

The use of registry data to support regulatory decisions

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Randomized Controlled Trials (RCT)



- One of the most powerful tools clinical researchers possess
 - Enables them to evaluate the effectiveness of new (or established) therapies while accounting for the effects of unmeasured confounders and selection bias by indication
- However, RCT reputation has suffered of late, owing to reasonable concern about excess complexity, expense, and time required to recruit study participants, as well as inadequate representativeness
 - E.g., results are not applicable to real-world patients

Basic Principles for Success

- Developing uniform definitions and CRFs for a particular area
- Defining relevant questions
- Establishing quality by design principles to ensure data quality and ability of registry to withstand audit
- Successfully addressing any relevant informed consent issues
- Developing incentives for sustainability of the registry



Registry Data:

Pre-Market Regulatory Perspective

- Division of Cardiovascular Devices (DCD) has actively worked with manufacturers and professional societies on cardiovascular projects
- Registries are useful data collection tools
- Proactive Collaboration
- Early engagement with industry, government agencies and professional societies

Registry Uses for Cardiovascular Devices

- Meeting post-approval requirements for new devices
- Leveraging the registry(ies) infrastructure to nest IDE studies
- More broadly contribute to a learning health model

Example of meeting post-approval requirements:

Type B Dissection Post-Approval Surveillance Program



- Vascular Quality Initiative (VQI) from the Society for Vascular Surgery (SVS)
- The Dissection VQI data set consists of four cohorts:
 - 1) Acute Dissection with five year follow-up,
 - 2) Chronic Dissection with five year follow-up,
 - 3) Acute Dissection with one year follow-up, and
 - 4) Chronic Dissection with one year follow-up.
- The 5 Year Acute and Chronic cohorts will enroll 200 patients each, and of the 200 patients in each cohort, at least 60 must be treated with a given device manufacturer.
- There will not be a minimum enrollment requirement for the 1 Year Acute and Chronic cohorts; however, there will be a maximum of 200 patients enrolled in those cohorts.



Example of Leveraging the registry(ies) infrastructure to nest IDE studies

- **Registry Assessment of Peripheral Interventional Devices (RAPID)**
 - Launched June 5, 2015
- **Goal**
 - Standardize core data elements that could serve as a **global case report form** for both pre- and post-market assessment of peripheral arterial interventional devices

RAPID Partners

- **3 Major U.S. Societies / Registries**
 - American College of Cardiology (**ACC**)
 - National Cardiovascular Disease Registry (**NCDR**)
 - Society of Interventional Radiology (**SIR**)
 - National Interventional Radiology Quality Registry (**NIRQR**)
 - Society for Vascular Surgery (**SVS**)
 - Vascular Quality Initiative (**VQI**)
- **5 International Partners**
 - Japan's Pharmaceuticals and Medical Devices Agency (PMDA)
 - Global Medical Device Nomenclature Agency (GMDNA)
 - Australian Vascular Audit
 - German Vascular Society
 - Northern German Association for Vascular Medicine

RAPID Partners

- **7 U.S. Agencies**
 - FDA (**CDRH** pre- and post-market, and **CDER**)
 - Agency for Healthcare Research and Quality (**AHRQ**)
 - Centers for Medicare and Medicaid Services (**CMS**)
 - Department of Defense (**DOD**) Healthcare Resources
 - Office of the National Coordinator (**ONC**)
 - National Heart, Lung and Blood Institute (**NHLBI**)
 - National Library of Medicine (**NLM**)
- **6 EHR / Registry / Clinical Research Companies**
 - Epic
 - M2S
 - MedStreaming
 - Healthjump
 - Boston Biomedical Assoc.
 - Novella Clinical, Quintiles



RAPID Partners

- **12 Device Manufacturers**

- Abbott
- Aortic Medical Inc.
- Avinger
- Boston Scientific
- Cardiovascular Systems Inc
- Cook Medical
- CR Bard
- Medtronic
- Spectranetics Corp
- Terumo
- Volcano Corp/Phillips Health Technology
- WL Gore

RAPID Leadership

- **Co-Chairs:**

- Pablo Morales

- Food and Drug Administration (FDA)

- Robert Thatcher

- Cardiovascular Systems, Inc. (CSI)

- Jack Cronenwett

- Society for Vascular Surgery (SVS) Vascular Quality Initiative (VQI)

- **Project Manager:**

- Rebecca Wilgus

- Clinical Informatics, Duke Clinical Research Institute (DCRI)

- **MDEpiNet Key Advisors:**

- Mitchell Krucoff, DCRI

- Danica Marinac-Dabic, FDA

Why RAPID?

