

Statisticians in Medical Device Post-Market Studies

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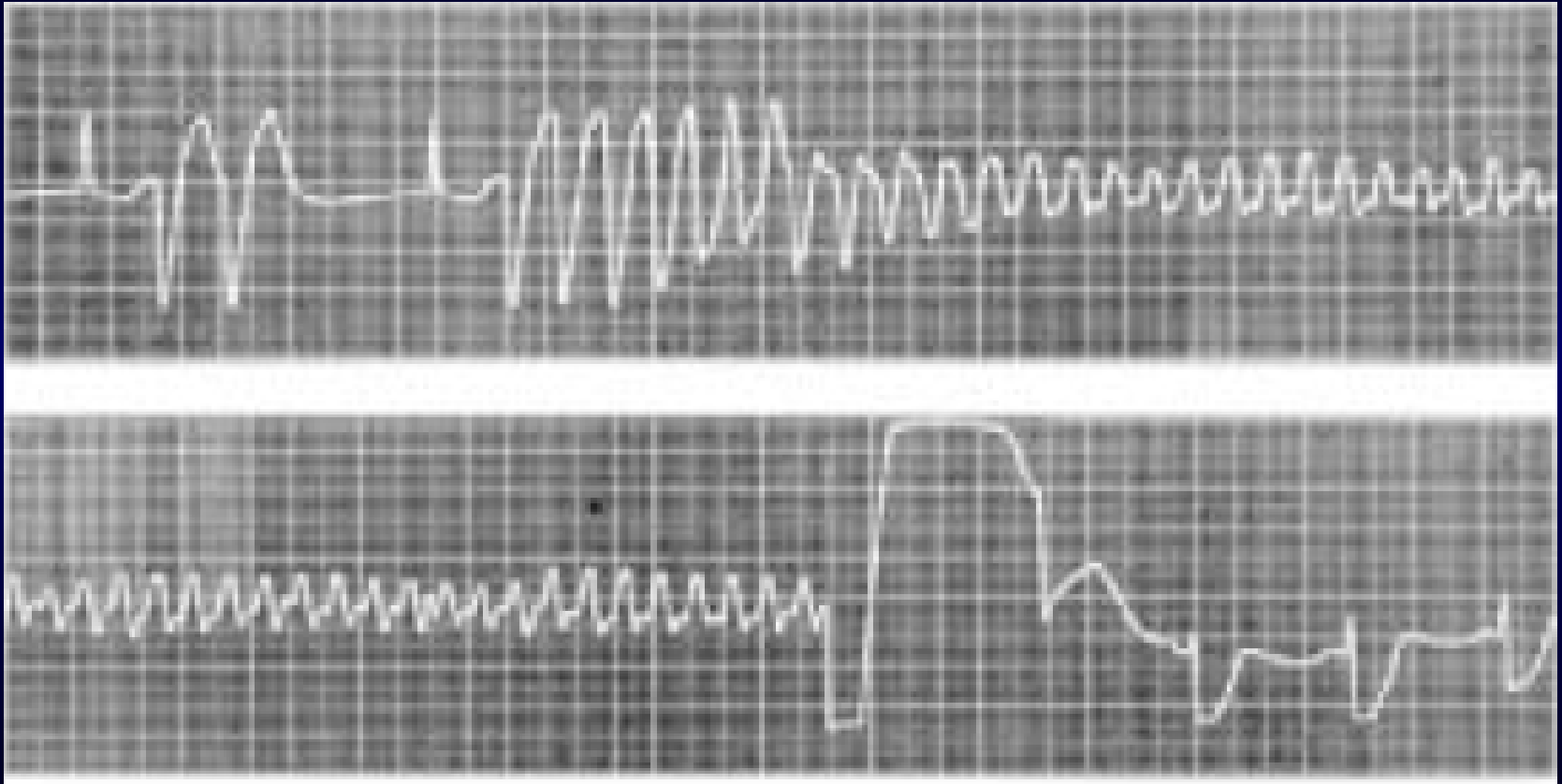
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Outline

- Background of implantable defibrillator studies
- Types of Postmarket Studies
- Future Directions

