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

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