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WORKING TOWARDS MEDICAL DEVICE HARMONIZATION IN ASIA

CENTRAL DRUGS STANDARD CONTROL ORGANIZATION
MINISTRY OF HEALTH, GOVERNMENT OF INDIA

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22nd Asian Harmonization Working Party Annual Meeting

MAKE IN INDIA

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4-8 December, 2017 I New Delhi

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Abbott

Dr. Justin (Seung Ho) Yoo

Ph.D.(Medical Doctorate) and MPH

- ✓ **Government Affairs, Health Economics & Reimbursement Manager at ST.JUDE MEDICAL KOREA (A family of Abbott)**
- ✓ **A member of AHWP WG5**
- ✓ **Vice Chair, Korean AHWP WG5**
- ✓ **Leader, Korean IMDRF STG4**
- ✓ **Leader, U-HealthCare Team at KMDIA**
- ✓ **Research Advisor at FARB Lab, Seoul National Univ. Hospital**

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Use of "Real World Evidence" in Clinical and Regulatory Decision from Industry Experience

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Contents

- Definition: RWE & Patient Registry
- FDA Guidance on RWE
- IMDRF Guidance on PR
- Patient Registries worldwide
- Values of RWE / PR
- RWE through Health Economics Outcomes Researches
- Total Products Life Cycle Management
- Suggestions

Definition

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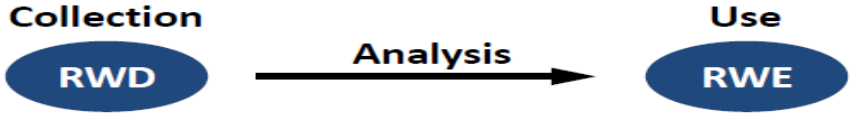
Turning Data into Evidence

Real-World Data (RWD)
Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources

Real-World Evidence (RWE)
Clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD



Guidance addresses issues related to processes of:

- Generation and collection of RWD
- Analysis of RWD
- When results might be considered valid scientific evidence

The term ***patient registry*** is generally used to distinguish registries focused on health information from other record sets, but there is no consistent definition in current use. E.M. Brooke, in a 1974 publication of the World Health Organization, further delineated registries in health information systems as "a file of documents containing uniform information about individual persons, collected in a systematic and comprehensive way, in order to serve a predetermined purpose."

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

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016

Dec. 2016

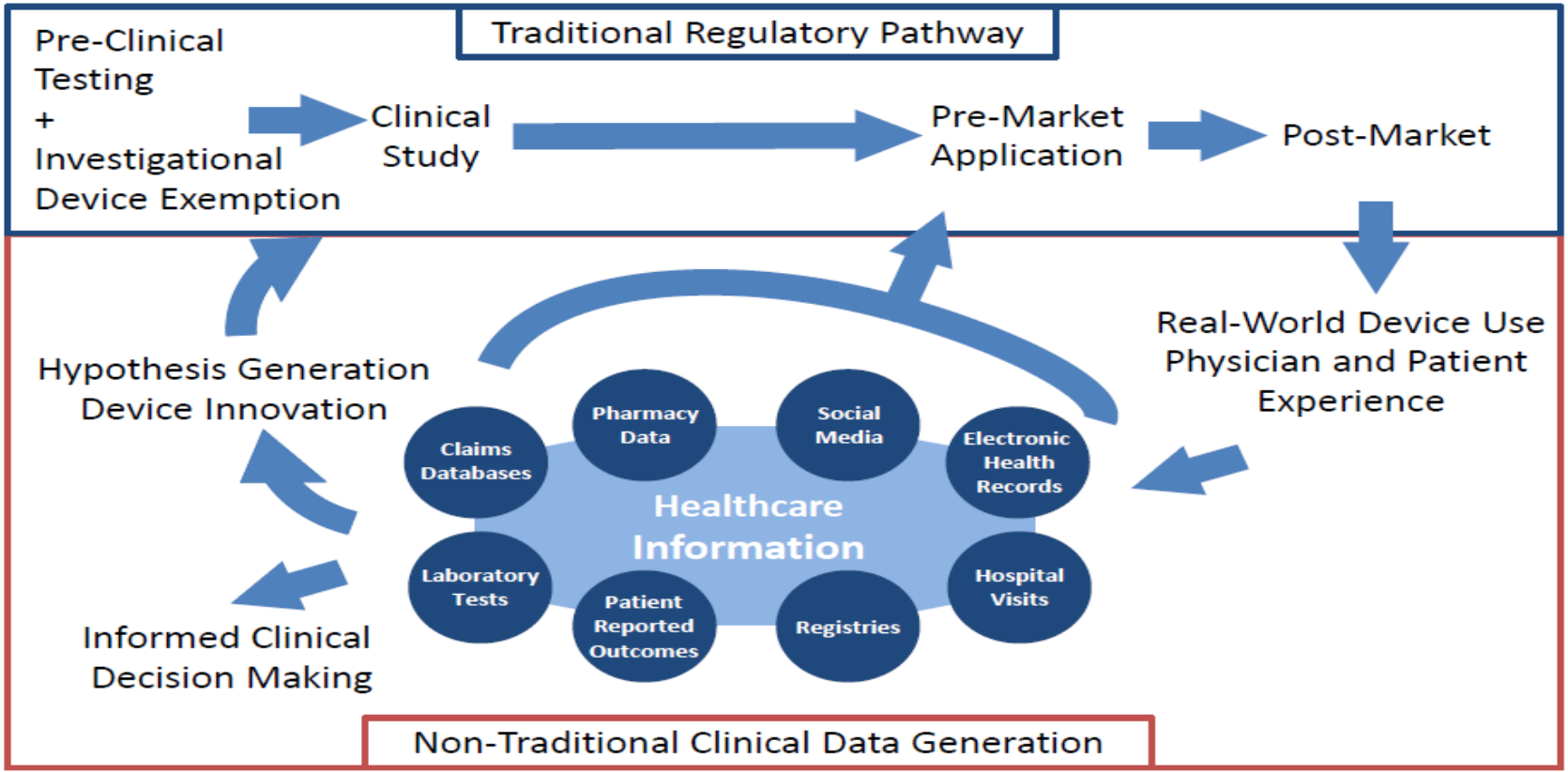
The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

