The Cardiac Safety Research Consortium enters its second decade: An invitation to participate

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The Cardiac Safety Research Consortium (CSRC), a transparent, public-private partnership established in 2005 as a Critical Path Program and formalized in 2006 under a Memorandum of Understanding between the United States Food and Drug Administration and Duke University, is entering its second decade. Our continuing goal is to advance paradigms for more efficient regulatory science related to the cardiovascular safety of new therapeutics, both in the United States and globally, particularly where such safety questions add burden to innovative research and development. Operationally, CSRC brings together a broad base of stakeholders from academia, industry, and government agencies in a collaborative forum focused on identifying barriers and then creating novel solutions through shared data, expertise, and collaborative research.

This white paper provides a brief overview of the Consortium's activities in its first decade and a context for some of our current activities and future directions. The growth and success of the CSRC have been primarily driven by members' active participation and the development of goodwill and trust throughout our membership, which have facilitated novel collaborations across traditionally competitive or contentious stakeholder boundaries. The continued expansion of our base of participating academicians, industry experts, and regulators will define the Consortium's success in our second decade. It is our hope that sharing our endeavors to date will stimulate additional participation in the CSRC and also provide a model for other groups starting to develop similar collaborative forums. (Am Heart J 2016;177:96-101.)

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The Cardiac Safety Research Consortium (CSRC),[1] a transparent, public-private partnership (PPP) established in 2005 as a Critical Path Program and formalized under a 2006 Memorandum of Understanding between the United States Food and Drug Administration (FDA) and Duke University, achieves its first-decade milestone in 2015-2016. The Consortium is chartered to advance regulatory sciences regarding the cardiovascular safety of new therapeutics, bringing together worldwide stakeholders from academia, industry, and government agencies. CSRC activities leverage novel and collaborative approaches to sharing data and expertise via a dedicated, precompetitive focus on cardiovascular safety issues, with emphasis on topics that could constitute barriers to the development of new therapeutics. During its 10-year history, the CSRC has not voted on issues, operating exclusively on a consensus basis.

The FDA's Critical Path Initiative (CPI), launched in March 2004,[2] reflected the agency's goal to stimulate and facilitate a national effort to modernize the scientific process through which a new small-molecule drug, biologic, or medical device is taken from proof-of-concept to marketing approval and clinical use. Collaboration, a central tenet of the CPI,[3–6]

