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 to 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 (National Institute of Environmental Health Sciences, National Toxicology Program)

Steering Team Members

Dr. Eugene Herman (National Institutes of Health)
Dr. Gary Gintant (AbbVie)
Dr. Eric Schultze (Eli Lilly and Company)
Dr. Jean-Pierre Valentin (UCB-Biopharma)
Dr. Michael Pugsley (Cytokinetics)
Dr. John Koerner (US Food and Drug Administration)
Dr. Marjory Brooks (Cornell University)
Dr. Frank Sellke (Lifespan Heart Center)

HESI Staff

Ms. Jennifer Pierson, MPH (jpierson@hesiglobal.org)
Dr. E'Lissa Flores (eflores@hesiglobal.org)

Webpage

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

2021 Committee Highlights

Participating Organizations

12 government/regulatory agencies, **27** academic/research institutes, **32** industry, and **1** clinical

Publications

1 published, **1** submitted, and **4** in progress

Scientific Meetings and Trainings

1 meeting

- Cardiac Safety Annual Meeting (February 2021, virtual; ~200 attendees)

Outreach

The committee has launched a newly designed Cardiac Safety newsletter to report on committee news, outreach opportunities, new publications, and more. The newsletter will be made available on the HESI Cardiac Safety Committee webpage.

Collaborations

3 external

- University of Surrey and Imperial College London
- Safety Pharmacology Society
- CiPA Steering Team

Geographic Representation

Australia, Belgium, Canada, France, Germany, Japan, Netherlands, Poland, South Korea, Sweden, Switzerland, United Kingdom, and 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 publication that included best practices for use of stem cell cardiomyocytes in cardiac safety assessments was published. A new group is planning a study to explore *in vitro* assay ability to detect cardiotoxicity.
- **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 published its anticipated high-throughput systems (HTS) ion channel work. A new subteam is scoping a conduction/sodium channel paper to discuss the history and challenges surrounding this topic.
- **Integrative Strategies Working Group.** This working group is currently developing a study to assess changes in blood pressure in the canine *in vivo* cardiovascular model using standard telemetry recording methods. The study will evaluate drugs that pharmacologically increase and decrease blood pressure by various mechanisms as a result of drug exposure for several compounds with known blood pressure effects in the clinic. The group has also continued their partnership with the University of Surrey and Imperial College London on a mathematical model to predict blood pressure changes. The Implanted Telemetry Subteam explored the impact of telemetry lead placement in toxicology studies (a collaboration with the Pro-Arrhythmia Working Group).

- **Cardiac Biomarkers Working Group.** This working group is dedicated to investigating preclinical cardiac biomarkers of hypercoagulability induced under a thrombotic state, in both normal and diseased states. A new study is in the planning stages using xenobiotics to induce procoagulant state and confirm measurements of biomarkers of interest. Several pilot studies have been performed using tissue factor and tranexamic acid prepare for the definitive study planned for 2022.
- **Cardiac Compound Tool (CCT) Database Subteam.** The Cardiac Safety Steering Team established this new subteam in early 2020 to develop and provide a structured resource for use when identifying compounds appropriate in a planned committee study. Delivery of this publicly accessible database is anticipated in early 2022.
- **COVID-19 Subteam.** This subteam was organized in May 2020 in response to the ongoing pandemic. Subteam members identified that emerging drug treatments for the novel coronavirus may have cardiotoxic effects. The group is exploring how to gather cardiac safety data on five emerging therapies, whether prospective or retrospective, and develop a publication.
- **Educational Outreach initiative.** This initiative was established to raise awareness of Cardiac Safety career paths and training for the next generation of scientists, as well as provide awards to help postdocs or early career scientists gain experience in the field and build collaboration networks. These activities will hopefully also increase academic sector committee participation. The committee's first activity will be to support an "Early Career Seminar Award Series" targeted to postdocs.

Areas of Focus for 2022

- 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.
- Launch new educational outreach initiatives to help train the next generation of scientists and recruit more academic members.

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 its impact on the 3Rs. They do this through collaborative work to test and validate new technologies that could allow for improved decision-making at earlier phases in drug development.

Catalysis of New Science

The committee is working to test and validate several new assay systems through the Stem Cell Working Group and FDA grants.

Enhancement of the Societal Knowledge Base on Human Biological Processes of Relevance for Protecting Human Health

The committee continues to share data through manuscripts, data repositories, and databases for the greater scientific community to benefit from the body of knowledge generated through the studies.

Development of Scientists Skilled in Translational Science

The committee aims to increase awareness about careers in the Cardiac Safety field, with the target audience of graduate students, postdocs, and early career scientists. The first activity that was launched is the Early Career Seminar Award Series. This award is an opportunity for postdocs to share their research, learn from, and network with experts in the toxicology and safety pharmacology fields from academia, regulatory agencies, and pharmaceutical companies. The committee plans to launch more initiatives over the next several years.

2021 Awards, Grants, and Recognition

- The HESI Cardiac Safety Committee was awarded two publicly funded grants in 2019, which were both renewed in 2020 and 2021. HESI completed the first two years of the U01: Consortium-Led Evaluation of Integrated Human-Relevant Approaches to Identify Drug-Induced Cardiovascular Liabilities. This grant is a multi-year grant to inform drug safety assessment for key cardiac "failure modes." In the first two years, an Advisory Team has overseen selection of a compound tool set and eight pilot studies.
- The second grant, a Broad Agency Announcement from the US FDA, focuses on assessing variability and reproducibility of manual and automated patch clamp platforms. HESI established subcontracts with six laboratories who are working to complete three manual and three 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.

- The committee was highlighted in the 2021 US FDA report titled "Advancing New Alternative Methodologies at FDA" which described progress the FDA has made in integrating alternative approaches into regulatory programs.

Publications

Published

Pugsley MK, Brooks MB, Fishman CE, Katavolos P, Chiang AY, Parish ST, Schultze AE, & Pierson JB (2021) Use of the ZDF rat to model dietary fat induced hypercoagulability is limited by progressive and fatal nephropathy. *Journal of Pharmacological and Toxicological Methods*. doi: 10.1016/j.vascn.2020.106933.

Submitted

Valentin et al. Why is it so difficult to predict drug effects on repolarization in humans? Submitted.

In Progress

Chaudhary et al. Understanding conduction issues in context of drug development. In preparation.

Miracourt et al. Incidence of spontaneous arrhythmias in telemetered beagle dogs, gottingen minipigs and cynomolgus monkeys: a HESI consortium retrospective analysis. In preparation.

Pierson et al. Building a compound tool database in support of improving our understanding of cardiovascular toxicology. In preparation.

Pugsley et al. Nonclinical and clinical concordance and cardiac risk assessment of four emerging drug treatments for COVID-19. In preparation.

Participating Organizations

Government/Regulatory Agencies

European Medicines Agency
Health Canada
Medicines and Healthcare Products Regulatory Agency (UK)
National Institute of Environmental Health Sciences, National Toxicology Program
National Institute of Health Sciences (Japan)
National Institutes of Health
National Institutes of Health, National Cancer Institute
Pharmaceuticals and Medical Devices Agency (Japan)
Pharmacological Evaluation Institute of Japan
US Environmental Protection Agency
US Food and Drug Administration
US Food and Drug Administration, National Center for Toxicological Research

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 Tubingen
Northwestern University
Ohio State University
Scintillon Institute
Stanford University, 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

Industry

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

Clinical

Lifespan Heart Center