Real-World Evidence — What Is It and What Can It Tell Us?

Rachel E. Sherman, M.D., M.P.H., Steven A. Anderson, Ph.D., M.P.P., Gerald J. Dal Pan, M.D., M.H.S., Gerry W. Gray, Ph.D., Thomas Gross, M.D., M.P.H., Nina L. Hunter, Ph.D., Lisa LaVange, Ph.D., Danica Marinac-Dabic, M.D., Ph.D., Peter W. Marks, M.D., Ph.D., Melissa A. Robb, B.S.N., M.S., Jeffrey Shuren, M.D., J.D., Robert Temple, M.D., Janet Woodcock, M.D., Lilly Q. Yue, Ph.D., and Robert M. Califf, M.D.

Evidence in Regulatory Decisions



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What is Acceptable?

FDA

- 21 CFR 860.7(c)(2)

  Valid scientific evidence is evidence from
  - Well-controlled investigations,
  - Partially controlled studies,
  - Studies and objective trials without matched controls,
  - Well-documented case histories conducted by qualified experts,
  - Reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.

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FDA

What is Not Acceptable?

- 21 CFR 860.7(c)(2) continued

  ...isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness. Such information may be considered, however, in identifying a device the safety and effectiveness of which is questionable.

Data Quality

'Fit for Purpose'

Data should be assessed for completeness, consistency, accuracy, and whether it contains all critical data elements needed to evaluate a medical device and its claims.

