CSRC White Papers

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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

8 published papers (3 in 2009, 5 in 2010)

4 white papers in progress

initiatives in planning phase

All involving academia, industry and regulators

Cardiac Safety Research Consortium ECG Warehouse: Database specifications and principles of use for algorithm development and

Accepted for publication Am Heart J, 2010

Developing the Safety of Atrial Fibrillation Ablati
Registry Initiative (SAFARI) as a collaborative

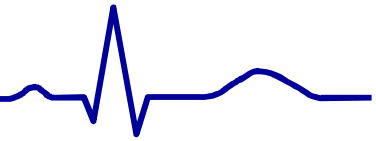
Am Heart J. 2010; 160(4):619-626

White Papers in Progress

- **Working Title**
  - **Troponin Measurements during drug development - Points to consider for monitoring and management of potential cardiotoxicity.**
- **Leaders**
  - Kristin Newby (newby001@dcri.duke.edu) and Rick Becker (richard.becker@duke.edu)
- **Current Status**
  - Open forum held on June 28th 2010 at the FDA Headquarters
  - Working on the final version
- **Expected publication date:**
  - 1Q 2011
- **Key messages/objectives**
  - Determine the role of troponin for assessing potential cardiotoxicity in all phases of drug development
  - Present practical approaches to use serum troponin as a biomarker for detecting potential cardiotoxicity in clinical studies. With recommendations on how to monitor cTn in clinical development, and how to interpret potential signals

White Papers in Progress

- **Working Title**
  - **QT/QTc Evaluation for Drugs with Autonomic Effects**
- **Leader**
  - Christine Garnet (Christine.Garnett@fda.hhs.gov)
- **Current Status**
  - Third draft complete – Open discussion ~ 1Q2011
- **Expected publication date**
  - 2 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 the 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**
  - First draft completed
- **Expected publication date**
  - 3Q2011
- **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 publication date**
  - 2nd half 2011
- **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

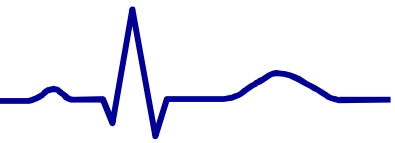
Other initiatives planned

- Procedures from Think-Tanks
  - TransRadial
  - Pediatric
  - Diabetes
- 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
- Cardiovascular safety monitoring in subpopulations (e.g. blood pressure in pediatrics, cardiotoxicity in oncology, etc)
- <*Add your proposals here*>

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



New precompetitive paradigms: focus on cardiac safety. Finkle J, et al. Am Heart J. 2009;157:825-

Assessing proarrhythmic potential of drugs when optimal studies are infeasible. Rock EP, et al. Am

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. 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 stakeholder critical path registry model: A Cardiac Safety Research Consortium “Incubator”

Electrocardiographic assessment for therapeutic proteins—scientific discussion. Rodriguez I, et al.