- **Current Challenge = Heterogeneity**

Devices Heterogeneity

- Multiple devices used at a given intervention
- Different technologies
 - Angioplasty Balloons
 - Plain, drug coated, cutting, cryoplasty
 - Atherectomy devices
 - Laser, mechanical
 - Total occlusion crossing devices
 - Stents
 - Bare metal
 - » Self-expanding, balloon expandable
 - Covered
 - Drug-eluting

Patient and Disease Heterogeneity

- Age, gender, diabetes influence outcomes
- Disease Severity
 - Claudication (life style) vs. Critical Ischemia (limb threat)
 - Differing lesion length, occlusion vs. narrowing, calcification
- Disease Location
 - Large (iliac),
 - Medium (SFA, popliteal),
 - Small (tibial) Arteries

Provider Heterogeneity

- Variable Physician Specialty, Training, Experience
 - Cardiologists, radiologists, surgeons
- Variable Treatment Options
 - Numerous device types, on- and off-label use in practice

RAPID Project Plan

- **Phase I: Identify minimal set of core data elements for registry assessment of lower extremity arterial devices**
 - Obtain data elements from existing registries and industry case report forms used for pivotal device approvals.
 - Develop structured comparison report of all relevant data elements to allow selection based on clinical expertise.
 - Select core data elements, develop technical specifications for each element and a method to integrate Unique Device Identifier (UDI) data for precise device specification.
- **Duke Clinical Research Center (DCRI)**

Informatics Team: Anne Heath, Mary Williams

RAPID Project Plan

- **Phase II: Develop data extraction interoperability across peripheral registries and hospital EHRs that provide patient-level data for core data elements**
 - The ACC, SIR and SVS peripheral intervention registries would incorporate the core data elements.
 - EHR manufacturers would be encouraged to develop smart data elements for the core data set.
 - Core data set would be provided to other national registries, such as the International Consortium of Vascular Registries (ICVR).

RAPID Project Plan

- **Phase III: Use a coordinated registries network (CRN) for studies supporting a regulatory decision.**
 - Projects would extract minimal core data from different registries or other data sources, such as centers using the same EHR system
 - Individual projects might need supplementary data
 - Prospective clinical trial, pre-market study
 - Post-market study, surveillance
 - Objective performance criteria creation
- **Goal:** Total Product Life Cycle evaluation of devices in real world practice.

RAPID

- It is one project in a series initiated to advance and demonstrate the interoperable flow of data and information across electronic health information systems as a precursor to the **National Evaluation System for Health Technology (NEST)** articulated by Drs. Shuren and Califf.

JAMA. 2016;316(11):1153-1154

RAPID Progress

Phase I: June, 2015 – April, 2016

Developed 3 Work Groups:

- **Clinical**
 - Select core data elements assembled by DCRI Informatics Team
- **Informatics**
 - Develop technical specifications to support interoperability
- **UDI**
 - Develop method to incorporate GUDID data into core data set
- Multiple stakeholders represented in each group
- Multiple teleconferences with broad participation

RAPID Progress

DCRI Informatics Team

- Received and anonymized data elements from:
 - 6 Society-based registry data forms:
 - 3 Major US Registries: ACC NCDR, SIR NIRQR, SVS VQI
 - 3 International Registries: Australia, Germany, Japan
 - 7 Device manufacturer case report forms
 - Bard, Boston Scientific, CSI, Cook, Gore, Medtronic, Terumo
- Analyzed 3,904 data elements
- Selected and organized 2,021 variables that were specific to peripheral arterial disease (PAD) device evaluation

