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OPC

The Use of Objective Performance Criteria in Medical Device Trials: An Industry perspective

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Outline

- What is an OPC
- Trial designs, benefits, and use
- Why Medical Devices?
- Global vs. Company-specific
  - Examples
- Disadvantages, and considerations

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What is an Objective Performance Criteria?

- Fixed number/bar for performance in lieu of control
- Used for endpoints in demonstrating the safety or effectiveness of a device
- Based on historical data
- Objective/recognized as or agreed to be an acceptable value
- Clinical value

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What is an Objective Performance Criteria?

Trial Design for OPC

- **RCT is still the gold standard**
- **New devices and indication trials are nearly always RCT**

"In some cases, a randomized trial with an active control may not even be practical or feasible. For example, in a rapidly advancing technology, it may be difficult and, sometimes, unethical to recruit patients for the control arm. In such cases, a single-arm study is often conducted."

Campbell G, Yue L, Pennello G, Barrick M. Medical Devices. Encyclopedia of Biopharmaceutical Statistics. 2003, Marcel Dekker

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Trial Design for OPC

Design hierarchy of evidence for submissions

- **RCT**
- **Non-randomized concurrent control**
- **Single arm trial with historical control**
- **Single arm trial with OPC based on historical data**
- **Field following – no endpoints – observe safety data**
- **No clinical trial – bench testing and GLP**

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Trial Design for OPC

When is it not appropriate to use OPC?

- **First-in-class devices (eg. Drug-eluting stents)**
- **New indication**
- **Comparative claims**
- **Available studies are too historical**
- **Historical data unavailable to the sponsor**

Trial Design for OPC

When may it be appropriate to use OPC?

- **Well established standard of care therapy**
- **Extensive experience with device type in question**
- **No apparent new concerns regarding safety or effectiveness**
- **If important new features are added to a device, i.e. diagnostic features**

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Benefits

- **May reduce sample size (as compared to RCT)**
  - **Fewer patients at risk**
- **May reduce the risk to the individual patient**
- **May save time and money**
- **Static criteria for success**
- **Keep the rapid pace of new technology development**

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Benefits – Reality Check

Use of OPC does not mean we can relax our standards

- **Trial must be well designed to hypothesis**
- **Still must control alpha for multiplicity**
- **Mitigation of bias**
- **May require more planning on conduct or trial and analysis of results**
- **Disadvantages**

Why Medical Devices?

Devices vs. Drugs

- **Development Differences**
  - **Increments**
  - **Pace**
- **Nature of therapy or use**
  - **Diagnostic vs. therapeutic**
  - **Local vs. systematic**
  - **User dependent / user error**

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Why Medical Devices?

- Often a great deal of prior information associated with a device under study
- Mechanism of action is often simple, local, and well understood
- Rapid pace of technology development
  - Smaller
  - Longer lasting (battery)
  - Easier to use, implant, remove, etc.
  - Additional functionality not core to device

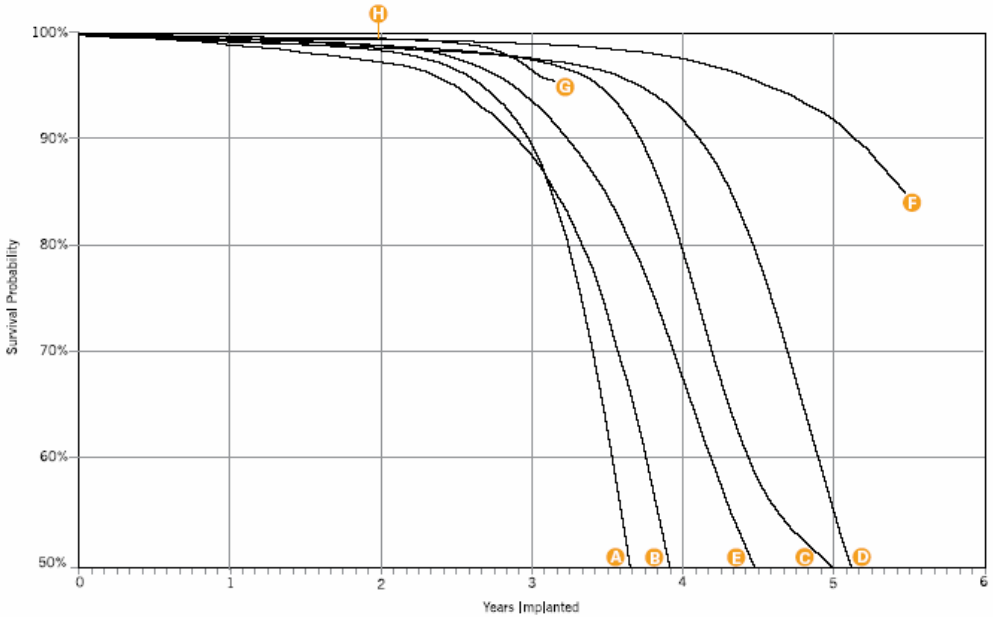
Why Medical Devices?

