

Cardiac Safety



Our Mission

The committee's mission is 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.

Chairs

Public Chairs

Dr. Norman Stockbridge (US Food and Drug Administration)
 Dr. Brian Berridge (until Mar. 2022, National Toxicology Program)
 Dr. Jean-Pierre Valentin (as of April 2022, UCB Bio Pharma)

Steering Team Members

Dr. Norman Stockbridge (US Food and Drug Administration)
 Dr. Jean-Pierre Valentin (UCB Bio Pharma)
 Dr. Brian Berridge (NTP)
 Dr. Ksenia Blinova (US Food and Drug Administration)
 Dr. Marjory Brooks (Cornell University)
 Dr. Sandy Eldridge (National Cancer Institute)
 Dr. Gary Gintant (AbbVie, Retired)
 Dr. Eugene Herman (National Institutes of Health)
 Dr. John Koerner (US Food and Drug Administration, retired)
 Dr. Michael Pugsley (CytoKinetics)
 Dr. Jose Vicente Ruiz (US Food and Drug Administration)
 Dr. Frank Sellke (Lifespan Heart Center)
 Dr. Eric Schultze (Eli Lilly and Company)
 Dr. Godfrey Smith (University of Glasgow/Clyde Biosciences, Ltd.)

HESI Staff

Ms. Jennifer B. Pierson, MPH
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Webpage

<https://hesiglobal.org/cardiac-safety/>

2022 Committee Highlights



Participating Organizations

12 government/regulatory agencies, 33 private industry, 27 academic/research institutes



Publications

1 publication, 4 in progress



Collaborations

5 external

- University of Surrey and Imperial College London
- Safety Pharmacology Society
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
- CiPA Steering Team
- US Food and Drug Administration



Scientific Meetings and Trainings

1 training course, 2 meetings

- ICH E14/S7B Q&A Training (virtual; 300+ attendees)
- Integrative Strategies Workgroup (in person at SPS; 4 attendees)
- Cardiac Safety Annual Meeting (virtual; 100 attendees)



Outreach

3 posters, 3 oral presentations

Safety Pharmacology Society Annual Meeting

- Poster: Assessment of chronic drug treatment-induced cardiotoxicity.
- Poster: Biomarker-Based *In Vitro* Evaluation of Chronic Drug Treatment-Induced Cardiotoxicity.
- Poster: JTpeak Assessment In Ambulatory Dog And Monkey.

Cardiac Safety Early Career Seminar Award Series



- *Computational Cardiotoxicology: Building an AI-assisted pipeline.* Dr. Shagun Krishna (NTP-NIEHS).
- *Human Atrial Cardiac Microtissues for Chamber-Specific Arrhythmic Risk Assessment.* Dr. Arvin Soepriatna (Brown University).
- *Understanding hemodynamic changes: Use of signal processing tools to advance preclinical blood pressure analysis.* Dr. Julia Hotek (Merck).



Geographic Representation

Australia, Belgium, Canada, China, Germany, Japan, Netherlands, South Korea, Switzerland, France, Sweden, South Korea, United Kingdom, United States

Working Groups

- **Stem Cell Working Group.** This group is working to understand and characterize use of stem cell-derived cardiomyocytes in cardiac safety assessments. A study exploring *in vitro* assay ability to detect chronic cardiotoxicity is ongoing. The data will be used to build confidence in assays as well as determine the utility of these mechanistic-based assays for cardiac liabilities.
- **Pro-Arrhythmia Working Group.** This working group is dedicated to investigating mechanisms of proarrhythmic risk. They continue to collaborate with the CiPA Initiative and ICH, and recently convened a training on the new E14/S7B Q&A Training Materials. A new subteam is developing a final draft manuscript on conduction/sodium channel challenges in drug safety.
-  **Integrative Strategies Working Group.** This working group has examined the sensitivity within a preclinical species to assess the function of contractility. They continue their partnership with U. of Surrey and Imperial College London on a mathematical model to predict blood pressure changes. A new subteam formed to explore blood pressure measurements. They are planning an interlaboratory study to assess changes in BP in the canine *in vivo* cardiovascular model using telemetry recording methods to detect positive and negative effects as a result of drug exposures for compounds with known BP effects in the clinic. A pilot study will be conducted in Fall 2022 to assess dosing of the compounds.
-  **Cardiac Biomarkers Working Group.** This working group is dedicated to investigating preclinical cardiac biomarkers of hypercoagulability induced, in both normal and thrombotic states. Two pilot studies have been completed this year using xenobiotics to induce a procoagulant state and confirm measurements of biomarkers of interest. The larger study design will be finalized in Fall 2022 with the study being conducted in Q1 2023.
- **Cardiac Compound Tool Database Subteam.** This subteam is developing a publicly accessible database, which will provide a structured resource for use when identifying cardiac compounds appropriate in a planned committee study. Delivery of this is anticipated by the mid-2023.

Areas of Focus for 2023

- Alignment to mechanistic, human relevant approaches.
- Generate de novo data through several of the Working Groups' planned studies.
- Commence the second phase of the CCT Database to include *in vitro* data.
- Convene a virtual Committee meeting to review the portfolio.
- Scoping new project and workshop opportunities.