Shocking a heart



Source: Keelan, *Heartwise*, 2000





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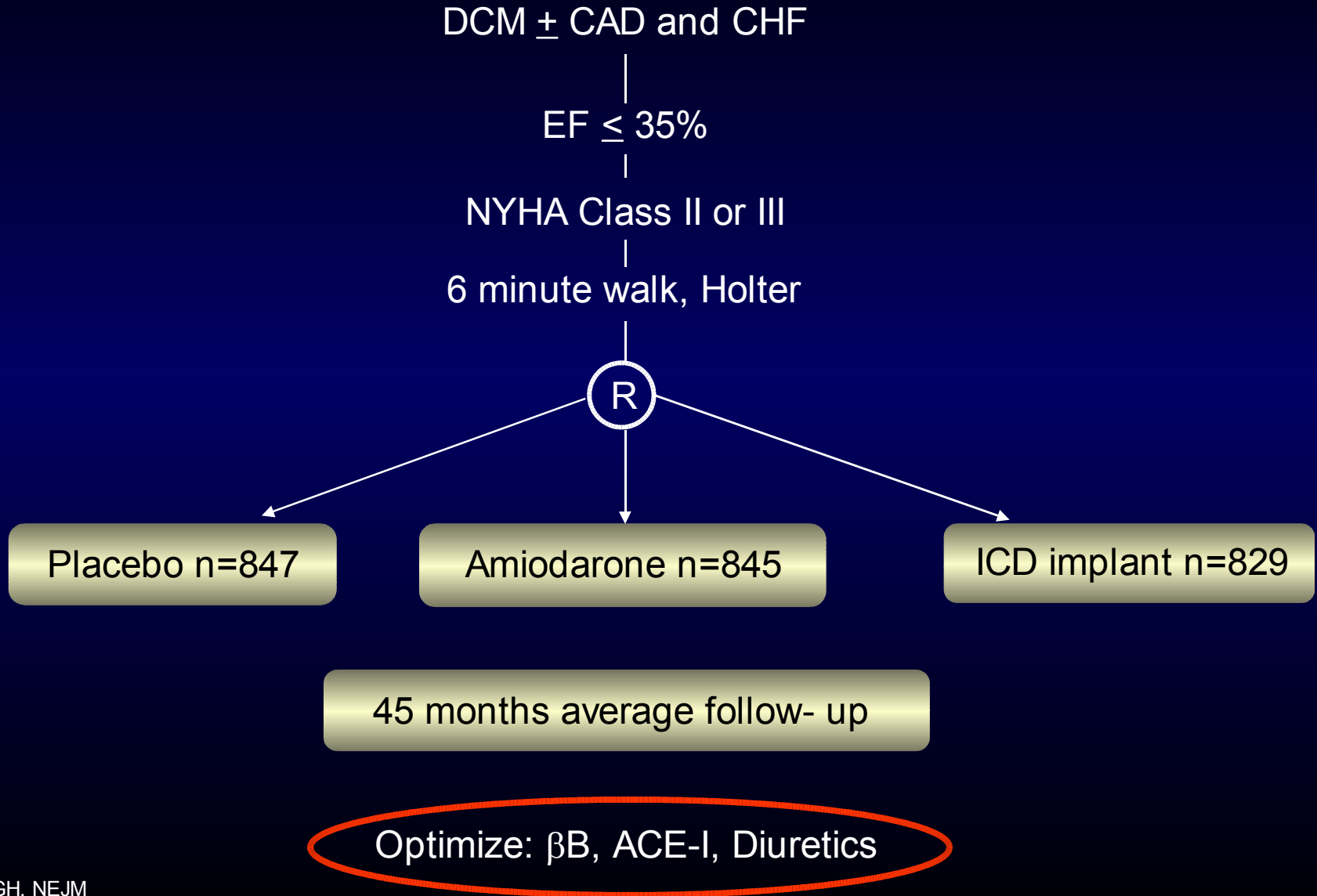
Four Types of Postmarket Studies

- #1 Industry-sponsored, academia-administered
- #2 Scientific Hypotheses
- #3 Registries
- #4 Product Performance Monitoring