Generation-to-Generation Product Comparisons

GENERATION-TO-GENERATION PRODUCT COMPARISONS

A fundamental goal of the Boston Scientific CRM Quality System is to demonstrate performance improvement with each successive product introduction. As part of our Corrective and Preventive Actions (CAPA) system, data from field performance, suppliers, and manufacturing operations are monitored to identify opportunities for improvements in existing products or subsequent generations. While not the case in every generation, the net result is high and improving performance in successive product generations. Shown below are survival probability comparisons between older and newer product generations, for ICDs. This graph demonstrates Boston Scientific's ability to maintain high performance while simultaneously reducing device size, increasing longevity, and providing enhanced diagnostic and therapeutic features.

ICD Evolution



High and rising performance while:

- √ *Reducing size*
- √ *Increasing longevity*
- √ *Expanding therapeutic features*
- √ *Enhancing diagnostics*

1991 — *Decreasing Size while Increasing Longevity and Enhanced Diagnostic and Therapeutic Features* — 2004

A	B	C	D	E	F	G	H
VENTAK P/PRx 145 cc	VENTAK P2/P3/ PRxII/PRXIII 97-144 cc	VENTAK MINI I/II/III/IV 39-78 cc	VENTAK AV/AVII/ AVIII/VR 51-85 cc	VENTAK PRIZM 38-45 cc	VENTAK PRIZM 2 31-32 cc	VITALITY/VITALITY AVT 30-40 cc	VITALITY 2 30-35 cc

Why Medical Devices? Regulatory Thoughts

Least Burdensome

- **Included in valid scientific evidence is "studies and objective trials without matched controls." (21 CFR 860.7 (c)(2)) "from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.**

Global vs. Company Specific

Global

- **OPC applies to product or product class across industry**
- **Agreed upon by interested/affected parties (regulatory, industry, physician community, academics)**
- **OPC is or becomes recognized standard**
- **Based on historical data from many sources**
- **Example: prosthetic heart valves**

Global Example: Heart Valves

Background

- **Implants since 1960**
- **Gersh et al.**
- **Draft Guidance**
- **Comment period**
- **Guidance developed**
- **Sources peer reviewed literature –**
- **Experience of 10,000 patients followed for 45,000 patient years**

Global Example: Heart Valves

Guidance – what does it say?

- **OPCs (average rates) for 14 complication rates ranging from 0.3% to 3.5% per year**
- **Significantly less than twice the OPC**
- **800 pt years required**

