



**Part A: QTc Exposure-Response Modeling Workshop: What is Required?**  
**Part B: Endpoints When Treating VT/VF in Patients with ICDs**

**December 7th, 2016**  
**Meeting Agenda**

**7:45am-8:00am Breakfast**

**Part A**

**8:05am-8:20am Session I:** Historical overview of the ICH E14 guidelines and the evolution to including C-QTc modeling **Christine Garnett, PharmD (FDA)**(15min)

**8:20am-9:00am- Session II:** The non-modelers version of expectations around the statistical analysis plan, report, and model(s) **Steve Riley, PharmD, PhD (Pfizer)**(40min)

**9:00am- 9:30am Session III:** Regulatory perspective for using C-QTc as the primary analysis: trial design, ECG quality evaluation, evaluation of modeling/simulation results, and decision making **Dhananjay Marathe, PhD (FDA)**(30min)

**9:30am-10:30am Session IV:** Clinical parameters of interest for concentration-QTc analysis of small studies **Borje Darpo, MD (iCardiac)**(15min)

**Discussion (45min)**

**Panelist: All speakers and Lars Johannesen, PhD (FDA)**

**Break: 10:30-10:45**

**Part B**

**Objective:** Reach consensus on regulatory- acceptable endpoints for clinical trials in ICD patients with ventricular arrhythmias. Definitions? Sources of Data? Analytical approaches?

**CSRC Welcome & Introduction**

**10:45am-11:15am Session I:** Background/Overview of Previous Endpoints

- VT/VF Endpoints used in previous ICD trials (please specify and where possible comment on strengths and weaknesses) and natural history of VT/VF variability. What are the pros and cons of different endpoints? **Wojciech Zareba, MD, PhD (University of Rochester Medical Center)**(10min)
- VT/VF Endpoints used in previous drug trials. What are the pros and cons of different endpoints?

**Discussion (20min)**

**11:15am-1:05pm Session II:** Endpoint Types: Strengths, limitations of specific endpoints or combinations of prospective endpoints

- Device Endpoints: eg Shocks, Shocks meeting certain criteria, ATP (is there a role?), discuss how to account for ICD programming- standardized in some manner? **Mintu Turakhia, MD (Stanford)**(10min)
- Clinical Endpoints: eg Death, arrhythmia, storm, VT ablation, and additional morbidities **Preston Dunnmon, MD (FDA)**(10min)
- Patient Reported Endpoints: eg QoL, Anxiety Scale, activity (?accelerometer) **Samuel Sears, PhD (East Carolina University)**(10min)
- Economic/Utilization Endpoints: eg Hospitalization, ER visits **Peter Kowey, MD (Lankenau Medical Center)**(10min)
- Potential effects of drugs on ICD function (e.g., lack VT recognition, threshold/impedance changes) and potential safety endpoints **James Reiffel, MD (Columbia)**(10min)

**Discussion (60min)**

**Lunch 1:05pm-1:35pm**

Potential endpoints that are most appropriate, relative strength and weaknesses. How should ablation be considered? Role and control of complementary therapies? How do you account for natural variability in arrhythmia? How do you account for ICD programming? How does length of trial effect evaluation? How do we deal with strength of evidence? What outcomes might need adjudication?

**1:35pm-3:15pm Session III:** Prioritization of Endpoints for VT/ VF Approval

- Endpoint analysis- secondary endpoints and alpha spending; potential use of ranked outcome measures **Jim Hung, PhD (FDA)**(10min)
- Composite Endpoints and potential safety endpoints(10min)



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- Key Role of Secondary Endpoints- support a claim vs supporting the primary endpoint(s). What is required for a claim **Norman Stockbridge, MD, PhD (FDA)**(10min)
- Primary Endpoints used for approval (this talk will need to be based on the Think Tank discussions **Jonathan Seltzer, MD (ACI Clinical)**(10min)

**Discussion (60min)**

**3:15pm-4:30pm:** Which endpoints are strong enough to stand alone to recommend approval? What are the design factors necessary for single and or composite endpoints to recommend approval? When should composite endpoints be used? What are methods for assessment of composite endpoints? Should components of composite endpoints be rank-ordered? What is proper safety –efficacy balance?

**Discussion (60min)**

**CONSENSUS RECOMMENDATIONS (15 min)**

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