Relevant & Reliable

Benefit

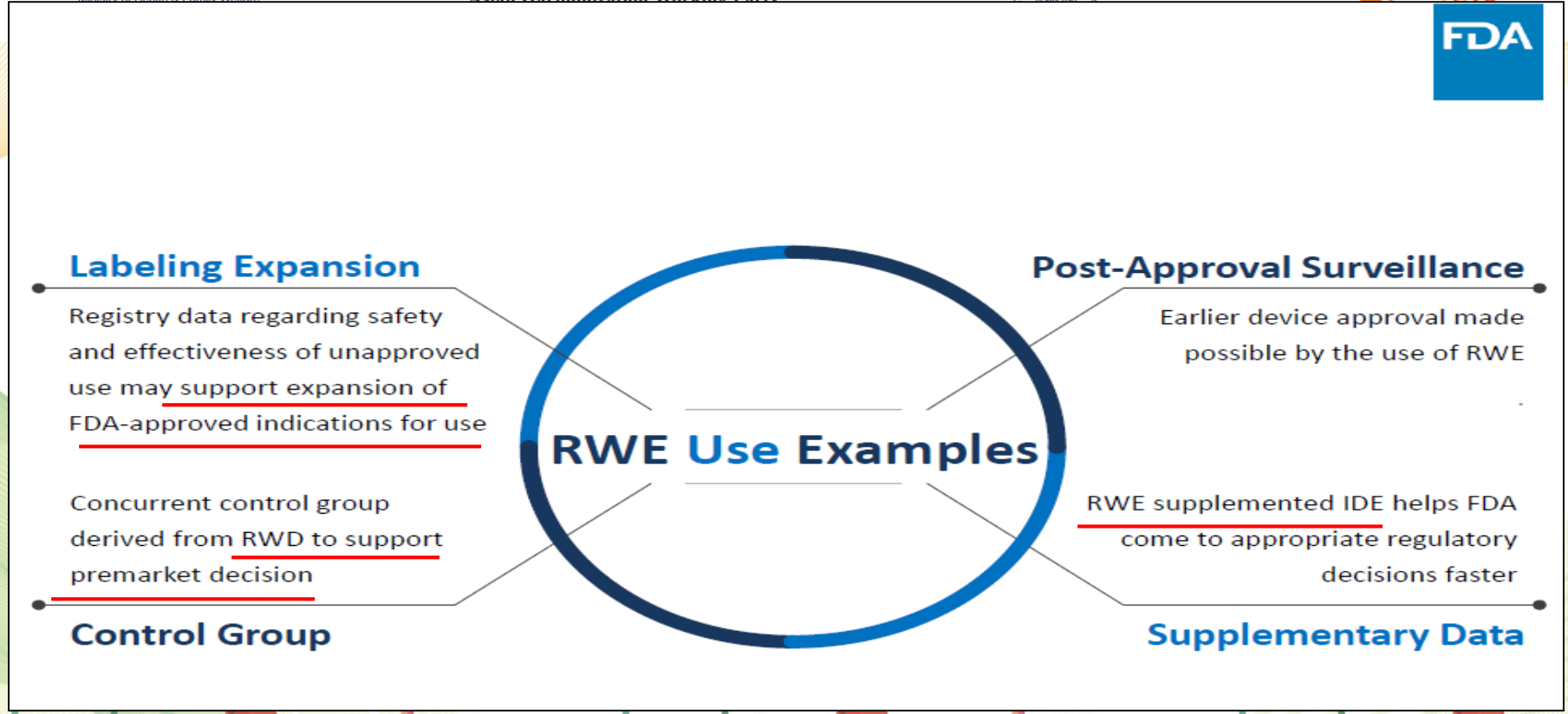
Risk

Safety

Are there reasonable assurances, based on valid scientific evidence that probable benefits to health from use of the device *outweigh any probable risks? [860.7(d)(1)]*

Effectiveness

Is there reasonable assurance, based on valid scientific evidence that the use of the device in the target population will provide *clinically significant results? [860.7(e)(1)]*


FDA
Labeling Expansion
Registry data regarding safety and effectiveness of unapproved use may support expansion of FDA-approved indications for use
Concurrent control group derived from RWD to support premarket decision
Control Group
RWE Use Examples
Post-Approval Surveillance
Earlier device approval made possible by the use of RWE
RWE supplemented IDE helps FDA come to appropriate regulatory decisions faster
Supplementary Data

Registry of Patient Registries

Patient registries offer significant opportunities for conducting clinical research.

PEOPLE

Raj Sabharwal, M.P.H., Rosina Pradhananga, M.P.H.

Data Sharing | Data Sources

SHARE

In December 2012, the Agency for Healthcare Research and Quality (AHRQ) launched the Registry of Patient Registries (RoPR), which is a database of existing patient registries that was designed with extensive stakeholder participation to promote collaboration, reduce redundancy, and improve transparency in registry-based research. In partnership with AHRQ, L&M Policy Research, and Truven Health Analytics, AcademyHealth facilitates implementation of RoPR and its related projects, with a particular focus on developing a virtual Community of Practice (CoP) to facilitate discussion of relevant issues related to registry design and use of registry data among diverse stakeholders.

Harmonization of Outcomes Using the Outcome Measures Framework

The RoPR project is also seeking to harmonize clinical definitions and outcome measures used in patient registries across five clinical areas, using the RoPR Outcome Measures Framework (OMF). The OMF is a conceptual model for classifying existing outcome measures that are relevant to patients and providers across most clinical conditions. Harmonizing these outcome measures is the key to improving the ability of registries to connect to other health IT systems. Through extensive stakeholder engagement, the harmonization will be conducted within select five clinical areas, and for each we will, 1) compare outcome measures to identify areas of harmonization; 2) work toward harmonization at series of in-person and web meetings; 3) produce common library of outcome measures for public comment; and 4) finalize library with feedback and post for public use.

IMDRF International Medical Device Regulators Forum

FINAL DOCUMENT

Title: Methodological Principles in the Use of International Medical Device Registry Data

Authoring Group: IMDRF Patient Registries Working Group

Date: 16 March 2017

Title: **Principles of International System of Registries Linked to Other Data Sources and Tools**

Authoring Group: IMDRF Patient Registries Working Group

Date: **30 September 2016**

Global Medical Device Registries

1) Orthopedic

- The National Joint Registry (NJR) of England, Wales and Northern Ireland
- Canadian Joint Replacement Registry
- Kaiser Permanente Total Joint Replacement Registry
- Australian National Joint Registry
- Dutch Arthroplasty Register
- Brazilian National Implants Registry

2) Vascular

- Vascular Quality Initiative
- Australian Vascular Audit
- UK National Vascular Registry
- Japanese Registry of Endovascular Aneurysm Repair

3) Cardiac

- The US Cath-PCI Registry
- The US Trans-Catheter Valve Therapies (TVT) Registry
- The Japan PCI (J-PCI) Reistry
- The Japanese Trans-Catheter Valve Therapy (TVT) Registry
- The Japan Adult Cardiovascular Surgery Database

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NCDR®
NATIONAL CARDIOVASCULAR DATA REGISTRY

The **AFib Ablation Registry™** assesses the prevalence, demographics, acute management and outcomes of patients undergoing atrial fibrillation (AFib) catheter ablation procedures. Its data will support the development of evidence-based guidelines for AFib treatments that will improve outcomes for patients.

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The **CathPCI Registry®** assesses the characteristics, treatments and outcomes of cardiac disease patients who receive diagnostic catheterization and/or percutaneous coronary intervention (PCI) procedures. This powerful tool captures the data that measure adherence to ACC/AHA clinical practice guideline recommendations, procedure performance standards and appropriate use criteria for coronary revascularization.

