Society for Heart Attack Prevention and Eradication
SHAPE
Mission: Eradicating Heart Attacks

Susan Monarez, Ph.D.
ARPA-H Deputy Director

Thursday, December 21, 2023

Sent via Email and Certified Mail

Dear Dr. Monarez,

Thank you for your letter dated 12/06/2023 in response to our abstract proposal titled "Developing an Artificial Intelligence System to Forecast Near-Term Sudden Cardiac Death and Adverse Cardiovascular Events in Asymptomatic Individuals with no History of Cardiovascular Disease (CVD)".

We would like to congratulate your team at ARPA-H for launching a series of highly innovative healthcare projects and wish you successful outcomes in your groundbreaking endeavors.

Based on the following, we would very much appreciate a second chance to present our proposal. We are making this request on behalf of the most distinguished physician scientists, clinicians, and researchers in the field of cardiovascular medicine who have spent decades of their life treating CVD patients and researching new solutions. They have supported this proposal because of the impact that such an AI-enabled solution can have on saving millions of lives worldwide.

Here are the comments we have collected in response to the points in your letter, and we would be grateful for an opportunity to present them in a more methodical way:

• The proposed work does not sufficiently bridge the gap between fundamental discovery and application for the field. It is unclear how the 1000 cases studied and modeled with AI algorithms will result in a toolkit with clear predictive advantages.

Over the past decades, the field of cardiology has developed numerous life-saving therapies and interventions. However, because the current standard of care cannot accurately detect individuals at an immediate risk for a fatal event, cardiologists are unable to deliver the needed emergency intervention to those who need it the most. People are needlessly dying as a result. Our proposal is to train the AI to identify those in gravest danger based on the 1,000+ unique cases who experienced a fatal event shortly after a comprehensive exam with imaging data and banked blood sample. We believe this training will provide the first AI of its kind for "pattern recognition" of such high-risk, yet asymptomatic, individuals. Such a patten recognition approach has been validated in numerous other medical AI projects, and there is no reason to believe that it would not work just as well for our proposed project.

• The proposed project does not include sufficient supporting information to suggest the key challenges are well understood to address prediction of adverse cardiovascular events. There are no validation tests provided or identification of the challenges in modeling complex cardiovascular symptoms.

As stated in our proposal, there are 14 major CVD cohorts worldwide, 4 of which will serve as testing and validation sets, while the rest will be used for training and calibration of the AI. The investigators supporting this proposal are world-renowned leaders in CVD studies and are well aware of the challenges involved in addressing the prediction of adverse cardiovascular events. These investigators are currently directing the largest CVD cohorts in the US, Europe and Asia, as listed in the proposal. Modeling complex cardiovascular symptoms, signs, and paraclinical findings can be achieved using comprehensive data from such longitudinal cohorts.

• Based on the information presented in the proposed project, it is unclear how the 20% forecasting percentage is obtained as compared to the state of the art. It is also unclear how the HeartLung.AI SaMD compares to prediction of adverse cardiovascular events in asymptomatic people. No compelling

argument is given that the training data contains the necessary information to provide a robust platform for predicting near term cardiovascular events.

The status quo has a median risk forecast of 2.5% and an average of 5.4% risk over **10 years**, whereas our proposed AI aims to achieve an average risk of 20% over **1 year (approximately 40 times more accurate)**. The HeartLung AI that received FDA Breakthrough status is an example of a feasibility study based only on one cohort (MESA, which has only 63 events in one year). It does not include heart attack and stroke prediction, which are the key elements of our ARPA-H proposal. Nonetheless, the HeartLung AI received an FDA Breakthrough designation because of its lifesaving potential for opportunistic detection of asymptomatic heart failure patients who are at risk of a sudden cardiac death. We anticipate achieving a similar FDA Breakthrough status once the deep learning technique is applied to the entire 1,000+ cases of events within 1 year that include cardiac imaging databases in addition to clinical and laboratory data. As stated in the proposal, no single CVD cohort can address this challenge. By inviting all CVD cohorts worldwide, this initiative will have the maximum chance to train the AI. It is noteworthy that all inventors and scientific leaders of HeartLung.AI have taken part in this proposal.

• As described, the project seeks to apply AI/ML methods to a novel dataset to extract predictive value, which in itself cannot be considered a major conceptual or technical leap. A similar effort has already been conducted with HeartLung.AI's AutoChamber™, which can detect high risk patients for heart failure and stroke and has received Breakthrough status from the FDA. There is no explanation of what entirely new technical developments will be necessary for the work proposed here.

The proposed deep learning AI technique by itself will not be a technical leap, however the resulting predictive power to detect very high risk (yet asymptomatic) individuals who are vulnerable to a fatal CVD event within 1 year will be **a major leap forward in cardiology**. The excitement generated by our proposal among leading physician investigators stems from the fact that predicting who will have a CVD event in the near future can create a paradigm shift in cardiovascular medicine and will allow for evaluating new treatment strategies. It will bring cardiology up to the level of diagnostic precision that currently exists in oncology, where detecting cancerous tumors undoubtedly predicts poor outcomes. By contrast, in today's cardiology, some patients with high cholesterol or high calcium score can live more than 80 years, which speaks for the poor predictive power of such traditional risk markers. With CVD accounting for over 35% of adult deaths in US population, such a breakthrough AI can have a major public health impact and can save millions of lives and billions of dollars lost to **unpredicted** sudden CVD events. Our current era in CVD prediction is analogous to the 19th century era of living through hurricanes without weather alerts and satellite insights. We aim to overhaul the status quo with our ARPA-H proposed AI-enabled solution.

On behalf of our distinguished colleagues identified below, we would be extremely grateful for a second look at our proposal and its potential to save millions of lives.

Executive Director: Morteza Naghavi, M.D.; Founder of HeartLung.AI and Executive Director of the SHAPE Task Force

Chairwoman: JoAnn Zawitoski, J.D.; Maritime Attorney and SHAPE Volunteer

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