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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

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Drs. Lauer and D'Agostino argue that the use of observational registries in conducting clinical trials could, in fact, be a game changer, especially in the current fiscal climate

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

- **R**egistry **A**ssessment of **P**eripheral **I**nterventional **D**evices (**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

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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/

Contains Nonbinding Recommendations

Draft – Not for Implementation

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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