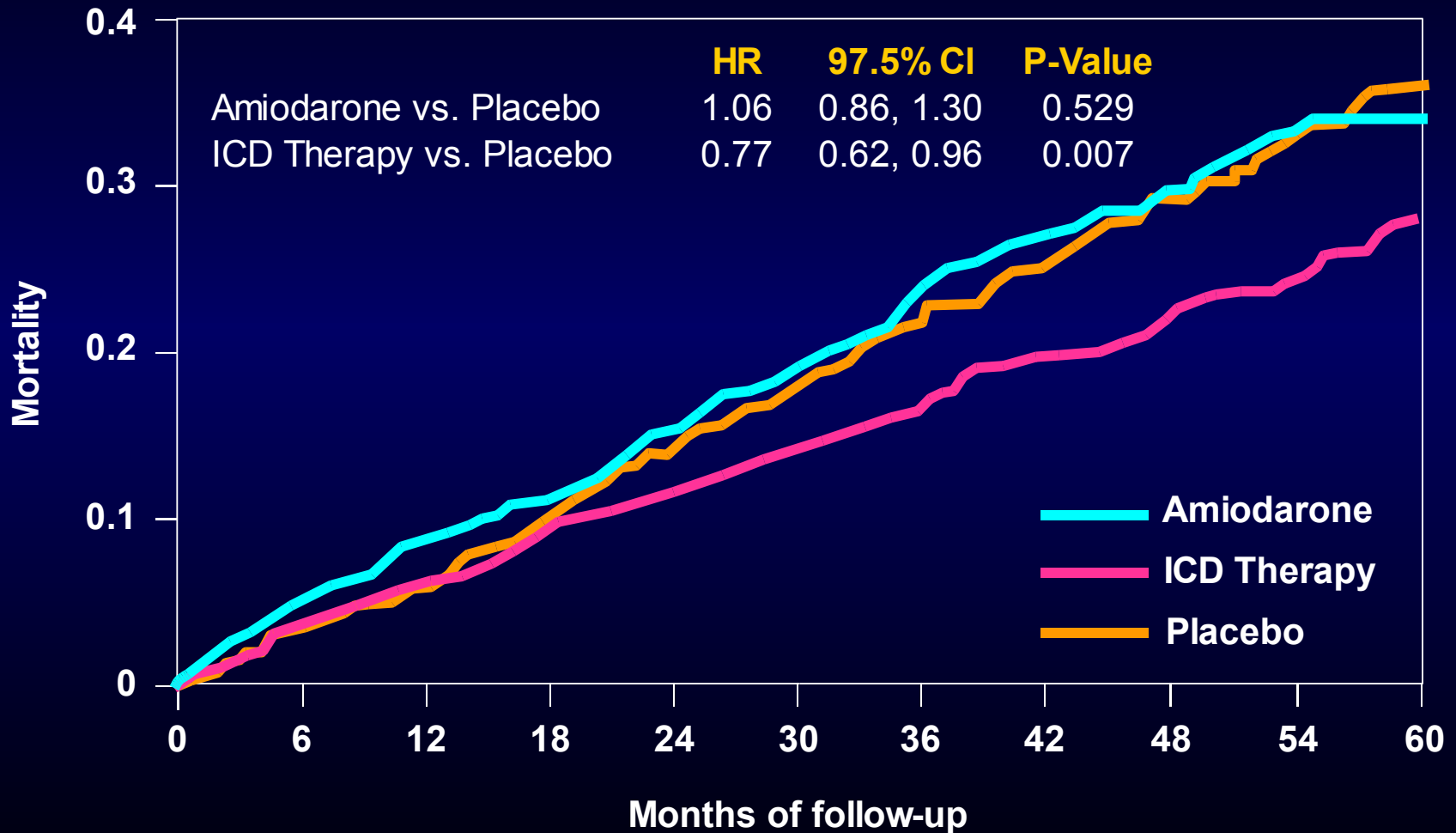
#1 - Academia-administered

- Example: SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial)
- Funded by NIH, Medtronic, Wyeth
- Study Design: 3 arms (ICD, amiodarone, placebo)
- Study Intent: Demonstrate that ICDs save lives when used prophylactically (primary prevention--new indication)

