering improved PE patients' outcomes and transforming the paradigm of pulmonary embolism treatment.

STS Topic

In 1906, the FDA was established as a US federal consumer protection agency primarily overseeing food and drugs. However, as fraudulent medical devices began flooding the market,

the FDA's authority expanded to regulating medical devices to ensure their safety and effectiveness in 1938 (Commissioner, 2019). Throughout its history, the FDA has consistently adapted and refined its regulatory framework for medical devices to address emerging public health concerns stemming from advancing technologies.

AI/ML-based medical devices hold both promises and concerns in healthcare. These technologies can significantly enhance healthcare by offering more precise diagnoses and optimizing treatment processes based on the latest data. However, AI/ML-based technologies can harm public health through misdiagnosis, treatment errors, inadequate safety checks, algorithmic bias, and data security threats. In response to these issues, the FDA enforced the risk management regulatory paradigms to ensure the safety and effectiveness of AI/ML-based devices. Under this approach, the FDA granted marketing authorization only to AI/ML-based SaMD using "locked" algorithms that do not evolve or use new data to alter their performance (FDA, 2019). The manufacturers would modify these locked algorithms at intervals and submit another FDA premarket application to receive marketing authorization for the updated algorithms.

With the emergence of AI/ML-based SaMD that utilizes "adaptive" algorithms, the FDA faced a challenge in keeping pace with evolving devices (FDA, 2019). Unlike the locked algorithms-based software, continuously learning algorithms adapt and improve their performance over time with new data and information, providing a more accurate and effective AI decision-making process. However, the evolving nature of these devices complicated the transparency in AI decision-making processes. Therefore, adaptive AI/ML-based medical devices challenged the FDA to ensure their safety and effectiveness under the existing risk management regulatory approach. Recognizing the significant benefits of adaptive AI/MD-based SaMD, the

FDA proposed a TPLC regulatory approach to ensure these advanced technologies outweigh the associated risks. In addition to the proposal of the TPLC regulatory framework, the FDA also asked for stakeholder feedback through the public docket and workshop, generating hundreds of comments from a wide array of stakeholders. In direct response to the stakeholder feedback, the FDA developed a "Medical Device Action Plan" to align the new regulatory framework with public opinion (FDA, 2021).

To understand how the new regulations will address the potential issues related to AI/ML, examining how the FDA constructed the TPLC regulatory framework is essential. I will compare the traditional risk management regulatory framework to the TPLC regulatory framework. From there, I will identify how the FDA developed the new framework.

Also, I will utilize the social construction of technology (SCOT) framework in this STS project to explore stakeholders' contributions in shaping TPLC regulatory paradigms. SCOT provides insights into the developmental process of technology through an alternation of variation and selection (Pinch & Bijker, 1984, p. 441). I will identify and categorize the stakeholders by examining the public docket and conducting literature reviews. Subsequently, I will analyze the primary arguments within each group regarding the issues and resolutions associated with AI/ML-based SaMD. To further contextualize stakeholders' perspectives, I will connect stakeholders' interpretation of AI/ML-based SaMD to the FDA's "Medical Device Action Plan" (FDA, 2021). This examination will provide insights into the involvement of stakeholders in shaping the new regulatory framework (FDA, 2021). Through these analyses, we can better understand how the new regulatory approach can tackle the challenges of adaptative AI/ML-based SaMD.

Conclusion

The advancement of AI/ML-based SaMD brought a new set of medical and regulatory challenges that could harm public health. In response, our technical project addressed the medical challenge of image segmentation by developing an adaptive AI/ML-based SaMD to effectively segment blood clots within vessels and precisely quantify the volume of blood clots on CT images. This automated volumetric analyzer has the potential to enhance the precision and efficacy of catheter-directed thrombectomy, ultimately leading to improved patient outcomes and mortality rates. In parallel, my STS project examines the collaborative efforts of both the FDA and stakeholders in shaping the proposed regulatory paradigms for AI/ML-based SaMD to mitigate the concerns associated with AI/ML-based medical devices. The successful development of the AI/ML-based volumetric evaluator and the insights gained from the STS project on regulatory framework would significantly advance patient care and safety by effectively addressing the challenges posed by AI/ML technology in the medical field.

