Cardiac Safety in Medical Product Development: Critical Path Collaborations, Public Private Partnerships & Comparative Effectiveness: Where Are We & Where Do We Need to Go?

CSRC Annual Meeting
Silver Spring, MD December 9, 2010

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Acknowledgements

- Steve Hammill, Sean Tunis, Dick Kovacs, Rita Redberg, John Rumsfeld and more
Health Care Reform
CER & Cardiac Safety

True “Tipping Points” for huge leaps in Cardiac Safety

ARRA Grants for CER
- Builds infrastructure also valuable for cardiac safety
- Funding for longitudinal databases

Improvement in patient matching
- ? Ever attaining the holy grail of UPI!

Increased alignment of payers (CMS), FDA, Industry and Academics
HealthCare Information Technology

More Tipping Points for Cardiac Safety

• Paper based records being replaced with:
  – Electronic Health Records
  – Device Telephonic Assessments
  – Computerized Databases
  – Standardized Data Definitions
  – Robust National Registries – although siloed and episodic/procedure based
  – Development of Linked Databases for true longitudinal assessment
Siloed Enterprises to Collaboratives

- “Mission Statement” of CSRC
- With CER infrastructure, IT developments, and the increased penetration of EHRs
  - Increasing “ease” of post-market surveillance
- Government now with increasing focus on CER but also Medical Errors and Safety
- Financial support ARRA and elsewhere along with the political climate offers huge opportunity
- We must through avenues such as CSRC build the collaboratives to leverage these wins
Registries for Evidence Development and Dissemination

- Concept
- Clinical Evidence
- Outcomes
- Multicenter Clinical Registries
- Guidelines
- Performance Indicators
- QI Initiatives
Tool for CER & Safety

Registries can:

- capture high quality clinical data efficiently
- be used for scientific discovery
  - track patients’ longitudinal care
  - track drugs/devices
  - be linked to biological/imaging data
- complement/support RCTs
  - and perhaps be backbone for these
National Cardiovascular Data Registry

Timeline and growth...

1998..... 2004 2005 2006 2007 2008 beyond

- CathPCI Registry
- ICD Registry
- CARE Registry
- ACTION Registry
- PINNACLE
- IMPACT Registry
- ICD Long Registry
- Imaging Registry
- AF Abl Registry
- PAD Registry
- Valve Registry
# Participants, Patient Records, & Vendors

<table>
<thead>
<tr>
<th>Name</th>
<th># of Participants</th>
<th># of Patient Records</th>
<th># of Certified Vendors</th>
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<tbody>
<tr>
<td>CathPCI</td>
<td>1350</td>
<td>10 million</td>
<td>16</td>
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<tr>
<td>ICD</td>
<td>1542</td>
<td>750,000</td>
<td>5</td>
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<tr>
<td>ACTION-GWTG</td>
<td>720</td>
<td>180,000</td>
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<td>CARE</td>
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<td>IMPACT</td>
<td>16 pilot sites</td>
<td>2000</td>
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<tr>
<td>PINNACLE</td>
<td>720</td>
<td>950,000</td>
<td>3 EHRs</td>
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Risk of Local Adverse Effects Following Cardiac Catheterization by Hemostasis Device and Gender

A Report from the NCDR in Partnership with the FDA

Dale Tavris, Syamal Dey, Albrecht Gallauresi, Richard Shaw, William Weintraub, Kristi Mitchell, Ralph Brindis

Grant from Office of Women’s Health, Food and Drug Administration
Risk of Local Adverse Effects Following Cardiac Catheterization by Hemostasis Device and Gender

A Report from the NCDR in Partnership with the FDA
Outcomes Following Coronary Stenting: A National Study of Long Term, Real-World Outcomes of Bare-Metal and Drug-Eluting Stents


Duke Clinical Research Institute
Duke University Medical Center
Goal and Population

Goal

- To examine comparative effectiveness and safety of DES vs BMS in a national PCI cohort

Study population

- All PCI pts ≥ 65 yo in NCDR CathPCI 1/04-12/06
- Follow up obtained through linkage to CMS inpatient claims data using indirect identifiers; 76% matched

Final cohort

- 262,700 pts
- 83% DES; 46% Cypher, 55% Taxus
Analysis

• **30 month outcomes**
  – Death, MI, Stroke, Revascularization, Major bleeding
  ● Overall and in important subgroups

▪ **Outcomes adjustments**
  – Inverse propensity weighted model (102 covariates)
  – Cox proportional hazards model (60 covariates)

▪ **Sensitivity analyses**
  • Results in ‘RCT-like’ population
  • Non-CV ‘cause’ of death
Outcomes Following Coronary Stenting
A National Study of Long Term, Real-World Outcomes of Bare-Metal and Drug-Eluting Stents
Landmark Display: Mortality
DES v BMS Population Sub-study

✓ To create a data set in which the national, real world outcomes following PCI can be assessed
✓ To examine the comparative effectiveness and safety of DES vs BMS
✓ To examine the comparative effectiveness in understudied and special populations:
  • Sex, age, race
  • Chronic kidney disease
  • Off label lesions
Off- Label Lesions

- 186,111 patients; Off label lesions in 128,507 (69%)
  - 109,734 (85%) received DES
  - 46% received SES and 54% received PES
- Specific lesions considered
  - 50% High risk, Type C
  - 12% bifurcation lesions
  - 6% in-stent restenosis
  - 6% chronic total occlusion
  - 4% left main lesions
  - 9% saphenous vein grafts
  - 1% arterial grafts

AHA 2009
ICD Registry Post Market Surv.