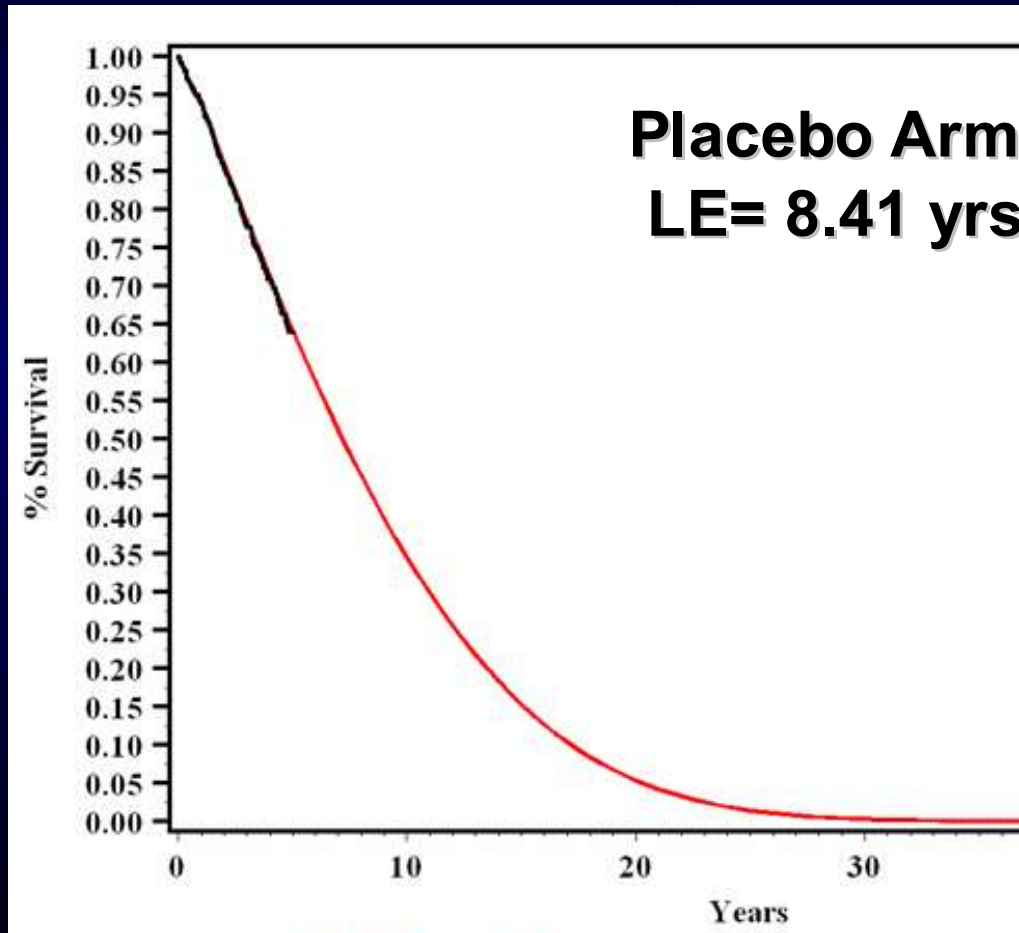
SCD-HeFT Protocol



Mortality by Intention-to-Treat



SCD-HeFT Cost-Effectiveness Analysis: Estimation of Life Expectancy



- LE estimation based on survival of 2521 SCD- HeFT pts (8447 person-yrs of follow-up)
- Modeled with 2-part Cox regression model (age based hazard function)
- Covariates included to permit subgroup estimates
- LE = area under lifetime survival curve

SCD-HeFT Cost-Effectiveness Analysis: Base Case Results

Lifetime costs ICD	—	Lifetime costs placebo		
\$159,147		\$90,759	\$68,388	
<hr/>			=	<hr/>
10.87 yrs LE ICD	—	8.41 yrs LE placebo	2.455 LYs	=

\$27,718 per life year
(undiscounted)

\$33,192 per life year added
(discounted at 3%)

\$36,886 per life year
(discounted at 5%)

Role of statistician

- Interact with academic, DCC statisticians
 - Not privy to interim results
 - Discuss analysis plans
 - Including cost-effectiveness
 - Interpret for corporate executives
- Calculate scenarios ahead of time
 - So company can quickly interpret analysis plan implications
- Eventually receive data
 - Oversee internal explorations

#2 - Scientific Hypothesis

- Typical: Randomized, possibly blinded, studying some new application of existing therapy
- Conducted by Sponsor
- Purpose: Investigate new programming strategy (within approved ranges) or in new types of patients (FDA IDE study)
- Often highlights unique feature of Sponsor's device
- Example: Simple Programming Strategy A vs Complicated Programming Strategy B
 - Endpoint: Noninferiority on proportion of patients shocked
- Example: Immediate shock vs delayed shock
 - Endpoint: superiority on proportions shocked
 - Endpoint: non-inferiority of time to arrhythmia termination