Table CSRC publications in its first decade

Authors (year of publication)	Title
Finkle et al (2009)[8]	New precompetitive paradigms: focus on cardiac safety
Rock et al (2009)[9]	Assessing proarrhythmic potential of drugs when optimal studies are infeasible
Piccini et al (2010)[10]	Current challenges in the evaluation of cardiac safety during drug development: translational medicine meets the Critical Path Initiative
Al-Khatib et al (2010)[11]	Planning the Safety of Atrial Fibrillation Ablation Registry Initiative (SAFARI) as a collaborative pan-stakeholder Critical Path registry model: a Cardiac Safety Research Consortium "Incubator" Think Tank
Min et al (2010)[12]	Evaluation of ventricular arrhythmias in early clinical pharmacology trials and potential consequences for later development
Al-Khatib et al (2010)[13]	Developing the Safety of Atrial Fibrillation Ablation Registry Initiative (SAFARI) as a collaborative pan-stakeholder critical path registry model: a Cardiac Safety Research Consortium "Incubator" Think Tank
Rodriguez et al (2010)[14]	Electrocardiographic assessment for therapeutic proteins: scientific discussion.
Kligfield et al (2010)[15]	The Cardiac Safety Research Consortium electrocardiogram warehouse: thorough QT database specifications and principles of use for algorithm development and testing
Newby et al (2011)[16]	Troponin measurements during drug development: considerations for monitoring and management of potential toxicity
Green et al (2012)[17]	Detection of QT prolongation using a novel electrocardiographic analysis algorithm applying intelligent automation: prospective blinded evaluation using the Cardiac Safety Research Consortium electrocardiographic database
Garnett et al (2012)[18]	Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic effects
Bates et al (2012)[19]	Pediatric cardiovascular safety: challenges in drug and device development and clinical application
Christian et al (2012)[20]	Cardiac imaging approaches to evaluate drug-induced myocardial dysfunction
Sager et al (2013)[21]	Assessment of drug-induced increases in blood pressure during drug development: report from the Cardiac Safety Research Consortium
Nada et al (2013)[22]	The evaluation and management of drug effects on cardiac conduction (PR and QRS intervals) in clinical development
Kligfield et al (2014)[23]	Comparison of automated measurements of electrocardiographic intervals and durations by computer-based algorithms of digital electrocardiographs
Sager et al (2014)[24]	Rechanneling the cardiac safety paradigm: a report from the Cardiac Safety Research Consortium
Darpö et al (2014)[25]	Cardiac Safety Research Consortium: can the thorough QT/QTc study be replaced by early QT assessment in routine clinical pharmacology studies? Scientific update and a research proposal for a path forward
Darpö et al (2014)[26]	The IQ-CSRC prospective clinical phase 1 study: "Can early QT assessment using exposure response analysis replace the thorough QT study?"
Darpö et al (2015)[27]	Results from the IQ-CSRC prospective study support replacement of the thorough QT study by QT assessment in the early clinical phase
Geiger et al (2015)[28]	Clinical development approaches and statistical methodologies to prospectively assess the cardiovascular risk of new antidiabetic therapies for type 2 diabetes
Seltzer et al (2015)[29]	Centralized adjudication of cardiovascular events in large-scale outcomes trials: a meeting report from the Cardiac Safety Research Consortium
Sager et al (2015)[30]	Cardiovascular safety outcome trials: a meeting report from the Cardiac Safety Research Consortium.
Sarich et al (2015)[31]	Novel oral anticoagulants and reversal agents: considerations for clinical development.
Heller et al (2015)[32]	Considerations for assessing the potential effects of antidiabetes drugs on cardiac ventricular repolarization: a report from the Cardiac Safety Research Consortium
Hess et al (2013)[33]	Embedding a randomized clinical trial into an ongoing registry infrastructure: unique opportunities for efficiency in design of the Study of Access site for Enhancement of Percutaneous Coronary Intervention for Women (SAFE-PCI for Women).
Sabol et al (2015)[34]	Cardiac Safety Research Consortium (CSRC): cardiovascular safety and adverse event case report forms

was adopted as an essential principle by the CSRC. Its objectives include the following[7]:

- Facilitate focused pragmatic research that will inform regulatory processes with regard to cardiovascular safety;
- Coordinate think tanks and public forums for open discussion and updates on topics in cardiovascular safety pertaining to medical product development and therapeutic use;
- Develop expert consensus around common nomenclature, standards, and key definitions;
- Author articles in challenging areas, describing what is currently known and unknown, and proposing paths forward to address such knowledge gaps.

To operationalize its mission, the CSRC established a highly interactive committee structure, including focus on think tanks and public programs, white papers and publications, and liaison interactions with other organizations interested in various aspects of cardiovascular safety. The committees report regularly to a governing Executive Committee, which includes representatives from academia, industry, and federal agencies.

As a representative summary of activities during the last decade, the Table[8–34] provides a list of 27 publications. These capture discussions and suggestions from CSRC think tanks and report results from CSRC-related research programs. These activities and publications have become the catalysts for subsequent think tanks, white papers, regulatory discussions, and research projects, and participation opportunities in all of these activities have been central to the growth of the CSRC's membership.

Attention now turns to examples of ongoing projects in the hope that individuals and organizations not currently participating in CSRC PPP projects will consider bringing their expertise to the Consortium's activities in our second decade.

The Comprehensive in vitro Proarrhythmia Assay initiative

The Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative is an integrated in vitro/in silico paradigm for the nonclinical mechanistic assessment of a drug's proarrhythmic liability.[24,35] Collaboration between CSRC, the ILSI Health and Environmental Sciences Institute, the Safety Pharmacology Society, and international regulators (FDA, the European Medicines Agency, the Japanese Pharmaceuticals and Medical Devices Agency, and Health Canada) is a hallmark of this initiative, which has been propelled by 2 separate think tanks.

CiPA focuses primarily on a set of comprehensive and multifaceted nonclinical investigations that provide for a more robust integrated risk evaluation of drug candidates, permitting a more direct assessment of whether a drug has a propensity to cause cardiac arrhythmias. Improving the efficiency and translatability of nonclinical assays could provide more accurate guidance concerning proarrhythmic risk and facilitate a move away from a focus on QTc interval prolongation, an imperfect biomarker. Should it provide a new assay of sufficiently predictive value, a policy-related consequence could be significant modifications of the ICH S7B[36] and ICH E14[37,38] guidelines addressing proarrhythmic cardiac safety investigations.