Strategic Impact Areas

Enhanced efficiency and accuracy in safety assessment practice

The HESI Cardiac Safety Committee works to increase efficiency and accuracy of the current drug testing paradigm as well as impacting the 3Rs. They do this through collaborative work to test and validate new technology platforms and assays that could allow for improved decision-making at earlier phases in drug development. The work has a direct impact on the 3Rs (replacing, reducing and refining use of animals in CV research) and informing regulatory guidelines.



Catalysis of new science

The Cardiac Safety is actively generating de novo datasets and contributing research to new technologies like induced pluripotent stem cells and new assay platforms.



Enhancement of the societal knowledge base on human biological processes of relevance for protecting human health

From novel data generation to capability development to database creation, the work of the Cardiac Safety Committee has a lasting impact on CV safety assessments.



Increasing the Audiences for Collaborative Safety Science

The FDA U01 grant allowed an opportunity to identify and expand partnerships with subawardee labs that were outside of the Cardiac Safety Committee in the field of Celiac disease, as well as continuing outreach globally to disseminate outputs of the committee and, in particular, disseminating the use and applications of the COMPARE database.



Development of scientists skilled in translational science

The Cardiac Safety Committee launched the Early Career Award Webinar Series to identify and highlight new scientists in the field. They also partnered with SPS to provide a new training opportunity around the ICH E14/S7B Q&As.



2022 Awards, Grants, and Recognition

- The HESI Cardiac Safety Committee was awarded two publicly funded grants in 2019, which were both renewed and granted no-cost extensions in 2022. HESI completed the third year of the *U01: Consortium Led Evaluation of Integrated Human-Relevant Approaches to Identify Drug Induced Cardiovascular Liabilities*. This grant is a multi-year grant that will support HESI in procuring and managing novel, invitro experimental studies to develop targeted mechanistic data to inform drug safety assessment for key cardiac 'failure modes.' An Advisory Team of experts is helping to guide this project and the 11 subawarded projects under the grant. Initial results from the pilot studies will be shared in upcoming virtual meetings.
- The second grant, a Broad Agency Announcement grant from the US FDA focuses on assessing variability and reproducibility of manual and automated patch clamp platforms. HESI established subcontracts with 8 laboratories who are working to complete 4 manual and 4 automated patch clamp studies. Results will provide objective data and confidence in the risk assessment approach proposed as part of CiPA, including further testing and validation of the *in silico* model.

Publications

Published

Valentin et al. 2022. The Challenges of Predicting Drug-Induced QTc Prolongation in Humans. *Toxicological Sciences*. <https://doi.org/10.1093/toxsci/kfac013>

In Progress

Chaudhary et al. An Overview of Drug-Induced Sodium Channel Blockade and Changes in Cardiac Conduction: Implications for Drug Safety.

Miracourt et al. Incidence of Spontaneous Arrhythmias in Telemetered Beagle Dogs, Gottingen Minipigs and Cynomolgus monkeys: A HESI Consortium Retrospective Analysis.

Building a Compound Tool Database in Support of Improving our Understanding of Cardiovascular Toxicology.

Pierson et al. A study of chronic drug actions in iPSC-derived cardiomyocytes assessed across multiple biomarkers and platforms.



Participating Organizations

Government/Regulatory Agencies

European Medicines Agency
 Health Canada
 Medicines & Healthcare Products,
 Regulatory Agency (MHRA)
 National Institute of Environmental Health Sciences
 (NIEHS), National Toxicology Program (NTP)
 National Institute of Health Sciences (Japan)
 National Institutes of Health (NIH)
 National Institutes of Health (NIH), National Cancer
 Institute (NCI)
 Pharmaceutical and Medical Devices Agency (Japan)
 Pharmacological Evaluation Institute of Japan
 US Environmental Protection Agency (EPA)
 US Food and Drug Administration (FDA)
 US Food and Drug Administration (FDA), National
 Center for Toxicological Research (NCTR)

Academic/Research Institutes

Bristol University
 Brown University
 Cornell University
 Fraunhofer Institute
 George Washington University
 Jagiellonian University Medical College
 Johns Hopkins University
 Karolinska Institute
 Michigan State University
 Natural and Medical Sciences Institute,
 University of Tübingen
 Northwestern University
 Ohio State University
 Scintillon Institute
 Stanford Cardiovascular Institute
 SUNY Buffalo
 Toho University Medical School
 University at Buffalo
 University of California, Davis
 University of California, Irvine, School of Medicine
 University of Glasgow
 University of Hamburg
 University of Louisville
 University of Michigan
 University of Nottingham
 University of Tokyo
 University of Washington
 Victor Chang Cardiac Research Institute

Private Industry

AbbVie
 ACEA Biosciences, Inc.
 Amgen
 AstraZeneca
 Axol Bioscience
 Bristol-Myers Squibb
 B'SYS GmbH
 Charles River Laboratories
 CiToxLab
 Curi Bio
 Cytokinetics
 Eli Lilly and Company
 ERT
 Fujifilm Cellular Dynamics, Inc.
 Genentech/Roche
 GSK
 innoVitro GmbH
 IPSyte Biosciences
 Janssen Pharmaceuticals
 Lapcorb Drug Development
 Merck & Co., Inc.
 MyoKardia
 Nanion Technologies
 NEXEL, Co.
 Novoheart
 Pfizer, Inc.
 Sanofi
 StemBioSys
 Stemina Biomarker Discovery
 Takeda Pharmaceutical Company, Ltd.
 TARA Biosystems
 UCB Biopharma SPRL