Role of Statistician

- Collaborate on Study Design
- Author stat section of protocol, SAP
- Team meetings
- Statistical programming
- Statistical analysis
- DMC reports
 - Usually unblinded
- Final reports
- Manuscripts, presentations

#3 - Registries

- No specified treatment regimen
- May have inclusion/exclusion criteria
- May study one or more types of devices
- Collect data in order to:
 - Understand physician practice patterns
 - Publish observational findings
 - Generate hypotheses for future research
 - Answer physician requests
 - Have basis for future sample size calculations
 - Have data to help understand the unexpected (e.g., battery depletion issues)

Role of the Statistician

- Collaborate on Study Design (light)
- Define objectives
- Author stat section of protocol, SAP
 - SAP takes relatively more work
- Statistical programming
- Statistical Analysis
- Publications (Manuscripts, abstracts)
- “Number cruncher” role

#4 - Product Performance

- Semi-Annual summary of product longevity
- Sent to FDA
- Published on Company Web Site
- Data are collected in various ways
 - Returned product
 - Passive and Active data collection
 - MDR, Adverse Event Reports



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CARDIAC RHYTHM MANAGEMENT PRODUCT PERFORMANCE REPORT

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Introduction

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ICD Charge Time

Advisories

References

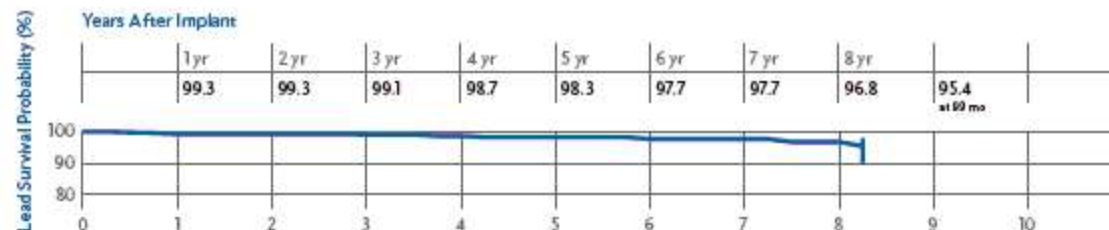
Technical Articles

Download Reports

4033 CapSure Z

Product Characteristics

US Market Release	Mar-94	Serial Number Prefix	LCA
Number of Leads Enrolled in Study	536	Type and/or Fixation	Transvenous, Vent., Tines
Complications in Study	9	Polarity	Unipolar
	Conductor Fracture 1	Steroid	Yes
	Failure to Capture 8		
Cumulative Months of Follow-Up in Study	26,989		
Advisories	None		



Role of the Statistician

- Participate in Standards (not typical)
 - ISO 5841 Implants for surgery -- Cardiac pacemakers -- Part 3: Low-profile connectors (IS-1) for implantable pacemakers
- Inherit legacy methods, code, data
- Statistical programming, validation
- Update report
- Meet new SOPs (e.g., validation, SAP)
- Determine impact of follow-up changes or analysis changes

The Progression

1. Strategic involvement

- Informing for decision-making
- ... But not decision-making
- Important role
- ... But still the sense that “We’ll call you if there is a statistical issue.”

2. Scientific involvement

- Little strategy
- Scientific Design/Analysis
- Blend of collaboration and number crunching

The Progression, cont'd

1. Number crunching

- Though some statistical work in SAP, defining questions, abstracts

2. Number crunching

- Just produce the report
- Don't change anything (except maybe colors, format, etc.)

Future Directions

- For small companies—
 - More post-markets studies?
 - More consultants/CROs?
- For large companies--
 - Statisticians becoming more strategically influential?
 - Statistician managers (high positions)
 - Need to step up in companies and demonstrate value
 - Take lead on questions of science, longevity, strategy, policy
 - Step outside our bounds
 - Parallel the Drug World, only younger

Future Directions, cont'd

- Longer-term safety assessments
- Outcomes studies
- Health economics
- Statistical challenges with increasing complexity of data
 - Device-based data
 - FDA Critical Path Opportunities List, guidance on patient-reported outcomes
 - Statistical opportunities
- QoL, QALYs
- Bayesian statistics?

Summary

- Medical Device World not monolithic
- Postmarket studies— how common?
- In large companies (w/ certain devices):
 - Four types of studies
 - Statistician role varies
- Ample opportunities for statisticians to lead
- As a profession, we should seize them