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The **ICD Registry™** establishes a national standard for understanding treatment patterns, clinical outcomes, device safety and the overall quality of care provided to implantable cardioverter defibrillator (ICD) patients. As the CMS-mandated registry for hospitals that perform ICD implantation procedures, the ICD Registry plays an important role in determining the association between evidence-based treatment strategies and clinical outcomes. Eighty percent of participating hospitals value the registry beyond the CMS-mandate – capturing all ICD implantations regardless of payer or indication.

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The **IMPACT Registry®** assesses the prevalence, demographics, management and outcomes of pediatric and adult congenital heart disease (CHD) patients who undergo diagnostic catheterizations and catheter-based interventions. Its data support the development of evidence-based guidelines for CHD treatment that will improve outcomes for CHD patients of all ages.

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The **LAAO Registry™** captures data on left atrial appendage occlusion (LAAO) procedures to assess real-world procedural outcomes, short and long-term safety, comparative effectiveness and cost effectiveness. LAAO provides a treatment option to manage stroke risk for non-valvular atrial fibrillation patients who are unable to maintain adequate anticoagulation through medication therapy. The LAAO Registry is approved by the Centers for Medicare and Medicaid Services (CMS) to meet the registry requirements outlined in the national coverage decisions for Percutaneous Left Atrial Appendage Closure.

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The **PVI Registry™** assesses the prevalence, demographics, management and outcomes of patients undergoing lower extremity peripheral arterial catheter-based interventions and includes carotid artery stenting (CAS) and carotid endarterectomy (CEA). The PVI Registry provides data collection and equips clinicians with decision-making data whether care is provided in a hospital cath lab, interventional radiology department, or an outpatient vascular center.

The **STS/ACC TVT Registry™** , created by a collaboration between the Society for Thoracic Surgeons and the ACC, monitors patient safety and real-world outcomes related to transcatheter valve replacement and repair procedures – emerging treatments for valve disease patients. Employing state-of-the-art heart valve technology, transcatheter heart valve procedures provide new treatment options for patients who are not eligible for conventional heart valve replacement or repair surgery. Learn more about the TVT Registry.

Values

- to observe the course of disease;
- to understand variations in treatment and outcomes; to examine factors that influence prognosis and quality of life;
- to describe care patterns, including appropriateness of care and disparities in the delivery of care;
- to assess effectiveness;
- to monitor safety and harm;
- to measure quality of care.

Through functionalities such as feedback of data, registries are also being used to study quality improvement.

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Real-World Evidence (RWE)

Complements RCT and takes advantage of Big Data collected for other purposes

Advantages

- Real-world cohort
- Lower cost than RCT
- No waiting for data to be collected
- Large datasets allow assessment in subgroups

Challenges

- Quality and resolution of datasets
- Unknown confounders
- Rigorous data handling and statistical methods
- Mechanistic explanation

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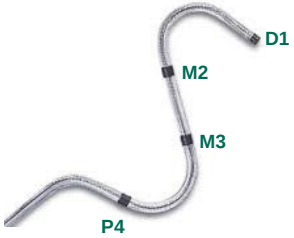
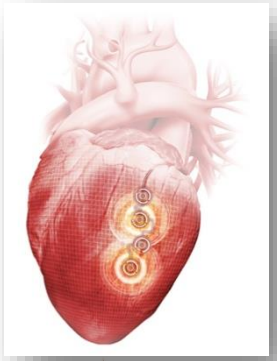
RWE through Health Economics & Outcome Researches

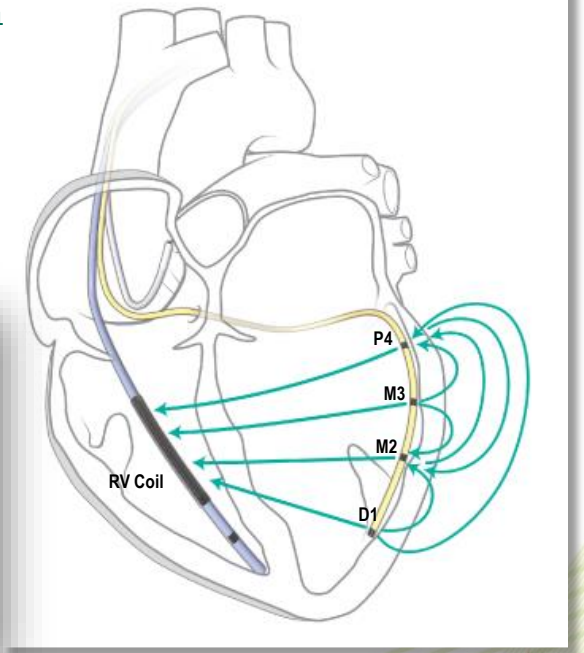
Case 1

Comparative effectiveness with real-world data : Quadripolar vs Bipolar Leads

- Cardiac resynchronization therapy (CRT) is used to restore contraction of the ventricles in heart failure
- Pacing leads are placed in right and left ventricles
- LV pacing location can have an impact on CRT response
- Abbott was the first to develop a quadripolar LV lead (Quartet™) with the ability to electronically adjust the pacing site







Data and study design

- **Clinical question: Is there a reduction in lead-related complications and mortality for patients implanted with quadripolar LV leads, compared to conventional bipolar leads?**
- **Methods: Retrospective Cohort study**
- **Data sources**