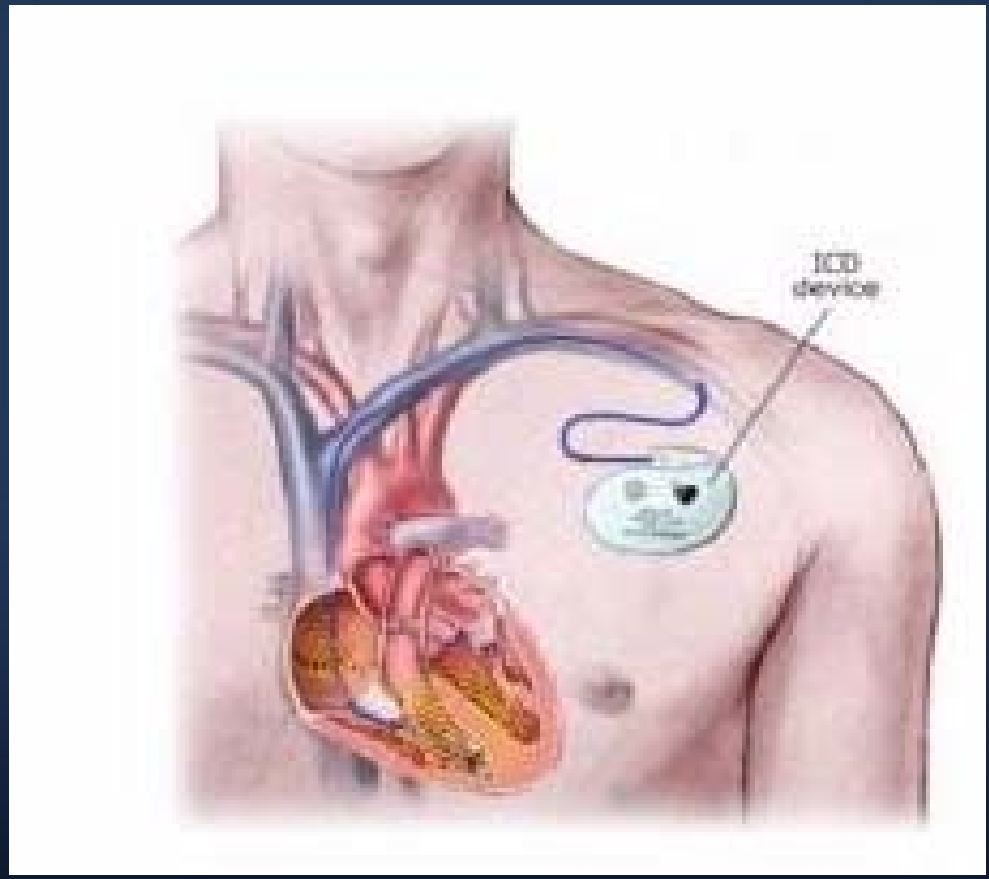
Global vs. Company Specific

Company specific

- **Based on one company's historical data**
- **Single product line**
- **Sound justification**
- **Negotiation/agreement**
- **Reassessed after each relevant trial**

Company Specific Example: ICD

- **New ICD with new detection algorithm intended to improve specificity of detection**



Company Specific Example: ICD

- **New detection algorithm**

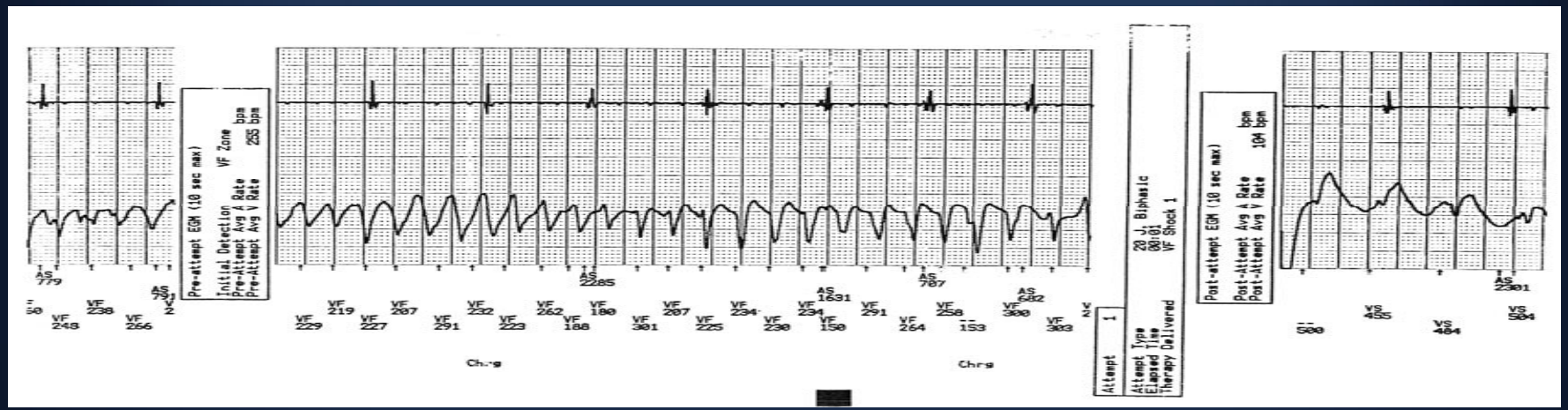
VF

Arrhythmia detection

VF – Device charging

Shock Delivered

Normal rhythm



Company Specific Example: ICD

Endpoints

- **Effectiveness was sensitivity and specificity**
- **Safety: detection time: OPC**

Company Specific Example: ICD

- **Ho: Induced VT/VF detection time for the device (= t1) is greater than 3.52 seconds by at least 3 seconds.**
- **$(t1 - t2) - \Delta \geq 0$, where $\Delta = 3$ seconds**

- **Ha: Induced VT/VF detection time for the device (= t1) is not greater than 3.52 seconds by 3 seconds.**
- **$(t1 - t2) - \Delta < 0$, where $\Delta = 3$ seconds**

Company Specific Example: ICD

Why OPC?

- **ICDs have been successfully implanted delivering therapy for over a decade**
- **Very similar to previous generation device**
- **Detection time collected by device, well understood and a great deal of data**
- **Control adds risk**

Disadvantages/Difficulties

- **Interpretation/Claims**
  - **Does not support comparison**
  - **Cannot claim superiority or equivalence**

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What is an Objective Performance Criteria?

Disadvantages/Difficulties

- **Interpretation/Claims**
  - **Does not support comparison**
  - **Cannot claim superiority or equivalence**
- **Need for periodic/constant review and update**
- **Close attention must be paid to inclusion/exclusion criteria (assumption of identical populations)**

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Summary

- **Devices are different from drugs**
- **OPCs can be a useful tool to get the information we seek possibly faster and with reduced risk to patients if the disease and therapy are well known, well understood, well documented, and stable**
- **Need to understand the difficulties and disadvantages**

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