CV Compound and Non CV Compound Registry Studies

Session II:
Event Identification and Ascertainment Strategies

Cardiac Safety Research Consortium

Adjudication Thinktank

*FDA White Oak, Silver Spring*

*November 6, 2013*

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Background Overview of Issue Under Discussion

- Harnessing the potential power of national registries to be a seamless infrastructure for event identification and ascertainment.
- Environment for event identification/ascertainment:
  - Standard Prospective RCT model
  - Observational Registry RCT model
  - In the routine clinical use of a registry
What Works Well Today!
2500 hospitals
> 2000 cardiologists
16 million clinical records

NCDR®
National Cardiovascular Data Registry

Trusted Third Party

STS/ACC TVT Registry™

ACTION Registry®-GWTG®

CARE Registry®

ICD Registry™

CathPCI Registry®


Helping Cardiovascular Professionals
PINNACLE Registry

• Linkage to other NCDR registries, such as ACTION-GWTG Registry and CathPCI Registry:
  – Collect data on patients with CAD, Diabetes, HTN and Atrial Fibrillation
  – Establishes a national standard for:
    • Understanding treatment patterns
    • Clinical outcomes
    • Drug safety
    • Overall quality of care provided to high-risk patients
      – Drug and anticoagulant dosing
      – Drug-drug and drug-device interactions
In the 2010 on-site audits, the overall accuracy of data abstraction for the CathPCI, ICD, and ACTION-GWTG registries were, respectively, 93.1%, 91.2%, and 90.0%.

*JACC* June, 2012
TVT Registry Collaborative Partnership

- Clinical Registry Program
- Quality/Outcomes Research
- Device Surveillance
- Post-Approval Studies
- IDE Studies
- Network for RCTs
Data Quality Program
Pre Data Collection

1. Software
   – Data collection structured with automatic warnings, errors and edit checks on data entry

2. Training and clinical support
   – 24 hour clinical support staff available via phone or email
   – Orientation
   – Monthly webinars
   – Annual conference
   – Reference materials (e.g. FAQs)
Data Quality Program

Data Submission

Data quality report – automatically generated when sites submit data to the data warehouse

- **Assessment:**
  - Errors identified (e.g. procedure aborted but device serial number documented)
  - Outliers verified (e.g. 500 kg weight)
  - Selections validated (e.g. not answering parent/child elements)

- **Completeness:**
  - Thresholds of completeness set for elements based on their importance in reporting and analysis.
Data Quality Program
Post Submission

Adjudication
– Verifies and provides additional information for key events (stroke, TIA and repeat intervention)

National audit program (starts in 2014)
– Evaluates accuracy and reliability
– Assesses proper and complete reporting of cases
– Voluntary and self audits

• Data Outlier Program
– Provides outlier alerts to Registry participants
Adjudication: TIA & Stroke

Adjudication:
- 07/05/2012 TIA
- 04/10/2013 Stroke

Ischemic, Hemorrhagic, Undetermined Stroke, TIA

- Date of Symptom Onset: 12015
- Neurologic Deficit with Rapid Onset: 12020
- Clinical Presentation: 12025
- Symptom Duration >= 24 hours: 12030
- Therapeutic Intervention Performed: 12035
- Neuroimaging Performed: 12040

Status: Deceased
Date of Death: 08/07/2012 (Deceased)
The Good News

In-hospital data completeness reports reflect high percentage (98+%) of completeness within critical elements, which are used to report:

• Risk adjustment (e.g. stroke, diabetes, and NYHA)
• Procedure variables (e.g. reason for procedure)
• Report metrics (e.g. Hgb and Cr to report bleeding events and acute kidney injury)
• VARC endpoints

Source: STS/TVT Registry - DCRI
Procedure completeness report
The CMS/TVT Registry Linkage Project

- **Purpose:** Long-term longitudinal follow-up of all US patients enrolled in the TVT Registry

- **Process:** Determine data linking methodology
  - Develop linked data file structure and Transmission
  - Create data use agreement that includes using the linked data for research and metric development.
  - Complete file transmission schedule
Using the MA state-wide PCI device dataset, explored the **cumulative** post-procedure myocardial infarction rate for new drug eluting stent as compared with propensity matched control DES.