Merlin.net™ Patient Care Network

Device programming, device diagnostics Alerts, compliance

PDT Patient Data Tracking

Basic patient demographics Explant, replacement, death

Death Master File (DMF)

Social Security Death Index

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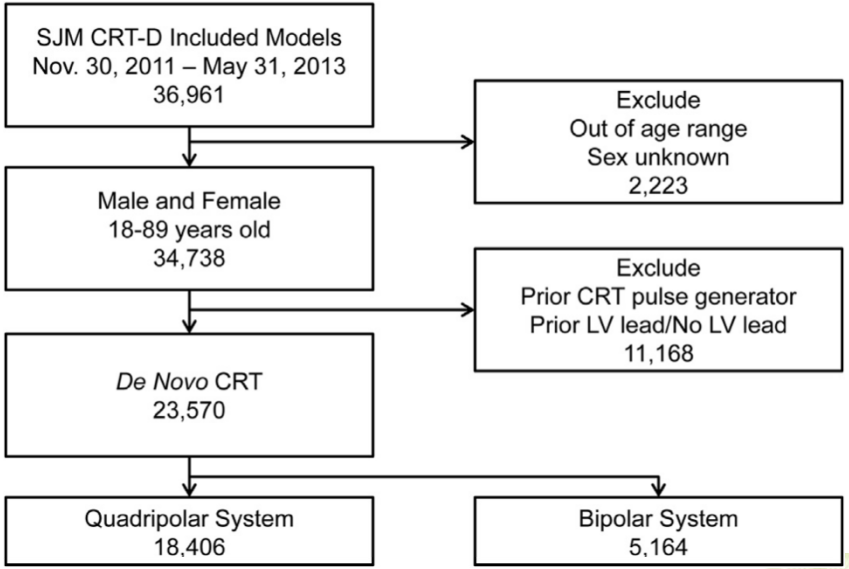
Methods

- **Inclusion: Implant of *de novo* CRT-D system in the U.S. 2011-2013**
- **Outcomes**
  - **Deactivation: Turning off LV lead (non-invasive programming)**
  - **Replacement: Implanting a new LV lead (invasive procedure)**
  - **Death**



Results

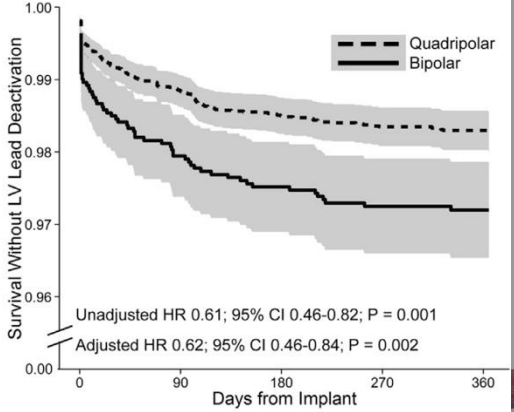
- **Compared to subjects implanted with CRT-D and a bipolar LV lead, those implanted with quadripolar LV leads were associated with:**

Basic characteristics

	Quadripolar (n = 18,406)	Bipolar (n = 5,164)
Follow-up time, days	388 (263-533)	556 (352-667)
Age, years	69.5 ± 11.1	69.4 ± 11.3
Male, %	13,202 (72)	3,749 (73)
Device monitoring, % enrolled	8,983 (49)	2,380 (46)
Household income of subject ZIP code, $	48,930 (39,523-63,606)	48,092 (38,685-60,803)
Proportion of persons ≥25 yrs of age with ≥4 yrs of college in subject ZIP code, %	21.6 (14.7-32.5)	20.5 (14.5-31.0)

