



HESI Cardiac Safety U01 FD006676-01 Request for Proposals 2020

Background

HESI is a nonprofit organization based in Washington, DC. HESI's mission is to collaboratively identify and help to resolve global health and environmental challenges through the engagement of scientists from academia, government, industry, clinical practice, research institutes, and NGOs. The Cardiac Safety Committee is one of the groups within HESI that focuses to improve public health by reducing unanticipated cardiovascular-related adverse effects from drugs or chemicals and develop innovative approaches to support early detection and prediction as well as improved understanding of cardiovascular toxicology and pathobiology. Learn more about HESI: <https://hesiglobal.org/>

In 2019, the HESI Cardiac Safety Committee was awarded a U01 grant from the US FDA on the "Evaluation of Integrated Human-Relevant Approaches to Identify Drug Induced Cardiovascular Liabilities." This grant will support HESI in funding and managing novel, *in vitro* experimental studies to develop targeted mechanistic data to inform drug safety assessment for key cardiac "failure modes." Part of this grant includes an open call for additional pilot studies to address evaluation of the cardiac failure modes.

Scope and Budget

HESI is seeking proposals for a 12-month subaward under this grant for studies involving human-relevant, mechanism-based assays evaluating cardiac safety liabilities.

HESI Cardiac Safety Committee members identified six main failure modes, CV liabilities contributing to drug attrition, as follows:

- i. Vasoactivity changes (blood pressure/heart rate)
- ii. Inotropy changes (contractility/ejection fraction)
- iii. Action potential changes (electrophysiology)
- iv. Cardiomyocyte/Myocardial injury (myocardial necrosis/hypertrophy)
- v. Valvular injury/proliferation (regurgitant flow)
- vi. Endothelial injury/coagulation (hemorrhage, thrombosis)

Defining human-relevant modeling systems for these modes of failure is the first step towards improving the current paradigm to predict cardiotoxicities. The ideal assay systems to predict failure

modes will require high confidence in the biology and in our capabilities for translation and extrapolation to human clinic experience.

Proposals will be considered for all of the failure modes with preference for (i.) vasoactivity changes and (vi.) endothelial injury/coagulation, which represent current gaps.

Proposals should highlight the following with regards to the assay or platform to be tested:

- Biological requirements that offer insights into maturity of cardiomyocytes and cell responses, endothelial cell and vascular systems, long-term cell and tissue viability;
- Technical attributes of platforms that are commercially sustainable and scalable; and
- Analytical attributes allowing for temporal stability, reproducibility and specificity and sensitivity.

Proposals should include the following sections (and page limits noted):

- Cover Sheet (1 page)
 - Project Title
 - PI Name, Contact Information
 - Organization/Institute Information
 - Total Budget Requested (cannot exceed \$50,000 USD)
- Abstract and lay person summary (2 pages)
 - The abstract should summarize the research project and describe what issue(s) the study addresses, the study's specific aims, relevant literature or prior research, how the study will be conducted and evaluated, and why the work will aid in the characterization or prediction of at least one of the cardiac failure modes.
 - The lay person summary should be included that is written in such a way that a non-technical/non-scientist will understand.
- Research Plan (4 pages)
 - Title
 - Background and Significance
 - Specific Aims
 - Research Design and Methods
 - Estimated Project Timeline
 - Research Personnel
- Budget and Justification (2 pages, template provided upon invitation to submit full proposal)
- Biographical Information (1 page per person)
 - Use NIH template, Biographical Sketch Format Page (non-fellowship), available here: <https://grants.nih.gov/grants/forms/biosketch.htm>
- Selected Publication List (1 page)
- Documents should be submitted as either .pdf or .doc/docx file formats.



Up to 3 awards will be available through this program. Awards will be made for 12 months and available funding up to \$50,000 USD per award. If indirect costs are included in the proposal, they must fit within the \$50,000 USD budget. Budget requests must be submitted in RR 424 format (template to be provided) as well as justification for all budgeted items. If awarded, a contract will be established between HESI and the awardee further specifying conditions.

Letter of Intent

Subawards for Consortium Led Evaluation of Integrated Human-Relevant Approaches to Identify Drug Induced Cardiovascular Liabilities, 1 U01 FD006676-01, will be required to first submit a Letter of Intent (LOI). A Selection Team will invite applicants to submit a full proposal and only those proposals will be considered for an award.

The letter of intent is designed to provide a general overview of the proposed research study with sufficient detail to allow for the evaluation of the scientific merit and feasibility of the study. Two pages (letter of intent form and research abstract) are required for submission and the remaining pages (biographical sketch and publication list, limit 4 pages) are optional. Letters of Intent are **due 8 June 2020**.

Eligibility

Any individual(s) with the skills, knowledge, and resources needed to carry out the proposed research as the Principal Investigator(s) (PI(s)) is invited to submit a Letter of Intent. Applicants may submit only one Letter of Intent. Principal investigator(s) must hold an advanced degree, M.D., Ph.D., D.V.M., or equivalent. All candidates must have an accredited faculty, medical institution, or other research institute appointment and have the ability to conduct independent research with publications in established peer-reviewed medical and scientific journals. Awardees must be based in the United States of America.

Important Dates

June 8 – LOIs due

July 6 – Invitations sent for full submission

August 3 – Full proposal submissions due

September 3 – Awardees notified, award period begins

Selection Process

Applications are reviewed in detail by the HESI U01 Advisory Team and will be discussed as a group to determine funding priority based on the following criteria:

1. Significance & Scientific Merit

- Does the study advance our ability to understand the mechanism of one or more of the failure modes?
- Does the study develop models (in vivo, in vitro, in silico) of cardiotoxicity?
- Does the research support the development and understanding of mechanisms of cardiotoxicity

2. Approach & Feasibility

- Are the conceptual framework, design, methods and analyses adequately developed, well integrated and appropriate to the aims of the project?
- Are potential risks and problems addressed and alternative methods recommended?
- Will the study be completed in the proposed timeframe and within the proposed budget?

3. Innovation

- Are the aims original and innovative?
- Does the project employ novel concepts, approaches and methods?

4. Investigator Qualification & Environment

- Does the investigator have the expertise and commitment to carry out the proposed work?
- Are all the required elements such as laboratory, technology, equipment, reagents, and human or animal subjects available for the project?