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Cardiac Safety Research Consortium (CSRC)

Annual Meeting, February 19, 2015

Proposed new CSRC initiative –
Collaborative Research Project:

Arrhythmia Normal Limits in Healthy Clinical Research Volunteers

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- Purpose: To define the normal ranges of arrhythmia findings from Holter recordings in healthy clinical research volunteers
- Rationale:
  - There is increasing use of Holter recordings in early human phase studies to perform intensive ECG monitoring
  - Arrhythmia data is easily derived from these studies
  - Arrhythmia findings are important biometric information
  - Researchers lack the ability to interpret arrhythmia data
  - Arrhythmia findings are either left unknown or ignored
- Benefits:
  - This will enhance determination of drug effects in clinical situations with a high potential for arrhythmia such as COPD and CHF
  - This will help define the appropriate use of arrhythmia data
  - This is in accord with the FDA's plans to require delivery of Holter data as part of their standard review

What is “normal” cardiac rhythm

DISEASE	PREVALENCE	STATISTIC SOURCE
ARRHYTHMIAS OVERALL	14.4 million in US	53 per 1,000 NIH study 1995
SINUS NODE DISEASE	N/A	No Information
TACHYCARDIA	4.4 million in US	16 per 1,000 NIH study 1955
ATRIAL FIBRILLATION	2.0 million in US	2 million NHLBI study 1995
WPW SYNDROME	272,000 in US	1-3 per 1,000 worldwide Genetics Home Ref. website
NON-SUSTAINED VEN. TACHY.	2.5% women > 65, many reports in seemingly normals	Katritsis and Camm 2003, many other authors
SINUS ARREST	Elderly former athletes	Jensen-Urstad 1998
SUPRA VENTRICULAR TACHY.	Unknown	No Information
PACs	Unknown	No Information
VPCs	Unknown	No Information
OTHER SERIOUS ARRHYTHMIAS	Unknown	No Information

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- Unique Resources of CSRC: Vast amount of data has been collected by core ECG labs during TQT studies during baseline and placebo sessions from carefully screened populations monitored under strict study conditions
- Sample estimate:
  - 5 labs, each with 20 protocols
  - Each protocol with 40 subjects with 2 study days each (Day -1 and Placebo)
  - = 8000 Holter sessions
  - = 4000 subjects
- Endpoints:
  - Normal ranges of key findings
  - per age and sex group
  - circadian variation: day vs night
  - Inter-subject variability
  - Intra-subject variability

- Practical Steps:
  - Determine labs willing to participate
  - Establish steering group to set goals
  - Select diagnostic entities to be determined
  - Create standard diagnostic criteria
  - Determine standard reporting format
- Each lab review archived TQT protocols
  - Determine appropriate studies
  - Identify study periods with no active treatment
- Review Holters
  - Automated analysis
  - Technician review
  - MD review of unusual or unexpected findings
- Export data
  - Anonymized protocol identifier
  - Subject demographics: age, sex
  - Holter findings

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- Assemble and quality control data
- Statistical Analysis
- Medical writing
  - Present findings
  - Present conclusions
- Independent Review
  - Review methods
  - Review results
  - Co-author report
- Prepare for publication
  - Present at CSRC meeting
  - Prepare for journal submission
- Create CSRS position statement on practicality and utility of arrhythmia determination in early human studies