NQF Perf. Measure- Risk adjusted/ICD Registry-
Medicare Claims Data for 30 and 90 day complications:
  • Death, pneumo/hemothorax, transfusion or surgical evacuation, tamponade or pericardiocentesis, system/lead revision, infection 90 days, ICD replacement 90 days.

ICD Registry data to support Boston Scientific's MADIT-CRT Post-Approval study

ICD Registry leads data to assess lead performance as part of the FDA sentinel network.
Kaiser Permanente and Comparative Effectiveness
Coronary Artery Disease Management, Oncology, And National Device Registries

Acknowledgement:
Paul Wallace MD
The Permanente Federation
Kaiser Permanente National Total Joint Replacement & Cardiac Device Registries

- 150,000 joint-replacement & cardiac implants across U.S. representing >1,000 MDs and 50 hospitals
- Analysis of implant statistics, complications, failures, replacements, usage, and costs
- Identifies most effective devices and surgical techniques
- Identifies patients at risk for re-operations and surgical complications
Knowledge Generation: The Kaiser Permanente National Joint Replacement Registry

[Evaluation] feedback changed practice with respect to: implant selection, minimally invasive procedures, uncemented knees, and surgical indications and preoperative care.

Significant outcomes of Kaiser Permanente TJRR & CDR:

- Immediate identification, monitoring, and notification of over 2,500 orthopedic and cardiac patients affected by 15 recalls in 2009 alone.

- Identification of patients’ risk factors for post-operative infections, hospital re-admissions, deep vein thrombosis, and other complications, resulting in significant changes in surgical indications and pre-operative care.
Clinical Registries & Automated Surveillance: Postprocedure Safety Signals of CV Devices

- Prospective propensity matched cohort analysis of 7 CV Devices via NCDR/MA data 2003-2007
- Safety alert if device > 95% CI of comparator device control
- Found sustained alerts in 2 devices in 75,000 patients
  - Stent with increased MI rate/major adverse cardiac events and a Closure device with increased vascular complications

Device Surveillance- Reaction to Proaction

- Voluntary reporting
  - Underreporting/under recognition, time lags, denominator data

- FDA’s sentinel networks in development- distributed data networks combined by remote analysis
  - Automated surveillance tool via registries for sentinel networks
    - Arbitrary boundaries for safety signals, observational
    - Signal-to-noise ratios
    - Lacks point of care/clinician input

- E.H.R.s and “Meaningful Use” for device surveillance
Claim SFI CATHPCI NCDR UPI NDI Pharm STS Registry
ACC/Duke Partnership: Develop a National Cardiovascular Research Infrastructure (NCRI)

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**Administering Institutes or Centers:**
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

**Project Funding Information for 2009:**

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<th>FY Total Cost by IC</th>
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<td>2009</td>
<td>NATIONAL HEART, LUNG, AND BLOOD INSTITUTE</td>
<td>$1,328,715</td>
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Prospective, observational study of antiplatelet treatment among AMI patients treated with PCI

Objectives: to evaluate
- long-term effectiveness and safety
- adoption of novel antiplatelet meds
- short- and long-term treatment patterns
- antiplatelet medication switching
- patient adherence
- economic cost implications

FOLLOW-UP – Validated events, medications, costs

Index AMI Hospitalization

Discharge

1  3  6  12  15  Months
FDA under Critical Path Initiative developing a partnership with Cardiac Safety Research Consortium (CSRC)

- ACC
- NCDR
- Data elements for Registry developed (Ben Eloff - FDA)
- HRS (Heart Rhythm Society), STS
- Industry - AdvaMed
- Government - NIH, CMS, AHRQ
- Academia, Payers, Hospitals
Safari Proposal

- Collect data on real-world characteristics of patients undergoing catheter ablation and clinical outcomes
- Effectiveness 12 months post-ablation
- Safety of the procedure
- Incidence and nature of late-manifesting and/or infrequent complications
- Generalizability of data to providers and patients not represented in existing clinical studies.
Safari Goals

• Establish a nationwide registry for collecting data related to AF ablation procedures
• Openly report the data contained in the registry to inform the public health
• Establish a core dataset to satisfy some FDA postmarket requirements
CER and Registries

Perfect Opportunity for Coverage with Evidence Development (CED)

– Offers the “Carrots” and “Sticks” for Registry participation
– Realizes opportunities to assess new technology in real world applications – non-RCT and off label uses

Percutaneous Aortic Valves

Atrial Fibrillation Ablation

New CV Imaging Technologies
Perfect Surveillance World

• Safety monitoring for drugs and devices hardwired into distribution system at point of care
  – Drugs and devices with real risk – need real time data gathered into existing databases managed at point of care and capable of tracking pts longitudinally – Device identifiers and UPIs!!
  – Post approval safety monitoring should be a public trust shared:
    • Sponsors, regulators, and trusted third parties (academics, ACC/HRS, patient advocates)
  – Real time data feedback to prescribers at “point of care”!
    (Hertz Car analogy)
Final Thoughts

• High quality clinical data as part of care delivery takes time and money
• Focus on maximizing potential for data for post market surveillance, quality improvement and CER not just one of these.
• Requires more thought, complexity and cost
• What CER questions best by RCTs and what best by Registries?
  – Polling of payers, academics, guideline developers, etc for input
  – Wider collaboration!- payers and health plans
Alternative Methodology for Surveillance and CER
“Paul the Octopus”