Within CiPA, multiple working groups are guiding various nonclinical investigations. The Ion Channel working group is expanding the ICH S7B focus on the cardiac potassium repolarizing current I_{Kr} to include multiple currents involved in the cardiac action potential. The relation between ion channel block, delayed repolarization/QTc interval prolongation, and proarrhythmia is dependent upon the extent of the overall effect on net outward and inward currents that is defined not only by the magnitude and time course of I_{Kr} block but also by the drug's effects on other channels active during cardiac repolarization. The In Silico working group is developing and validating the best in silico model of human ventricular electrophysiology for action potential reconstruction of drug effects, integrating the effects on multiple ion channels: in silico modeling offers the potential "to provide integrative, cost-effective, and high-throughput solutions to predict drug-induced changes in action potential duration."[35] This model will form the basis for assessing proarrhythmic risk at the cellular level as reflected in changes in the time course of, and ability to disrupt, ventricular repolarization.

The Stem Cell working group's mandate is to define best practices and utility of human induced pluripotent stem cell–derived cardiomyocytes to validate results obtained from ion channel/in silico modeling investigations and to reveal effects that, for whatever reason, are not observed in either ion channel or in silico investigations. Similarly, the Clinical Translational group is developing electrocardiographic (ECG) biomarkers to use in early human studies to determine whether clinical ECG data reveal human electrophysiological effects that would not have been anticipated based on the nonclinical ion channel data (eg, human-specific metabolites and differences in protein binding).

The ultimate goal of this initiative is to integrate information from all 4 components to facilitate definition of a drug's proarrhythmic propensity, rather than relying on a simplified definition of risk based on QT prolongation, a nonspecific biomarker of proarrhythmic risk.[24]

A recent partnership case study

Collaboration with nonmember organizations is of considerable importance to our activities, representing opportunities to find common goals and synergies. Collaboration with some organizations, including Health and Environmental Sciences Institute and Safety Pharmacology Society, has already been noted and is captured in various publications in the Table. A recently established partnership with the Drug Information Association (DIA) is also noteworthy.

The DIA/CSRC Cardiac Safety Education Collaborative

The DIA, an independent nonprofit organization with offices worldwide,[39] and the CSRC both recently announced the creation of the Cardiac Safety Education Collaborative (CSEC). For more than 50 years, DIA has functioned as a global platform for more than 30,000 health care product development professionals, researchers, regulators, clinicians, academics, and patient advocates to collaborate to improve health globally through the advancement of lifesaving medicines and

technologies. The organization provides global stakeholders a neutral and transparent forum for the collaborative exchange of ideas, an approach essentially identical to the core principles of the CSRC. The CSEC brings together the DIA's expansive, global network; informative content; and convening excellence with the CSRC's unique and focused research portfolio with the specific goal of advancing the dialogue on medical product cardiovascular safety to facilitate the delivery of therapies to patients. Although the CSRC and DIA had already developed a track record of partnered educational programs on cardiac safety, the creation of the CSEC formalizes the development of a comprehensive series of Signature Programs on cardiac safety themes. These themes proceed through didactic programs, yielding state-of-the-art publications, with progression to think tank/incubator programs. These programs further yield consensus white papers and pilot projects applying enhanced principles of regulatory science to cardiovascular safety issues.

Social listening and safety surveillance

As use of social media becomes more prevalent, much attention is focusing on how a blended strategy encompassing targeted pharmacovigilance, "big data" approaches, and electronic tools can be developed and leveraged on behalf of more efficient regulatory science.[40–42] One approach is to meld safety signal detection goals with the advantages and broad access of social media screening (termed *social listening*) to yield earlier, actionable insights regarding patient reports of medical product adverse events.[43] The use of social media for the detection of adverse event information will not replace existing mechanisms for safety signal detection; rather, it is expected that it will supplement and enhance current safety surveillance systems.

Compared with mandatory reporting of clinical trial adverse event data, voluntary spontaneous reporting from health care providers and consumers suffers from underreporting. Social media can provide an additional resource of potential product information because various Internet postings can be actively screened for this type of information. Some individuals (ie, social media "reporters") may not be inclined to report adverse events to manufacturers or government regulatory agencies yet choose to discuss aspects of their medical history and treatment in an Internet setting. As a result, social media data represent an untapped resource for postmarketing safety surveillance.