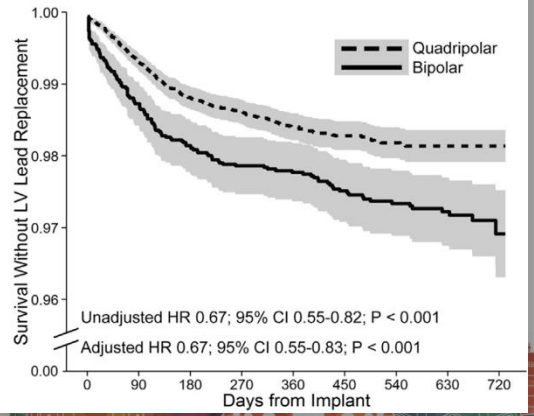
38% reduction in deactivations

Freedom from LV lead deactivation



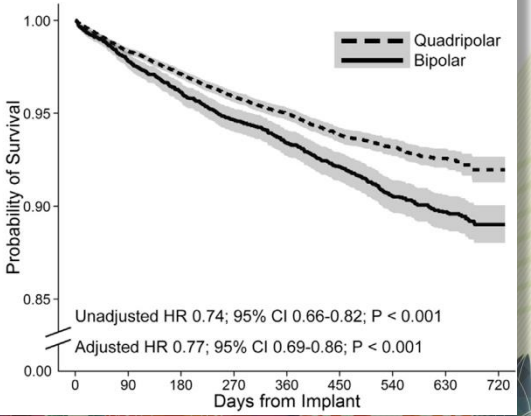
33% reduction in replacements

Freedom from LV lead replacement



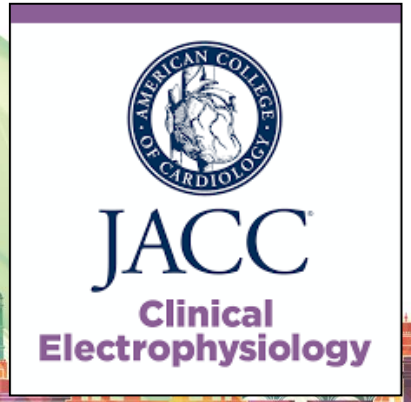
23% reduction in deaths

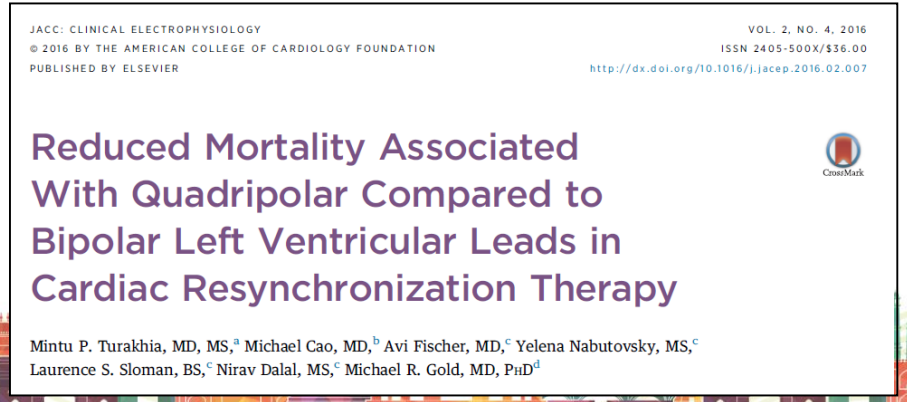
Survival free from mortality



Discussion

- Learnings
  - Large nationwide cohort
  - Results are in line with reductions in HF hospitalization observed in other studies
- Limitations
  - Clinical information such as heart failure progression and cause of death are not available
  - Lack of detailed demographics and clinical characteristics

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Reduced Mortality Associated With Quadripolar Compared to Bipolar Left Ventricular Leads in Cardiac Resynchronization Therapy

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Case2

Clinical and economic outcomes : Cardiac rhythm device monitoring with “digital health” technology

- Newer cardiac rhythm devices (pacemakers and ICDs) have automatic wireless monitoring
- Arrhythmia can be reported to the clinic on the same day, instead of every 3-6 months at office visits
- In the past decade, 30-50% of implanted devices have been enrolled in device monitoring
- Previous studies have shown that device monitoring for pacemakers, ICDs, and CRTs is associated with reduced mortality

Varma N, Piccini JP, Snell J, Fischer A, Dalal N, Mittal S. *JACC* 2015.
Akar G, Bao H, Jones PW, et al. *Circ Arrhythm Electrophysiol* 2015.

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Data and study design

- **Clinical question: Is device monitoring associated with any difference in hospitalizations?**

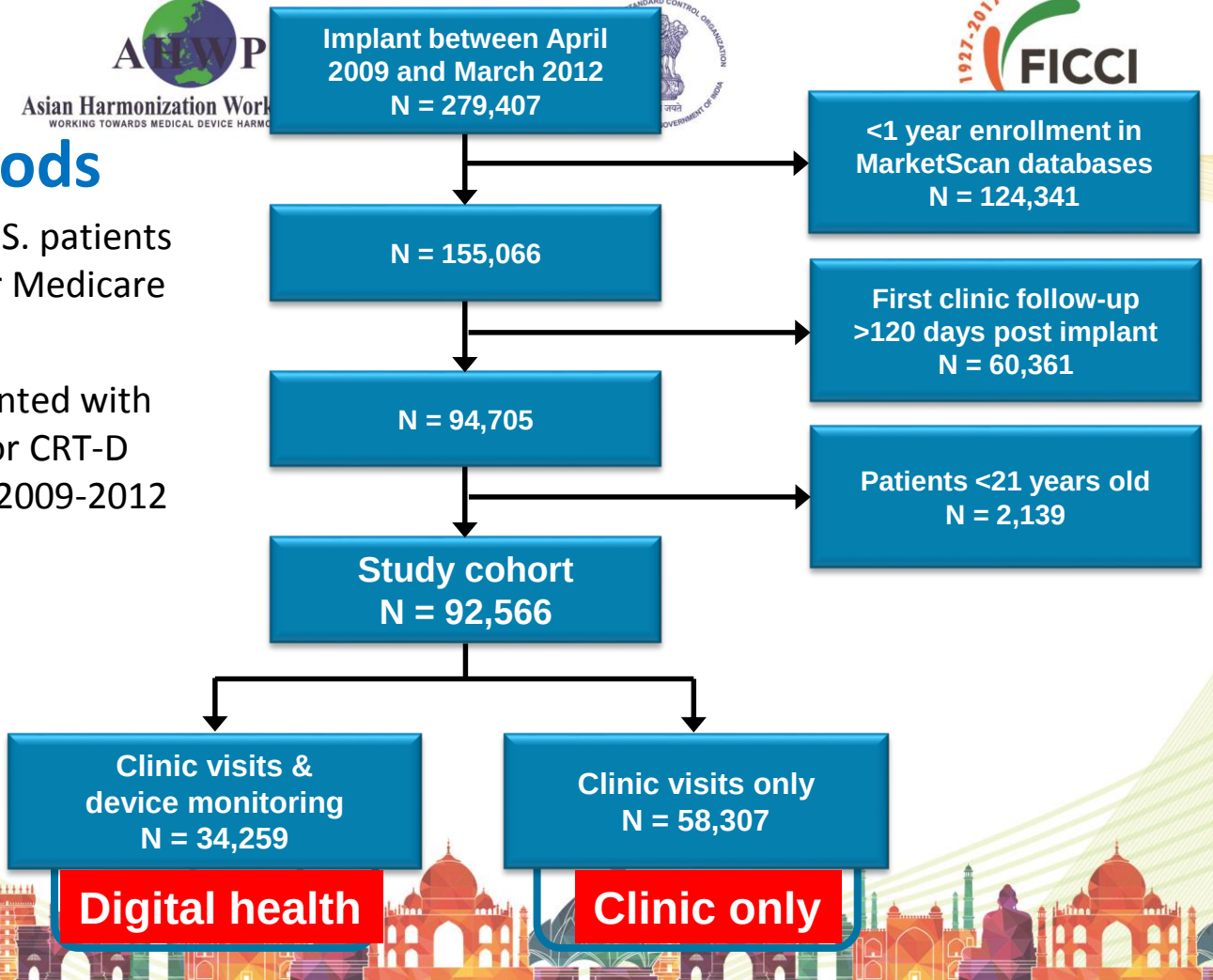
- **Methods: Retrospective Cohort study**