Using 38 clinical variables in propensity match a total of 81.5% of 18,277 new stents were analyzed.
Using pooled data from *three* high volume centers, DELTA performed a propensity matched analysis of 859 Fidelis lead implants versus traditional leads. By 25 months of analysis (dashed line) 3% of Fidelis leads had fractured (red line) whereas only 0.1% (1 of 859) alternative ICD leads had fractured.
ACC/Duke Partnership: Develop a National Cardiovascular Research Infrastructure (NCRI)
NCRI’s Infrastructure Opens Doors

Site Descriptor Database
- Database of research ready sites within the NCDR
- An approach for targeted recruitment

Data Transfer System
- Connects CathPCI with an EDC System
- Provides mechanism for modified CRFs, additional data collection

Randomization
- Connection with EDC system allows us to track randomized patients within the registry

SDTM Output
- Data Collection tool/ EDC system that can export data in SDTM compliant structure (ready for FDA submission)

Data Standards
- Create CV standards in CDISC and HL7
- Load all standards in NCI repository for future uses in trials

Enhance Site Research Readiness
- Employ educational webinars/ training to NCDR sites to become research ready

Future Research
- Ready for large randomized clinical trials
- Post approval studies and CER
SAFE-PCI for Women Study

Study of Access Site For Enhancement of Percutaneous Coronary Intervention for Women

DCRI
- Study Coordinating Center

ACC
- Registry Platform

Pilot study for the National Cardiovascular Research Infrastructure (NCRI) grant
SAFE-PCI Methods - Endpoint definitions

Primary efficacy endpoint

• BARC Bleeding
  – Type 2: Overt, actionable bleeding not meeting criteria for type 3, 4, or 5 bleeding
  – Type 3:
    • Overt bleeding with hgb drop ≥ 3 g/dL (corrected for transfusion)
    • Transfusion with overt bleeding
    • cardiac tamponade
    • bleeding requiring surgical intervention or intravenous vasoactive drugs
    • intraocular bleeding or ICH
  – Type 5: Fatal bleeding
• Vascular complications requiring intervention
  – AV fistula
  – Pseudoaneurysm
  – Arterial access site occlusion

Primary Feasibility Endpoint

• Access site crossover
  – Inability to complete the procedure from the assigned access site

CEC Adjudication of all suspected bleeding or vascular complication events
SAFE-PCI Research implications

• As the first registry-based randomized trial in the US, the SAFE-PCI for Women trial demonstrates a new paradigm for conducting efficient pragmatic clinical trials using The National Cardiovascular Research Infrastructure
  – High quality data
  – Adjudication possible
  – CFR Part 11 compatible – IND and IDE applications
  – Faster enrollment, Reduced site workload
  – Reduced costs (total budget for SAFE-PCI for Women ~ $5 million)

• Promising approach for future clinical investigations
What Works Well

• NCDR provides a ready-made network of highly reliable sites for data acquisition (culture).
• Faster, cheaper and proven reliable
• Can be transparent to both sponsor and regulator, and open to adjudication committees – all see the same data.
What is Missing…..
Does not Work Well Today

“Opportunities for improvement”

– Avandia story might have been quite different with a robust registry in place
– Dearth of routine observational registries for CV and non CV drugs – slow penetration of PINNACLE
– Facilitating smoothing the interface between registries, FDA, CMS and industry for streamlining RCT study designs, IRB requirements, data collection needs
– Variable funding mechanisms & related challenges
Highest Priority
Short Term 1-3 Years

Also Not There Yet……..

• **Global Reach** – need Global Registry harmonization
• Direct links to imaging needed to adjudicate events
• EMR integration
• 100% data availability
Sustainability is reliant on stakeholders commitment to using registries for needed purposes

Sustainability is reliant on financial support:
1. Participant Subscription
2. NCD/CED Mandates
3. Payer/Health Plan Support
4. Industry Grants
5. Government/Non-profit Grants
Highest Priority
Long Term 3-5 years

• National Consortium- advisory body for registry derived RCTs with all potential stakeholders
  – NHLBI, FDA, CMS, PCORI, AHRQ, patient groups, Industry, academia, etc.
• Real-time analysis of data captured
• Stable funding and sustainable registry and registry derived RCT model
• Clinical registries to be viewed as the standard infrastructure for conducting pre and post market research.