References

Bělohlávek, J., Dytrych, V., & Linhart, A. (2013). Pulmonary embolism, part I: Epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. *Experimental & Clinical Cardiology*, *18*(2), 129.

Benjamens, S., Dhunnoo, P., & Meskó, B. (2020). The state of artificial intelligence-based FDA-approved medical devices and algorithms: An online database. *Npj Digital Medicine*, *3*(1), Article 1. https://doi.org/10.1038/s41746-020-00324-0

Chandra, V. M., Khaja, M. S., Kryger, M. C., Sista, A. K., Wilkins, L. R., Angle, J. F., & Sharma, A. M. (2022). Mechanical aspiration thrombectomy for the treatment of pulmonary embolism: A systematic review and meta-analysis. *Vascular Medicine*, *27*(6), 574–584. https://doi.org/10.1177/1358863X221124681

Commissioner, O. of the. (2019). Medical Device & Radiological Health Regulations Come of Age. *FDA*. https://www.fda.gov/about-fda/histories-product-regulation/medical-device-radiological-health-regulations-come-age

Gerke, S., Babic, B., Evgeniou, T., & Cohen, I. G. (2020). The need for a system view to regulate artificial intelligence/machine learning-based software as medical device. *Npj Digital Medicine*, *3*(1), 53. https://doi.org/10.1038/s41746-020-0262-2

Liu, Z., Yuan, H., & Wang, H. (2022). CAM-Wnet: An effective solution for accurate pulmonary embolism segmentation. *Medical Physics*, *49*(8), 5294–5303. https://doi.org/10.1002/mp.15719

Milioglou, I., Farmakis, I., Wazirali, M., Ajluni, S., Khawaja, T., Chatuverdi, A., Giannakoulas, G., Shishehbor, M., & Li, J. (2023). Percutaneous thrombectomy in patients with intermediate- and high-risk pulmonary embolism and contraindications to thrombolytics:

A systematic review and meta-analysis. *Journal of Thrombosis and Thrombolysis*, *55*(2), 228–242. https://doi.org/10.1007/s11239-022-02750-1

Muehlematter, U. J., Daniore, P., & Vokinger, K. N. (2021). Approval of artificial intelligence and machine learning-based medical devices in the USA and Europe (2015–20): A comparative analysis. *The Lancet Digital Health*, *3*(3), e195–e203. https://doi.org/10.1016/S2589-7500(20)30292-2

Pinch, T. J., & Bijker, W. E. (1984). The Social Construction of Facts and Artefacts: Or How the Sociology of Science and the Sociology of Technology might Benefit Each Other. *Social Studies of Science*, *14*(3), 399–441. https://doi.org/10.1177/030631284014003004

Rivera-Lebron, B., McDaniel, M., Ahrar, K., Alrifai, A., Dudzinski, D. M., Fanola, C., Blais, D., Janicke, D., Melamed, R., Mohrien, K., Rozycki, E., Ross, C. B., Klein, A. J., Rali, P., Teman, N. R., Yarboro, L., Ichinose, E., Sharma, A. M., Bartos, J. A., … Channick, R. (2019). Diagnosis, Treatment and Follow Up of Acute Pulmonary Embolism: Consensus Practice from the PERT Consortium. *Clinical and Applied Thrombosis/Hemostasis*, *25*, 1076029619853037. https://doi.org/10.1177/1076029619853037

Tang, X. (2019). The role of artificial intelligence in medical imaging research. *BJR Open*, *2*(1), 20190031. https://doi.org/10.1259/bjro.20190031

United States Food & Drug Administration. (2019). Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD). https://www.fda.gov/media/122535/download

United States Food & Drug Administration. (2021). Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan. https://www.fda.gov/media/145022/download

Yuba, M., & Iwasaki, K. (2022). Systematic analysis of the test design and performance of AI/ML-based medical devices approved for triage/detection/diagnosis in the USA and Japan. *Scientific Reports*, *12*(1), Article 1. https://doi.org/10.1038/s41598-022-21426-7