RAPID Progress

Clinical Work Group - Schuyler Jones, MD

- Reviewed and prioritized 2,021 data elements with goal to select 100-125 PAD most relevant variables
- Discussed use cases for RAPID data elements
- Prioritized variables applicable to most devices, for most use cases, across TPLC, already being used by stakeholders
- Organized by Condition, Test, Treatment, Device, Outcome
- Selected 113 candidate variables

RAPID Progress

Informatics Work Group - James Tcheng, MD, Chair

- Identified minimum meta-data required for each variable to allow interoperability
- Discussed with ONC and decided to develop data element specifications based on Clinical Information Modeling Initiative (CIMI)
- Identified several data models (PCORNet, Sentinel, OMOP) to evaluate for potential data aggregation in Phase II

RAPID Progress

UDI Work Group - Terrie Reed, MSIE

- Identified set of GUDID data elements required for RAPID
- Company, brand, product number, GMDN term, size, model, etc.
- Documented the method to extract these data from GUDID so that registries, EHRs, others can link device information
- Evaluated usefulness of categories used in Global Medical Device Nomenclature (GMDN)
- Issues with devices used off-label and non-US approved devices
- Identified relevant device information not included in current GUDID data that requires supplemental dataset
- Capturing UDI at point of use is key for registries, EHRs

RAPID Progress

- Meetings: June 5, Nov 6, 2015
April 13, September 14, 2016

Timetable:

- Phase I:
 - July, 2015: Finalize core data element selection
 - Dec, 2015: Finalize meta-data specification
- Phase II:
 - 2016-2017: Incorporation core data elements into registries, EHR systems
- Phase III:
 - 2017: Initiation of device evaluation project

Potential Scenarios of Clinical Studies to be Nested

- Developing objective performance goals (e.g., for tibial artery treatment in diabetic patients based on current real world practice)
- Expansion of approved device indications
- Comparison of two existing treatment modalities (e.g., atherectomy vs angioplasty in popliteal or any comparison of new device type with historical treatment.)
- Randomized Clinical Trial – (e.g., Does direct thrombin inhibitor improve patency of SFA interventions?)

Deliverables

- RAPID should allow for Standardization and Homogeneity
- Global CRF with respective definitions should lower the reviewer regulatory burden as well as decrease cost to sponsors
- Facilitate International Device Evaluation
- GUDID / NLM should allow:
 - for device-specific outcomes searches
 - lessen the cost for device data entry
 - optimize accuracy of device data

Deliverables

- Potential to facilitate the assessment of devices and interventions by developing a “global case report form”
- Leads to ability to analyze large amount of data to allow for device-specific analysis (safety and effectiveness)

Take home message

- We have built up the foundation to assess medical devices being used for peripheral artery interventions
 - National and International
- Multi-stakeholder collaboration is essential to move in the right direction
- Registries are here to stay and if we develop them together they can work on our behalf

“This is an important step toward establishing the National Evaluation System for Health Technology” CDRH Director Jeff Shuren, MD, JD
<https://www.dcri.org/mdepinet-rapid-project-seeks-improve-quality-efficiency-peripheral-interventional-device-evaluation/>



Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Real-World Data (RWD) is data collected from sources outside of traditional clinical trials. These sources may include large simple trials, or pragmatic clinical trials, prospective observational or **registry studies**, retrospective database studies, case reports, **administrative and healthcare claims**, **electronic health records**, data obtained as part of a public health investigation or routine public health surveillance, and **registries** (e.g., device, procedural, or disease registries). The data is typically derived from **electronic systems used in health care delivery, data contained within medical devices, and/or in tracking patient experience during care, including in home-use settings.**

Real-World Evidence (RWE) is the evidence derived from **aggregation and analysis** of RWD elements.

Examples of registry data used to support regulatory decisions

Trans-Aortic Valve Replacement (TAVR)

- Original indication for TAVR was for transfemoral access or insertion only
- **Registry data used** – Available clinical data from nested single-arm registry in PARTNER trial (100 pts) and TVT Registry data from “off-label” use (real world evidence – about 500 patients in the TVT registry had off label insertion, and their results were compared to the overall results of 7000 trans-femoral insertion)
- Updated indication: transfemoral restriction removed to allow alternate access (e.g., transapical, trans-aortic, trans axillary or subclavian artery) for device insertion



THANK YOU

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