TITLE (SHORT, 200 CHARACTERS MAX.):

THE INFLUENCE OF MITOCHONDRIAL GENETICS ON SURVIVAL AFTER CARDIAC ARREST

MAIN HYPOTHESES TESTED (2 MAX)

We hypothesize that patients with mitochondrial DNA (mtDNA) haplogroup H will have increased survival following cardiac arrest (CA) as compared to other haplogroups.

Haplogroup H is a late evolutionary haplogroup possibly conveying an advantage in survival in colder climates through lower coupling efficiency of the respiratory chain, resulting in more heat production. Haplogroups H have been shown to be a strong predictor of positive outcome after sepsis, and have reduced likelihood of cardiovascular disease. The mechanisms whereby haplogroups affect susceptibility to disease are not fully understood, but mostly focus around mitochondrial reactive oxygen species (ROS) production.

SINGLE CENTER [ ] , MULTICENTER [X] PICO

Patients: All patients included in the primary TTM2 trail will be eligible.

Prognostic factor: Prognostic relevance of mtDNA haplogroups

Comparison: mtDNA haplogroup H versus all other haplogroups

Outcome: Primary outcome: Mortality 180 days post-CA. Secondary Outcome: A) Glasgow Outcome Scale-extended (GOS-E) at 180 days

DATA NEEDED FOR THE ANALYSIS (SPECIFY VARIABLES AND MOTIVATE ANY PROPOSED ADDITIONS TO THE ECRF)

No additions to the ECRF required. Samples should be collected as early as possible, preferably at the acute time point (0-2 hours after cardiac arrest), for inclusion of patients with early mortality. Analysis can however be made with samples from any time point if there is a limitation in availability of early samples. Any vials for collection of blood samples can be used. Whole blood or any pellet, including platelet only, from a centrifugation step where plasma is recovered or any cell-containing supernatant. The sample should be stored at -80°C until analysis.

LOGISTICS – HOW WILL ADDITIONAL DATA BE GATHERED?

Samples will initially be stored in the common biobank of TTM2 and will be shipped in a single common batch for mtDNA analysis at the Center for Mitochondrial and Epigenomic Medicine (CMEM) at the Children's Hospital of Philadelphia, USA. No additional clinical data than already included in the main CRF will be gathered.

BRIEF STATISTICAL ANALYSIS PLAN AND SAMPLE SIZE ESTIMATE

The TTM2 trial is powered for an inclusion of 1036 patients (1200 prior to loss to follow-up). The study is powered for an additional estimated drop out of 10%, therefore we have completed the power calculations below based on 936 patients in our sub-study.

The proportion of the haplogroup H in European populations, and populations of European descent, is reported to be 44%. The independent variable in the TTM2 trial is hypothermia, but in our sub-study the independent variable is haplogroup H or other haplogroup. Expecting survival of 60% in the haplogroup H group, and survival of 50% in the combined group of the other, we have 87 % power to demonstrate a difference in mortality of 20% with alpha 0.05. For the primary outcome, survival at 180 days post CA, a multiple logistic regression analysis (due the dichotomous outcome survival/non-survival) will be performed, controlling for the treatment arm in TTM2.

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FUNDING (IF APPLICBABLE)

Coverage of cost for initiation of the project is secured from existing funding of the research group. The mutli-national consortium of investigators will conduct the above described study as part of a larger programmatic investigation on mitochondrial function and its influence on cardiac arrest. Funding for this larger project, including the mtDNA analysis and associated costs, is currently under review as part of an NIH RO1 application, where professor Hans Friberg will be included as co-investigator. However, the investigators have exploratory funds available to complete this project in its entirety, if these grants are not successful. Together the investigators currently have approximately 10 million USD in funding.

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