- **Data sources**

CMS, private payers
Outcomes, billing codes, cost

Methods

- MarketScan claims for U.S. patients with private insurance or Medicare
- Inclusion: Subjects implanted with pacemaker, ICD, CRT-P, or CRT-D from any manufacturer, 2009-2012
- Outcomes
  - Hospitalizations
  - Healthcare cost



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Clinical results

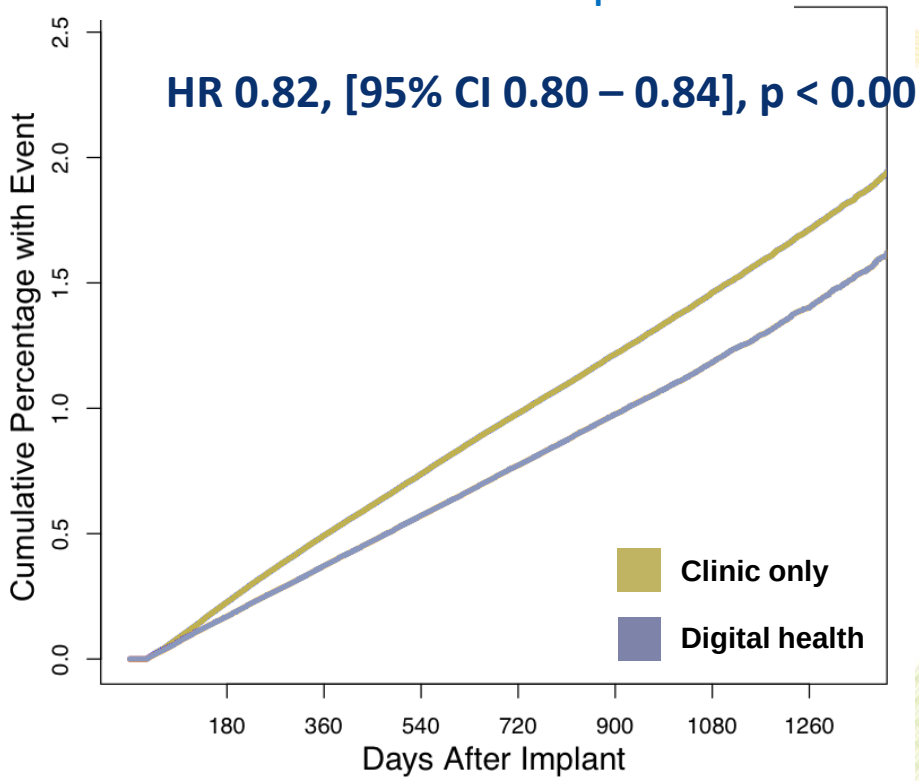
N = 92,566 patients
37% with device monitoring

Mean Length of Stay

- Digital health:5.3 ± 9.6 days
- Clinic only: 8.1 ± 15.7 days

p < 0.001

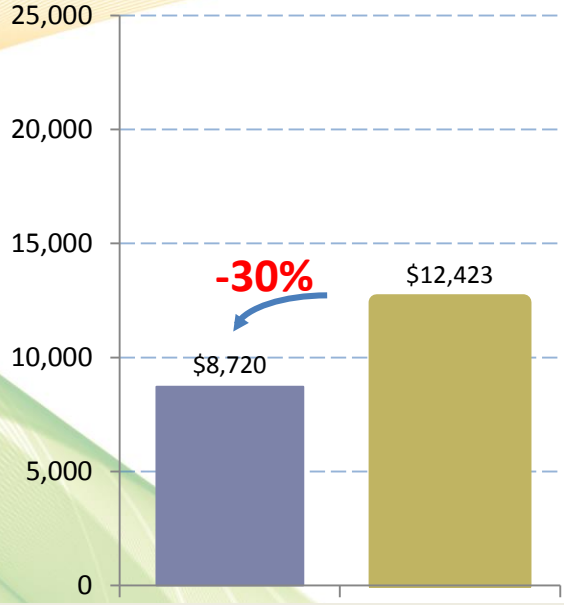
Cumulative risk for all-cause hospitalization