In November 2015, the CSEC delivered a webinar addressing how social listening and safety surveillance can be of benefit to the pharmacovigilance community. The speakers emphasized both the complementary nature of social listening to established pharmacovigilance approaches as well as the need to develop social listening strategies and methodologies. Topics addressed included the ethical implications of social listening activities on patient and consumer privacy, and regulatory perspectives on the use of social listening as a supplement to current postmarket surveillance of cardiovascular safety signals. A follow-up think tank is scheduled for June 2016.

Collaboration, cardiac safety, and children

The importance of knowing how to conduct clinical research in pediatric populations and the realization that too many young individuals who appeared to be healthy have died suddenly in athletic and nonathletic circumstances have prompted the CSRC to focus on ways to approach pediatric cardiovascular safety more effectively. Various think tanks on pediatric medical product safety have highlighted the complexities associated with defining cardiac abnormalities in children and, moreover, have noted that a clearer understanding of what is "normal" over the course of development in this population is needed to better understand and monitor potential drug-related, genetic, and other cardiovascular abnormalities.

In 2015, the CSRC launched an initiative entitled "Prevention of Sudden Cardiac Death in the Young: Developing a Rational, Reliable, and Sustainable National Health Care Resource." This initiative has already resulted in collaborations with DIA; the Pediatric & Congenital Electrophysiology Society; and other professional societies, universities, and sports organizations. Deliverables from these collaborative efforts of benefit for pediatric populations are expected to include the following: white papers on current pediatric cardiovascular screening efforts in the United States and globally; the development of a structured, consensus minimum core data set for pediatric screening; a consensus on definitions and electronic formats for descriptors, ECG, and imaging data; and the establishment of a national pediatric cardiac safety "normal" database resource to enhance global efforts to identify more accurately genetic or drug-induced abnormalities in key pediatric groups.

The Medical Device Epidemiology Network Initiative

The Medical Device Epidemiology Network Initiative (MDEpiNet), historically part of the Epidemiology Research Program at the FDA's Center for Devices and Radiological Health,[44,45] is currently entering its third year as an independent PPP. MDEpiNet objectives and function have many similarities to CSRC, promoting a collaborative, precompetitive forum in which multiple stakeholders focus on novel, more efficient, and more informative approaches to device benefit-risk assessments and safety surveillance challenges. Its mission is

to develop and maintain national and international scientific infrastructure and methodological approaches to overcome and eliminate discontinuities in device benefit-risk evaluation and safety surveillance over the total product lifecycle.

Novel quality and efficiencies using registry-based infrastructure for prospective randomized trials have been central to several CSRC research projects.[33] In August 2015, a Draft Report entitled "Recommendations for a National Medical Device Evaluation System: Strategically Coordinated Registry Networks to Bridge Clinical Care and Research,"[46] prepared by MDEpiNet and the Medical Device Registry Task Force, was released for public comment: the revised version will be submitted to the FDA. Sharing the approach taken by CSRC white papers, the spirit of these recommendations is not to present a fully fledged proposal for a national system; rather, it is to complement and extend current perspectives "with additional, pragmatic considerations that could help define immediate next steps for system development and launch." Central to these recommendations is the focus on "a scalable system architecture supporting a staged implementation of the National System, beginning in selected priority device areas."[46]

In March 2016, the CSRC and MDEpiNet sponsored a think tank addressing needs and best practices for endpoint adjudication in medical device trials.

Concluding comments

As rare but catastrophic cardiac safety concerns constitute a profound area of attention and cost barriers for new drug development, the effectiveness of the CSRC in leveraging uniquely collaborative approaches to address such concerns is reflected in a decade of growth and increasing impact. Given its formation shortly after the release of ICH guidelines S7B[36] and E14,[37] documents whose adoption by regulatory agencies effected their governance of the cardiac safety regulatory landscape, the CSRC's initial attention focused predominantly on drug-induced influence on ECG intervals, particularly the QT interval, as cardiac safety biomarkers. Although this is a topic of continued interest and ongoing evaluations,[22,26,27] other publications in the Table and the examples of ongoing initiatives presented in this article bear witness to the Consortium's expanded interests in multiple areas of cardiovascular safety.

We welcome academicians, regulators, and individuals involved in the medical product industry across the entire lifecycle of such products to add their expertise to the Consortium's activities in our second decade, thereby working collaboratively with us to enhance cardiovascular safety at both the individual patient and public health levels.

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