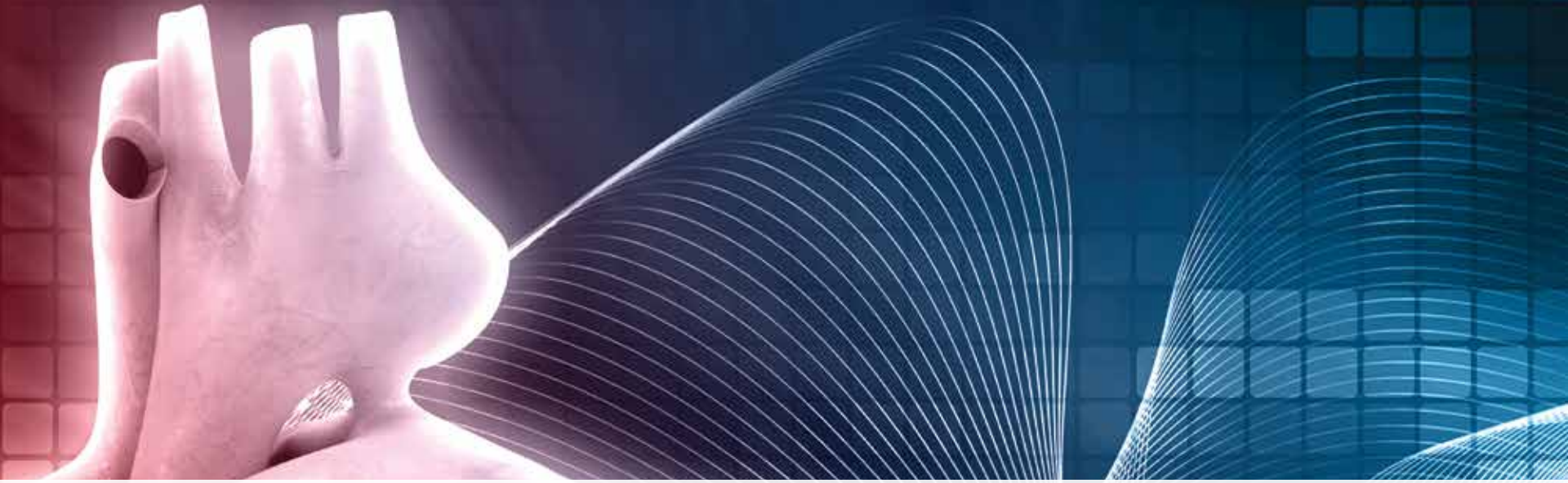

CELEBRATING 10 YEARS OF EXCELLENCE IN CARDIAC SAFETY RESEARCH

CARDIAC SAFETY
RESEARCH CONSORTIUM

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CSRC

CELEBRATING **10 YEARS** OF EXCELLENCE
IN CARDIAC SAFETY RESEARCH

A Letter from the CSRC Co-Directors:
Celebrating a Decade of Advances in Cardiac Safety Regulatory Science

In 2006, the Cardiac Safety Research Consortium (CSRC) was launched under FDA's Critical Path Program as a public-private partnership (PPP). The mission of the CSRC was to establish a neutral, transparent organization that could bring together thought leaders across the stakeholder spectrum—patients, physicians, manufacturers, regulatory authorities, professional societies, and academics—to identify cardiovascular safety barriers to therapeutic innovation, and to develop pragmatic, innovative solutions to lowering or removing those barriers as a means to enhance regulatory science.

In 2016, we celebrate the first decade of CSRC activity with two associated reports. Part I consists of a series of personal perspectives from individual professionals who have participated in the CSRC's growth and had an impact on our nation's public health.

In Part II, the full publication and activities report includes the programs, participants, and more than 30 peer reviewed publications of think tank/incubator white papers, scientific project and clinical trial reports, and perspectives generated by the CSRC.

Over the last 10 years, the CSRC has supported ongoing efforts to address key areas of cardiac safety concern, including the need for more efficient means of detecting pro-arrhythmia, considerations for blood pressure and biomarker monitoring, cardiac imaging, and cardiac safety in special populations, such as diabetics, women, and an expanded program focused on pediatric cardiovascular safety. Some new areas of great interest and current exploration include enhanced ECG algorithmic detection of prolonged QTc and QT syndromes; antidotes for novel oral anti-coagulant agents; cardiac safety concerns with biologics; enhanced clinical science processes, including registry-based randomized trials; development of a standardized cardiac event reporting structure; use of social media for safety surveillance; and the role of event adjudication for cardiac safety events – just to name a few!

In the midst of the world of health care and health care science and innovation, characterized by progressively accelerated change, one thing about the CSRC remains constant, as described in the 5-year report we published in 2011 "The fabric of the CSRC and the key to past and future success is our membership – engaged, creative individuals with diverse professional backgrounds…a brain-trust of unique breadth and depth…Our members have developed trust in each other and in the CSRC's pre-competitive PPP processes…trust that we come together to listen to each other…to exchange and discuss ideas….[and] trust that our pragmatic emphasis is productive, with deliverables that have impact on the landscape of cardiac safety."

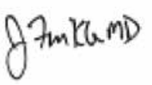
In addition to our members, the CSRC has been privileged to work with a wide range of dedicated independent organizational partners, including the American College of Cardiology, Centers for Medicare and Medicaid Services, Drug Information Association (DIA), FDA, Health and Environmental Sciences Institute (HESI), and the Society for Cardiac Angiography and Interventions (SCAI). A full list of our partners is located in the publications and activities report.

The CSRC committees – Membership, Scientific Oversight, Program Planning, ECG Data & Waveform Warehouse, Inter-organization Liaison, and Executive – continue to stimulate and organize our activities. Each committee also provides opportunities for our members to be involved and to take leadership roles according to its interests. Growth in the size, scope, and productivity of the PPP, as evidenced in our 10-year reports, are a testimonial to the potential of pre-competitive collaboration to accomplish public health objectives that no single stakeholder could achieve on its own. In that spirit, moving forward into our second decade of activity, it seems fair to say that in its first 10 years, the CSRC has literally taken to heart the African proverb shared at one of our pediatric safety think tanks:

"If you want to go fast, go alone.
If you want to go far, go together."

With our two reports, we celebrate going into our second decade, and going there together.

Mitchell W. Krucoff, MD, FACC, FAHA
Professor, Medicine/Cardiology
Duke University Medical Center



John K. Finkle, MD, FACC, FACP
Vice President, Global Clinical Safety and Pharmacovigilance,
GlaxoSmithKline

"We've built a highly impactful organization over the past 10 years, and it continues to become bigger, more collaborative, and more interactive."

JOHN K. **FINKLE**

John K. Finkle, MD, FACC, FACP

Vice President, Global Clinical Safety and Pharmacovigilance, GlaxoSmithKline

I've been in the CSRC since the very first informal meetings and have enjoyed starting an organization with such an impact. Often organizations try to do what we did and are unsuccessful. I've enjoyed the dedicated core group of people who've been involved since inception, driving the organization forward but sharing leadership roles with others.

One major highlight was our initial meeting with the FDA about eight years ago to discuss ways to evaluate the QT interval in oncology drugs. This milestone followed two years of hard work writing a charter for the CSRC, doing the legal work, and building an organizational structure. The oncology project was "low-hanging fruit" with significant impact. We wrote a white paper and engaged the FDA, which led to a meeting of approximately 30 agency people and 3 of us from the CSRC. Our discussions formed the basis of a paper in the American Heart Journal, whose editorial board agreed to accept CSRC papers automatically for publication due to our broad-based input. This first hot topic was rapidly taken up by industry and became a best-practices paper for evaluating QT in oncology compounds.

The biggest challenge was getting our first few projects done. All the work was performed "after hours." Then, as the momentum began to build, our published white papers and think tanks achieved recognition, our membership increased, and we formed many external collaborations with groups such as the Health and Environmental Sciences Institute, Drug Information Association, American College of Cardiology, American Heart Association, International Cardioncology Society, and others. As we reached more people, our impact snowballed, and we're now over 40 think tanks and 25 publications.

I'd like to highlight the contributions of Mary-Beth Sabol, MD, medical director in Global Clinical Safety and Pharmacovigilance at GSK. Dr. Sabol drove development of CSRC's cardiovascular Safety and Adverse Event Case Report forms based on earlier work at our company. These forms are designed for use in noncardiovascular clinical trials to encourage collection of the minimum information needed to adjudicate a cardiovascular event. This is crucial, because small imbalances in cardiovascular events in such trials may lead to concerns about potential CV safety issues. The forms are freely shared through CSRC's website, a great example of our nonproprietary, precompetitive collaboration to improve patient safety.

We've built a highly impactful organization over the past 10 years, and it continues to become bigger, more collaborative, and more interactive. In the future, I'd like the CSRC to continue to grow and collaborate even more extensively with external organizations to bring the appropriate stakeholders to the table and expand efforts to resolve problems that we face in medical-product development.

I'd describe the CSRC as an inclusive organization of dedicated people from diverse career backgrounds who've come together to improve the cardiovascular safety of drugs and medical devices. To date, we've been highly successful in our venture, and I would absolutely recommend that others participate. In fact, I'm always trying to get people involved!

"We are potentially saving lives by creating a collaborative environment and bringing synergies to data that we collect, analyze, and publish."

CINDY **GREEN**

Cindy Green, PhD

Assistant Professor, Biostatistics & Bioinformatics,
Duke University School of Medicine

It's been extremely fulfilling to be involved in a consortium with such great potential. I've really enjoyed the ability to work with other people with shared interests to collect data and collaborate on projects. For anyone who isn't aware of the CSRC, I'd say that we are potentially saving lives by creating a collaborative environment and bringing synergies to data that we collect, analyze, and publish. This makes a huge difference and will help guide the direction of future drug and device studies.

Looking back, our biggest challenge was our "free the waveforms" project. Its purpose was to convince sponsors to share their 3600 stored ECGs in a collaborative database that would benefit everyone involved. This effort took several in-person meetings to achieve, and I remember Norman Stockbridge, MD, of the FDA wearing a T-shirt that said "Free the FDA 3600"! Once we had access to ECG data, or "the waveforms," from representative TQT studies, this got the ball rolling on the expansion of the CSRC and opened up new possibilities for what we could do next.

This initial focus on the waveforms has evolved over the years to include much broader and more diverse cardiac-safety projects, with many great studies, manuscripts, white papers, and think tanks. We're much more efficient at data collection now. The data are also evolving. When we started, the waveforms were recorded as static ECGs, but now we're looking at collecting 24-hour continuous data files. We've moved from small data sets to large ones and have the ability to store much larger amounts of data, thanks to developments such as the cloud. As co-chair of the Data Warehouse Committee, I'd like to put out a plea for even more data sharing—especially of those continuous TQT files.

One of the biggest highlights from the past 10 years was the completion of the groundbreaking IQ-CSRC study, which brought together experts on QT data to develop novel analysis methods. This study provided evidence to support replacement of the TQT study with ECG assessments in early clinical development to exclude small QT effects by a new drug.

I'd particularly like to highlight the contribution of Executive Committee Chair Mitch Krucoff, MD. It was his vision and leadership that really started the CSRC and has brought us to where we are now. I have enjoyed a great working relationship with Mitch for more than 20 years, having started at the DCRI as his statistician, and I have him to thank for recruiting me to the CSRC.

The CSRC has already achieved so much. Over the next 10 years, there are sure to be additional breakthroughs, both technologically and medically, and the CSRC will serve as a model for how we can successfully analyze and share data among organizations.

"My fondest memory was when we finally obtained access to the waveforms, ultimately including tens of thousands of ECGs, from a dozen or so thorough QT studies released by sponsors."

PAUL **KLIGFIELD**

Paul Kligfield, MD, FACC

Professor of Medicine, Weill Cornell Medical College,
Division of Cardiology

As part of the CSRC, I've most enjoyed gaining insights into the technology underlying the electrocardiogram. It's also been fascinating to see how the FDA works and how pharma industry people think. This high level of cooperation among regulators, investigators, and sponsors would be virtually impossible without the CSRC. I really enjoy the spirit of inquiry the CSRC fosters.

The consortium can be traced back to an effort by Norman Stockbridge, MD, PhD, at the FDA to improve the use of electrocardiograms—and specifically the QT interval—for evaluating cardiac-safety risks of drugs. Thorough QT studies in healthy volunteers were standard practice at that time. While it was important to make sure no drugs were approved that might result in episodic sudden death in the general population, the other side of the coin was that potentially useful drugs were being discarded because of potential arrhythmogenic "signals" that might not accurately predict that problems would occur.

Back in 2002, Dr. Stockbridge convened FDA public meetings on improving and standardizing the format of ECGs in drug safety. I attended because I was working on electrocardiography at Cornell at the time, with interests in practical interpretive issues and technical aspects of ECGs and in trying to develop cross-platform databases of ECGs. An outcome of these sessions was that a standard format was established for digitized ECGs to be submitted to the FDA, which were then collected in a database provided by Mortara Instrument.

It quickly became clear that it would be useful to have these initial 3600 stored ECGs available for academic research. However, this proprietary information belonged to pharma companies.

An extended effort began to open up the ECG "warehouse" through the CSRC. To emphasize some frustration with the pace of progress, I ordered T-shirts—1960s demonstration-style, emblazoned with "Free the FDA 3600"—for CSRC attendees at a meeting at Duke in 2007. A turning point for the CSRC came at that meeting, when Mitchell Krucoff, MD, FACC, became more involved in CSRC leadership. Robert Califf, MD, then in a leadership position at Duke, and now FDA Commissioner, made more of Duke's resources available for the CSRC. This was a powerful moment in the evolution of the CSRC.

My fondest memory was when we finally obtained access to the waveforms, ultimately including tens of thousands of ECGs, from a dozen or so thorough QT studies released by sponsors. I'd like to highlight the cooperation from the pharma industry, although regrettably, by then, the data weren't as useful as they would have been several years earlier. We've since expanded the ECG database beyond thorough QT studies, including a repository of tracings from French patients with congenital long QT syndrome, a relatively rare genetic disorder, which is now continuously being updated.

Over the coming 10 years, I'd like to see the CSRC stay on the same track, encouraging and facilitating even greater direct support for individual and cooperative research projects.

"I would encourage others to become involved in the CSRC as one of the few forums where we can meaningfully interact with all drug-development stakeholders."

PETER R. **KOWEY**

Peter R. Kowey, MD, FACC, FAHA, FHRS

Professor of Medicine and Clinical Pharmacology, Jefferson Medical College, and William Wikoff Smith Chair in Cardiovascular Research, Lankenau Heart Institute

As a member of the CSRC, I have enjoyed working with people from other disciplines and areas of medicine. I have learned a good deal about the regulatory side of medicine, and thanks to the CSRC, I have a much better appreciation of the pressures people are under when making decisions about the development and approval of drugs, biologics, and devices.

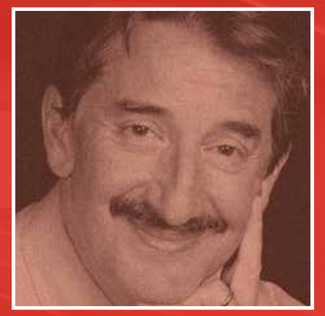
The CSRC's growth has been the most important aspect of our evolution over the past 10 years, from a small organization of like-minded people to a much larger one, including academics, industry representatives, and regulators. We have succeeded in bringing together stakeholders with different vantage points for meetings to confront difficult issues in cardiovascular safety. We also have gone from being primarily U.S.-focused to becoming a global initiative, engaging people from other parts of the world in our discussions.

I would encourage others to become involved in the CSRC as one of the few forums where we can meaningfully interact with all drug-development stakeholders. The CSRC has established a strong reputation, based on first-rate projects and manuscripts, and has had an enormous impact in helping to demonstrate cardiovascular safety in clinical trials. Among the highlights from the past 10 years are our two think tanks on anticoagulant antidotes and reversal agents. The output from these meetings included important publications in the American Heart Journal and, more importantly, helped to put into place a way forward for the regulatory approval of these very important agents.

Pharmaceutical consultant Dr. Philip Sager comes to mind as someone whose efforts I'd like to highlight. Philip was involved in the very beginning of the CSRC and has contributed a tremendous amount of work in championing our organization and serving as a touchstone for think tanks and white papers. I'd also like to acknowledge the work of Executive Committee Co-Chair Mitchell Krucoff, MD, of the DCRI, whose efforts also have been integral to our success.

For the future, I believe that we will need to consider several additional aspects of cardiovascular safety. In the beginning, we focused on electrophysiology, and we have moved into other areas. We'll need to expand these efforts. We should also attract younger people to the CSRC as part of their education about drug development and clinical research. If we continue to do our job well, we should be able to streamline the path to approval for safe drugs, making them available sooner for our patients. This will involve evolution of tools now increasingly in play, including mining of "big data."

Although the CSRC was set up to address cardiovascular safety, a similar model could be used in other disciplines. I would encourage people to think about how this kind of structure could be used as a template to understand liver toxicity and suicidality and other safety issues we confront commonly during drug development.



"I'm pleased with this ability to keep making progress while staying open to new ideas. This is proof that the CSRC is very much a living organization."

MITCHELL W. **KRUCOFF**

Mitchell W. Krucoff, MD, FACC, FAHA

Professor, Medicine/Cardiology at Duke University Medical Center and Director of the Cardiovascular Devices Unit and eECG Core Laboratory at the Duke Clinical Research Institute

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At the CSRC's very first think-tank meeting in 2005, we asked our colleagues from industry whether they would be willing to share ECG waveforms from patients who had been exposed to placebo. "Absolutely not," they replied, and we launched our first CSRC project, "Free the waveforms." Yet today, through the activities of the CSRC, these same highly competitive pharmaceutical manufacturers lead the way in their willingness to share precompetitive information and understanding of the value of this kind of ecosystem-oriented collaboration. To me, that is the most dramatic and memorable marker of how far we've come.

Over the past decade, the relationships and level of trust among CSRC members have matured enormously. Our working processes have increased in resilience, and today we have a robust track record of projects and publications, all included in our multivolume 10-year report. I'm also happy to see a progressive increase in the involvement of young people with new ideas, while keeping the founding leadership group together. I'm pleased with this ability to keep making progress while staying open to new ideas. This is proof that the CSRC is very much a living organization.

The contribution of two individuals who have mostly stayed in the background, but who were critical to the launch and success of the CSRC over the past decade, should be mentioned: Robert Califf, MD, who was then at Duke, and Janet Woodcock, MD, who was then in the Office of the Commissioner of the FDA and who launched the Critical Path program in 2004. Without their support, the CSRC wouldn't be where it is today. The hard work of all the founding members of the CSRC Executive Committee has also ensured our group's success.

The greatest challenge we've faced has been creating broad visibility and understanding of CSRC's mission and potential as a resource for better approaches to cardiac safety-related issues. Through future efforts and collaborations, I'd like to see the development of greater public awareness of the power of this type of multi-stakeholder, precompetitive collaboration to do things that no single stakeholder can do alone. I'd encourage anyone with an interest in advancing public health to join the CSRC—they are sure to find an opportunity to contribute.

Over the next 10 years, I hope the CSRC can expand the avenues through which we have helped in the drive to a more efficient, higher-quality, and less expensive way of evaluating cardiac-safety concerns with new therapeutics. Our alliance with the Drug Information Association is one step in the right direction, as is our interaction with the FDA's Medical Device Epidemiology Network Initiative (MDEpiNet). We need to improve public health by removing artificial barriers between clinical research and clinical practice. This concept is central to the CSRC and will grow in importance, supported by increased mining of electronic medical records.

Far and away the most enjoyable part of being a member of the CSRC is the people, whose passion and vision leads them to give their time to make our consortium work. Every one of our members has a full-time day job, in roles such as public servants, patient advocates, industry leaders, and academics. It is a privilege to work with and get to know this extraordinary group of people.

"I appreciate the structure of CSRC meetings, with their focus on the bigger picture and fluid dialogue throughout the day, addressing issues based on member and committee suggestions."

KRISHNA **PRASAD**

Krishna Prasad, MD

Group Manager (Cardiovascular, Oncology and Anti-infective teams) at the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and Consultant Cardiologist (Hon) at St Thomas' Hospital

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The CSRC's fundamental achievement has been its ability to bring stakeholders—including industry, cardiologists, and regulatory agencies—together in a high-level forum to communicate about scientific issues. This is a remarkable step forward. It's not easy to get people from around the globe to participate actively, yet this is what the CSRC has done.

The biggest challenge the CSRC has taken on has been to bring stakeholders together to use common thinking and decision-making processes. We should build on this important contribution, including producing more position papers that represent common ground on how to move science forward today. Kudos to the CSRC steering committee for deciding not to create more guidelines. Instead, we've focused on position papers on relevant and timely topics, summarizing agreed positions and the state of the science and retaining the ability for people who weren't engaged in the original discussion to contribute. The choice of suitable topics is challenging, and the CSRC has done it well.

Over the past 10 years, the CSRC has expanded from its original intense focus on cardiac safety, enlarging our membership to be more inclusive and covering broader topics with a cardiology component. Most societies and teams grow rapidly and then phase down. The CSRC is making constant efforts to expand to more stakeholders, which is a very good thing.

As a member of the CSRC, I've most enjoyed the scientific discussion and camaraderie. I appreciate the structure of CSRC meetings, with their focus on the bigger picture and fluid dialogue throughout the day, addressing issues based on member and committee suggestions.

This differs from typical scientific meetings, with their focus on presenting new research findings. The CSRC's intent is to come to a reasoned discussion point and conclusion, and all our meetings have been useful in having very solid, in-depth discussions until an agreed solution is reached and we can move forward. This is the most enjoyable part of CSRC meetings, along with the camaraderie that follows naturally.

Credit should go to DCRI project manager Valarie Morrow, MD, for being instrumental in the CSRC's success. Others who have been key in moving the initiative along include the FDA's Norman Stockbridge, MD, PhD; pharmaceutical consultant Philip Sager, MD; Peter Kowey, MD, of Jefferson Medical College; and Borje Darpo, MD, PhD, of iCardiac Technologies.

In the future, I hope we'll see more of the types of initiatives that have been successful to date, including meetings that address wider contexts. Developing new databases has been a huge contribution in moving the field forward. This support for scientific research will continue to be important in the future, including nonclinical aspects of cardiac safety. I'd like the CSRC to expand globally into areas such as Australia, New Zealand, China, and Southeast Asia. I encourage colleagues who belong to clinical and regulatory stakeholder groups—including individuals who are not cardiologists—to join the CSRC, bring their issues, and engage in dialogue to find solutions.

"I very much enjoy this open and neutral platform for sharing ideas about how to optimize drug development."

IGNACIO **RODRIGUEZ**

Ignacio Rodriguez, MD

Senior Safety Science Leader, Roche

Cardiovascular safety is one of the many critical issues in drug development that can best be solved by all interested parties joining forces. I'm happy and proud to be part of the CSRC; in the last 10 years, our consortium has become an excellent role model for a successful public-private partnership (PPP). I've had the opportunity to be involved with other such initiatives, and the CSRC is one of the most efficient and productive collaborative platforms I've seen. The level of active participation by regulators, pharmaceutical companies, clinical research organizations, and academia has made this a very successful PPP, with many concrete examples of useful deliverables.

After the release of the ICH E14 and S7B guidance documents, there were many questions regarding their implementation. Through many think-tank meetings, publications, and clinical research programs, the CSRC has played a critical role in achieving full implementation of regulatory guidance for ECG monitoring in clinical development. Examples include concrete proposals for ECG collection in areas such as oncology, biologics, compounds that affect heart rate, and compounds that alter glucose metabolism, as well as alternative approaches to the dedicated ECG studies recommended in E14. While ECG monitoring was the "lowest-hanging fruit" (and a clear unmet need in drug development), the CSRC's work has expanded to other areas of cardiovascular safety.

Participating in the CSRC is a win-win for everyone. We learn a lot from each other, and this collaborative learning has led to recommendations that can be implemented across the board by sponsors, regulators, and academia. I very much enjoy this open and neutral platform for sharing ideas about how to optimize drug development.

For people in the biopharma industry who aren't aware of the CSRC, I would say that the type of work we do is a very good investment of time. At launch, the CSRC included just a few clinical-trial sponsors and the FDA, focusing primarily on electrocardiography and the QT interval. Since then, we've evolved into a bigger and more-mature forum involving a much larger group of sponsors, CROs, central vendors, and regulators. We've also added international regulators, including representatives from Health Canada, the UK Medicines and Healthcare products Regulatory Agency, and Japan's Pharmaceuticals and Medical Devices Agency. Our consortium continues to evolve from an interesting concept to a solid reality.

I'd like to highlight the efforts of Norman Stockbridge, MD, PhD, Director, Division of Cardiovascular and Renal Products, at the FDA. Dr. Stockbridge's involvement and commitment have been critical for the CSRC's success. Consistent participation from the FDA is a foundation that attracts the interest of all the other parties. From the very beginning, Dr. Stockbridge has been a champion for this initiative, and his hard work and endorsement have made a real difference.

In the future, I'd like to see continued success and hard work from our group. We need to keep working to identify improved data-sharing platforms and continue paving the way for optimum cardiovascular safety monitoring and risk management in drug development that translate into benefits for patients in need.

"This is an exciting group that has given me the opportunity to work and interact with terrific people in a very collaborative way."

PHILIP **SAGER**

Philip Sager, MD, FACC, FAHA, FHRS

Pharmaceutical Consultant and Cardiovascular Safety Expert

The CSRC's success has stemmed from engaging diverse stakeholders—such as U.S. and global regulators, academicians, industry experts, clinical research organizations, and individuals—to collaboratively work together to advance the science related to cardiac safety in pharmaceutical and device development.

This unique partnership has made a profound impact in dealing with difficult cardiac-safety issues. We've been able to move the science forward by creating an exceptionally effective platform and process. Notable successes include: 1) the CSRC's efforts to perform a prospective study, in conjunction with the FDA, leading to a new pathway using early clinical trials to complete the required assessment of a drug's proclivity to prolong the QTc interval, obviate the Thorough QT Study, and revise ICH E14 (the QT guidance); 2) creating a new mechanism-based paradigm to assess a drug's potential arrhythmic effects that will likely profoundly affect drug development (the Comprehensive In Vitro Proarrhythmia Assay [CIPA]); 3) creating an accelerated regulatory pathway for the reversal agents for novel anticoagulants; and 4) major efforts to determine the use and roles of cardiovascular safety-outcome studies, cardiovascular-event adjudication, and evaluation of the hypertensive effects of medications.

Our consortium started out with fewer than 10 people. Gaining traction was the largest initial challenge. This is now behind us, but for the first few years, it was an experiment to see if we could secure a foothold sufficient to have real impact. Over the years, the CSRC has evolved by involving a diverse range of stakeholders and creating effective approaches that result in a significant impact on drug development.

As a member of the CSRC, I've really enjoyed making a difference and having an impact. This is an exciting group that has given me the opportunity to work and interact with terrific people in a very collaborative way. I'd particularly like to mention the contribution of Norman Stockbridge, MD, PhD, at the FDA, who played a truly critical role in getting us started and continues to provide very significant support and leadership to the organization.

Over the next 10 years, I'd like to see the CSRC expand further into additional areas. We were initially focused on ECGs and cardiac safety and are now branching out into areas such as the adjudication of cardiac events; the role of post-marketing data to supplement the safety database and, in some cases, possibly reduce what is required during phase III; stem-cell therapy; and prevention of pediatric sudden death. In the future, we will be even more inclusive of all issues of cardiac safety for both drugs and devices.

For someone who isn't aware of the CSRC, I'd describe our group as bringing together the full range of global stakeholders to collaborate on fostering the science regarding cardiovascular-safety issues in drug and device development. This consortium and its approaches have real impact. I'd definitely recommend that others become involved—it's been a great experience for me from the very beginning.

“CSRC meetings provide important opportunities for open discussion, with all participants having a chance to hear the frank opinions of worldwide experts.”

KAORI **SHINAGAWA**

Kaori Shinagawa, MD, PhD

Senior Scientist for Clinical Medicine, Pharmaceuticals and Medical Devices Agency (PMDA), Japan

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The CSRC has given me great opportunities to meet people from academia and industry who are active at the forefront of drug development, especially in cardiovascular safety, as well as people from other regulatory bodies who evaluate cardiovascular drugs. This networking presents new opportunities for collaboration.

My work as a cardiologist at the PMDA includes clinical-trial consultations and reviews of new drugs for cardiovascular diseases, assessments of cardiac safety of various new drugs, and creation of new guidelines for Japanese drug applications. In this work, it can be difficult to have open discussions with other stakeholders about drugs under development. CSRC meetings provide important opportunities for open discussion, with all participants having a chance to hear the frank opinions of worldwide experts. There are simply no other occasions like this.

I’ve been a member of the CSRC Executive Committee since 2013. Our workshops and meetings give me plenty of opportunities to obtain updated information. CSRC leaders always choose trending topics for meetings, which helps with my work at PMDA. Journal articles don’t always cover this information.

In addition, CSRC activity supports smoother and appropriate implementation of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, which are very important in advancing more efficient global drug development. During my involvement with ICH E14/S7B-related activities since 2005, highlights have included publications and meetings related to QT assessment.

The IQ-CSRC prospective study is of particular importance. These efforts have had a great impact on proarrhythmic risk assessment in drug development.

As the first person from Japan to participate in the CSRC Executive Committee, I feel that the consortium is gaining influence outside of the U.S. and Europe. As global drug development increases in popularity, sharing information about methodology for evaluating efficacy and safety, along with extrinsic and intrinsic ethnic factors, is becoming more important, from the planning stage through analyzing the clinical studies. In reviewing global clinical trials at PMDA, these ethnic factors are checked and the results from the Japanese population compared with the entire study population. It is very important for us to consider whether there is consistency between the results from the entire population and the Japanese population.

In the future, I hope the CSRC will continue expanding its base of participating experts from around the world and providing opportunities to share information through workshops, publications, and other activities. I hope the CSRC will continue to identify obstacles to efficient drug development and make suggestions to overcome them. I’d also like to see more people from Asia, including others from Japan, become more engaged in CSRC’s activities. I would definitely recommend that others with an interest in cardiac safety participate in the CSRC, which provides a unique and relatively small forum for conversations with worldwide experts.

"The most important thing the CSRC has accomplished is to set up a pathway that enables me to get input in a setting that is cognizant of but not restricted by conflicts of interest."

NORMAN **STOCKBRIDGE**

Norman Stockbridge, MD, PhD

Director of the FDA Division of Cardiovascular and Renal Products (DCaRP)

In my role at the CSRC, I've most enjoyed building great working relationships with a large number of people in academia and industry. I enjoy our fruitful discussions on topics that are far broader than those discussed in formal interactions with the FDA.

From my viewpoint, the most important thing the CSRC has accomplished is to set up a pathway that enables me to get input in a setting that is cognizant of but not restricted by conflicts of interest. Typically, there's a well-trodden pathway for me to get external advice: through an advisory committee or another FDA process for which contributors must pass stringent conflict-of-interest screening. At the CSRC, I'm able to propose a topic and convene a meeting in which people freely disclose conflicts of interest, but those don't interfere with their ability to speak on a subject. This procedure is quite efficient and produces a richer discussion.

Our biggest challenge of all was to get the CSRC launched; it took quite a while for our first real think tank to get off the ground. There was a long period in which it wasn't clear that we were going to get full participation by the various stakeholders. Since then, the CSRC has been productive and stable. Our success reflects the efforts of the Duke contingent and membership committee in drawing people together. I give a lot of credit to founding member Christopher H. Cabell, MD, MHS, who initially represented Duke and worked hard to drive the group forward.

In our first decade, we've been extremely productive in identifying topics of interest to our stakeholder community and running useful meetings. We've had a number of joint research projects, and my hope is that, in the next 10 years, such projects will become more prominent, with more advances in the sharing of data. A key step has been for our scope to evolve into areas of cardiovascular safety beyond the proarrhythmic potential of drugs. I'd like to nurture still more collaboration with colleagues within the FDA and with other cardiovascular-safety groups. We should also work on topics that bridge both the clinical and nonclinical cardiovascular-safety communities.

Nonmembers should be aware that the CSRC offers a very productive and friendly environment for addressing issues that are common to multiple parties interested in drug development. For anyone with a potential drug-safety or biomarker-related issue, our group provides a great way to get other people involved, obtain regulatory input, and move the discussion along.

"Please become involved, and bring your expertise to complement what we have already. The benefit would be to patients and the greater good."

J. RICK **TURNER**

J. Rick Turner, PhD, DSc, FASH, FACC

Senior Scientific Director, Clinical Communications, and Chief Scientific Advisor, Cardiac Safety Services, Quintiles; Adjunct Professor of Pharmacy Practice, Campbell University College of Pharmacy & Health Sciences

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The most satisfying part to me of being a member of the CSRC is playing a facilitator role. I assist in putting materials in a more accessible format for people outside our discipline to understand the importance of cardiac safety.

For the past seven years, I've been a member of the White Papers and Publications Committee, writing papers based on think-tank discussions for publication, mainly in the American Heart Journal. It's been a real joy to work with multiple authors to create these manuscripts as a tangible, permanent record of our discussions. This helps our experts' voices be heard.

Our papers examine the state of the art, areas with and without consensus, the data needed to answer outstanding questions, and what additional thinking will help reach consensus. They spell out what we want to accomplish as well as the small, incremental steps we must take over the next two or three years to close the knowledge gap. This process helps all stakeholders in a noncompetitive way.

We're winning the battle and engaging more people. My personal goal is to get more people involved from allied professions, both directly with the CSRC and in sharing the results of our work. If I met someone who wasn't aware of the CSRC, I'd say, "Please become involved, and bring your expertise to complement what we have already. The benefit would be to patients and the greater good."

Many of us have "day jobs" with organizations that compete, but within the CSRC, we work collaboratively to advance the science. Since we're mostly volunteers, it can be difficult to find a time when people are available for discussions, but as they say, if you want something done, ask a busy person. This is a great group of people, and I've made some very good friends.

Looking ahead, I'd like us to move the CSRC's work into the mainstream, reflecting its fundamental importance. Today, our work is viewed by some as being rather esoteric. I'm working on introducing more cardiac-safety education into the PharmD curriculum, and there's also the opportunity to teach this topic to medical and nursing students. Moreover, in the future, I'd like to see more CSRC papers in mainstream journals.

Typically, our focus has been on the premarketing space, including the regulatory requirements for approval. Even with the best of intentions, though, we can't expect to learn everything we need to know from randomized trials. We need to put more energy into observational post-marketing research, where the rules of engagement are less clear and statistical and methodological challenges remain. I'm especially looking forward to this year's CSRC Annual Meeting and the next day's think tank, which will focus on post-marketing data collection for assessing cardiovascular safety. It may take a few years for us to catch up in the post-marketing arena, but this think tank will be a big step forward.

"Our members did a great job developing partnerships and keeping lines of communication open for the greater good of providing safer drugs and devices to market sooner."

THERESSA **WRIGHT**

Theressa Wright, MD

Senior Medical Fellow for Cardiology & Early Phase Medicine, Eli Lilly and Co.

Since the formative years of the CSRC, I've truly appreciated and enjoyed being Eli Lilly and Company's representative. It is an honor to partner with distinguished colleagues from industry, academia, and government with the common mission of making patient safety paramount in the advancement and understanding of cardiac safety.

A common theme early in the history of the CSRC was our focus on proarrhythmic potential for non-antiarrhythmic drugs as defined by QT/QTc interval prolongation. Through CSRC's interests and support of research, coupled with its unique ability to collaborate with various stakeholders from industry, academia, and governments, we have been able to demonstrate that, with carefully orchestrated nonclinical and clinical early-phase assessments of drugs and devices, we can successfully evaluate cardiac-safety risks early in the development cycle. These landmark advancements have been a 10-year journey. Now many are accepted paths for drug and device development in the United States and abroad. Effective collaborative efforts have enhanced the ability to protect patients earlier while allowing for a huge reduction in time and cost in the development of drugs and devices. In short, patients benefit from our role in getting effective, safe drugs and devices to market sooner.

There have been many challenges during this 10-year journey of improving cardiac-safety assessments. We sought answers to such questions as: What are the right parameters? Should the early phase assessment be done for all drugs, or should some be excluded? If a drug was previously excluded, is an assessment needed if filing for a new indication? How can we maintain objectivity? Despite these uncertainties and many others, our members did a great job developing partnerships and keeping lines of communication open for the greater good of providing safer drugs and devices to market sooner.

The CSRC has and shall continue to evolve over the years. Originally, our scope was primarily focused on cardiovascular risks and identification of appropriate cardiac-safety biomarkers. Due to our ability to partner effectively, we've now broadened our bandwidth. New representatives from industry, academia, and government agencies are joining the CSRC because they believe in and support the collaborative and effective approach through which the CSRC tackles important cardiac-safety questions.

I am very proud and honored to be part of the CSRC. Our consortium has strong leadership, hardworking teams, and dedicated committees, but I'd especially like to highlight the major contributions of Dr. Valarie Morrow, CSRC program/project coordinator. Dr. Morrow's personable, professional talents and expertise have taken organizational responsibility to a new high. She successfully interacts and engages with individuals and organizations at all levels. She is instrumental in organizing productive face-to-face and teleconference meetings that may involve hundreds of people. Although it is not easy, she is able to enlist key people for critically important meetings in a timely manner. It takes a unique personality to work with diverse groups and bring them together for a common cause under the umbrella of the CSRC. Dr. Morrow's ability to effectively execute and implement is just one of the many reasons for the consortium's success.

"Over the next 10 years, I expect the consortium to continue to grow and make an impact on drug development, and I anticipate greater patient involvement in our projects."

VALARIE **MORROW**

Valarie Morrow, MD

Project Manager, Duke Clinical Research Institute

As the project manager for the CSRC, my perspective differs from that of other members. I have two main goals in this leadership role: first, to make everyone involved with the CSRC understand that they are an important part of the organization; and second, to keep the consortium and its projects moving forward.

The greatest challenge we've addressed has been to give all stakeholders an equal voice in cardiac-safety discussions, including companies of all sizes and several regulatory bodies. The CSRC has stepped up to the plate to provide a platform where all voices can be heard in a pre-competitive or post-competitive space. I'd describe the CSRC as an organization where collaboration is key, and where issues that affect all stakeholders are addressed in an efficient, non-bureaucratic manner. I would definitely encourage anyone with an interest in cardiac safety to become involved.

A key achievement has been for the consortium to continue to grow and attract outstanding companies and regulators. The number of members has increased, bringing a level of expertise not found in most consortia. We've succeeded in bringing in experts in all of our focus areas and work collaboratively with them to move the field forward.

We've expanded from the starting point of building an ECG database to currently examining diverse topics such as pediatrics and stem cell drug development. The CSRC continues to gain momentum due to the high quality of our projects, think tanks, and papers. Over the next 10 years, I expect the consortium to continue to grow and make an impact on drug development, and I anticipate greater patient involvement in our projects.

Most of all, I have enjoyed getting to know the CSRC's members and having the opportunity to work with some of the greatest minds in cardiac safety and drug development. I have learned a lot about cardiac safety and the importance of collaborative relationships for the betterment of public health.

Interactions with individuals such as Dr. Mitchell Krucoff and members of the Executive Committee over the years have helped me grow professionally. I am happy to say that because of these interactions, I can call many of you friends.


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