Propensity score adjusted for age, gender, state, and 20 baseline comorbidities

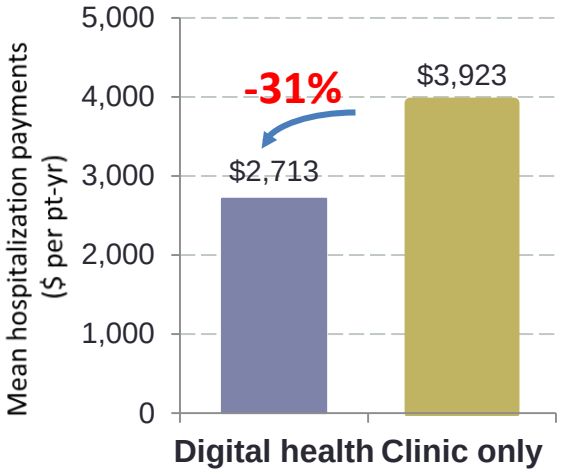
Economic results

All-cause hospitalizations



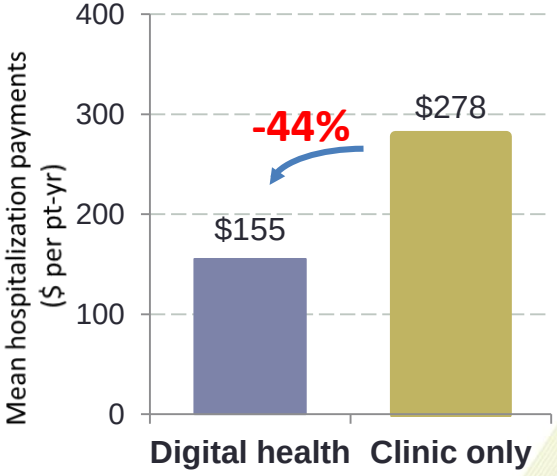
N = 92,566
p < 0.001

Heart Failure hospitalizations



N = 43,280 with baseline HF
p < 0.001

Stroke hospitalizations



N = 41,850 with baseline AF
p = 0.007

Device monitoring is associated with significantly lower payments for : All-cause hospitalizations

- **HF hospitalization in patients with baseline HF**
- **Stroke hospitalization in patients with baseline AF**

Discussion

- **Learnings**
  - Large nationwide cohort from all manufacturers
  - Quantified real-world hospitalizations and healthcare costs
  - Non-clinical data set used to inform clinical decision making

- **Limitations**
  - Unknown why some subjects use device monitoring but others do not
  - There may be additional confounders not measured in the data

HeartRhythm Heart Rhythm Society

Impact of remote monitoring on clinical events and associated health care utilization: A nationwide assessment

Jonathan P. Piccini, MD, MHSc, FHRS,[*] Suneet Mittal, MD, FHRS,[†] Jeff Snell, AB,[‡] Julie B. Prillinger, PhD,[§] Nirav Dalal, MS, MBA,[§] Niraj Varma, MD, PhD, FHRS[‖]

From the [*]Duke University Medical Center, Durham, North Carolina, [†]Valley Health System, Ridgewood, New Jersey, [‡]Data Informs, LLC, Chatsworth, California, [§]St. Jude Medical, Inc., Sylmar, California, and [‖]Cleveland Clinic, Cleveland, Ohio.

Real-world data universe

Industry

Merlin.net™ Patient Care Network

Device programming and diagnostics
Alerts, compliance

PDT Patient Data Tracking

Basic patient demographics
Explant, replacement, death

Industry-sponsored studies and registries
Demographics, outcomes, QOL, economic data

Institutions


Hospital Admin

Administrative dataset
Costs, collections, penalty, resource utilization

eHR Electronic Health Record

Clinical data
Comorbidities, medical status, HCU, events, QOL, death


Hospital Billing

Coding, billing, collections

Public Sources

National death datasets, census, socio-economic

Public insurance and private payers
Outcomes, billing codes, cost

NCDR® National Cardiovascular Data Registry

Society registries
Implant demographics, outcomes

Patients


Patient Reported

Patient-reported outcomes
Satisfaction, QOL


Wearable Devices

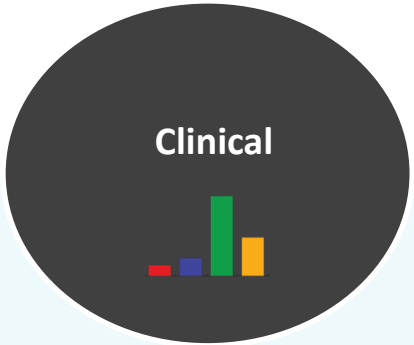
Apple Watch, