



CSRC White Papers

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Ignacio Rodriguez, MD

Clinical Safety Risk Management
Hoffmann La Roche

ignacio.rodriguez.ir1@roche.com



CSRC “White Papers”

- Position papers usually cover challenging areas of cardiovascular safety, describing what is known and unknown, and propose paths forward to address such knowledge gaps
- Focus on the available scientific data for a particular matter, explore areas for further evaluation, and present potential approaches to better understand cardiovascular safety issues in drug development
 - No guidance documents
 - Consensus is good but not mandatory
 - Summary of CSRC sponsored ‘Think Tanks’
- CSRC ‘White Paper’ publication policy available on-line
<https://www.cardiac-safety.org/>

Current Status

9 published papers (3 in 2009, 5 in 2010, 1 in 2011)

- Cited in 26 (non-CSRC) published papers

4 white paper writing groups actively working

3 white paper writing groups being formed

All involving academia, industry and regulators

Published papers

**Troponin measurements during drug development—
considerations for monitoring and management of
potential cardiotoxicity: An educational collaboration
among the Cardiac Safety Research Consortium, the
Duke Clinical Research Institute, and the US Food and
Drug Administration**

L. Kristin Newby, MD, MHS,^a Ignacio Rodriguez, MD,^b John Finkle, MD,^c Richard C. Becker, MD,^a
Karen A. Hicks, MD,^d Elizabeth Hausner, DVM,^d Ruth Chesler, MD,^d Courtney Harper, MD,^d Shari Targum, MD,^d
Brian R. Berridge, DVM, PhD,^c Eric Lewis, MD,^c Dana B. Walker, MD,^f Colin Dollery, BSc, MB, ChB,^g
J. Rick Turner, PhD,^h and Mitchell W. Krucoff, MD^a *Nutley, NJ; Upper Providence, PA; Silver Spring, MD;
Durham, NC; Wallingford, CT; and London, United Kingdom*

Am Heart J 2011;162:64-73

White Papers in Progress

- **Working Title**
 - **Methodologies to characterize the QT/QTC interval in the presence of drug-induced heart rate changes or other autonomic effects**
- **Leader**
 - Christine Garnet (Christine.Garnett@fda.hhs.gov)
- **Current Status**
 - Incorporating suggestions from the open forum discussion (webinar June – 2011)
- **Expected submission date**
 - 4 Q 2011
- **Key messages/objectives**
 - Summary of reasonable approaches to evaluate the QT or QTc interval for therapies that have HR and/or autonomic effects.
 - Some methods include: individualized QT/RR correction, PK-PD modeling, Holter bin analysis, dynamic beat-to-beat analysis, and QT assessment during constant heart rate (i.e., pacing).
 - At present, there is not enough information to select one as the optimal method. Therefore, the group chose to describe methods that can improve this assessment and encourage further research in the area.

White Papers in Progress

- **Working Title**
 - Non-QT interval ECG evaluation in clinical development (emphasis in PR and QRS)
- **Leader**
 - Adel Nada (adel.nada@abbott.com)
- **Current Status**
 - Incorporating regulatory feedback for first draft
- **Expected submission date**
 - 2012
- **Key messages/objectives**
 - Clinical relevance of PR and QRS interval monitoring as safety biomarkers in clinical development
 - Epidemiological evidence and expected variability
 - Expert and consensus state-of-the-art understanding of how to best profile drug induced PR and QRS liabilities in clinical development

White Papers in Progress

- **Working Title**
 - Scientific discussion on blood pressure evaluation in clinical development
- **Leader**
 - Jeff Heilbraun (jheilbraun@medifacts.com)
- **Current Status**
 - Working on the first draft
- **Expected submission date**
 - 2012
- **Key messages/objectives**
 - Relevance of BP as a safety biomarker in clinical development
 - BP assessment methodologies
 - BP monitoring in clinical development
 - Evaluation of BP changes
 - Issues to consider in special populations & indications

White Papers in Progress

- **Working Title**
 - **Cardiac imaging approaches to evaluate drug-induced myocardial dysfunction and heart failure**
- **Leader**
 - Jennifer Christian (jennifer.b.christian@gsk.com)
- **Current Status**
 - Finalizing the first draft
- **Expected submission date**
 - 2012
- **Key messages/objectives**
 - Importance of monitoring cardiotoxicity by cardiac imaging
 - Focus on echocardiogram, nuclear imaging, and MRI (evaluation of advantages and disadvantages of each technique)
 - Application of imaging techniques in preclinical evaluation, clinical trials and in clinical practice
 - Future directions

White Papers in Progress

- **Working Title**
 - **Designs and statistical approaches to assess CV risk of new type 2 diabetes therapies in development**
- **Leader**
 - Mary Jane Geiger (geiger_mary_jane@lilly.com), Brenda Gaydos (gaydos_brenda@lilly.com)
- **Current Status**
 - Proposal endorsed by the SOC
 - Writing group is being formed
- **Expected submission date**
 - tbd
- **Key messages/objectives**
 - Propose concrete options to meet current FDA regulatory requirements regarding evaluation of major cardiovascular endpoints for compounds in development to treat diabetes

White Papers in Progress

- **Working Title**
 - Practical considerations for assessing cardiac repolarization of diabetes drugs
- **Leader**
 - Theresa Wright (theressa.j.wright@lilly.com), Helle Linnebjerg (linnebjerg_helle@lilly.com), and Ingrid Hensley (hensley_ingrid_edgemon@lilly.com)
- **Current Status**
 - Proposal endorsed by the SOC
 - Writing group is being formed
- **Expected submission date**
 - tbd
- **Key messages/objectives**
 - Summarize literature available on glucose- and insulin-mediated changes in the QT interval
 - Discuss preclinical and clinical challenges to evaluate drug-induced QT prolongation for compounds that cause changes in insulin and/or glucose levels
 - Discuss alternatives for thorough QT/QTc evaluation for agents that cause hyperinsulinemia and hypoglycemia

Proceedings from Think Tank

PEDIATRIC THINK TANK

•Leaders

- Katherine E. Bates (BATESKE1@email.chop.edu)
- Vicky Vetter (VETTER@email.chop.edu)

•Status

- Finalizing the first draft

•Expected submission date

- 2012

•Key messages/objectives

- Summary of the discussions
- Challenges in drug and device pediatric development
- Suggestions for future directions

Other initiatives under discussion

- Clinical safety options to monitor potential drug-induced changes in left ventricular function
- Developing drugs with preclinical or early clinical cardiovascular safety signals: Review of marketed compounds that had signals for cardiotoxicity
- Novel cardiovascular biomarkers
- Cardiovascular safety monitoring in subpopulations
 - Pediatrics (ECG, Blood Pressure, devices, etc)
 - Oncology
 - Specific indications
- *<Add your proposals here>*
- *<Who wants to do what?>*

Comments

- Time required to complete the paper
- Conflicts
- **Goodwill**
- Consensus
 - “good to have” but “no need to have”
- Present areas of controversy and areas where further research is needed
- No guidance documents or regulatory requirements
- Great forum for knowledge sharing!

Thank you



Published papers



- New precompetitive paradigms: focus on cardiac safety. Finkle J, et al. [Am Heart J. 2009;157:825-826.](#)
- Assessing proarrhythmic potential of drugs when optimal studies are infeasible. Rock EP, et al. [Am Heart J. 2009;157:827-836.](#)
- Current challenges in the evaluation of cardiac safety during drug development: Translational medicine meets the Critical Path Initiative. Piccini JP, et al. [Am Heart J. 2009;158:317-326.](#)
- 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. Al-Khatib SM, et al. [Am Heart J. 2010;159:17-24.](#)
- Evaluation of ventricular arrhythmias in early clinical pharmacology trials and potential consequences for later development. Min SS, et al. [Am Heart J. 2010;159:716-729.](#)
- 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. [Am Heart J. 2010;160:619-626.](#)
- Electrocardiographic assessment for therapeutic proteins—scientific discussion. Rodriguez I, et al. [Am Heart J. 2010;160:627-34.](#)
- The Cardiac Safety Research Consortium electrocardiogram warehouse: Thorough QT database specifications and principles of use for algorithm development and testing. Kligfield P. et al [Am Heart J. 2010;160:1023-8](#)
- Troponin measurements during drug development - considerations for monitoring and management of potential cardiotoxicity: An educational collaboration among the Cardiac Safety Research Consortium, the Duke Clinical Research Institute, and the US Food and Drug Administration Newby LK et al [Am Heart J. 2011;162:64-73.](#)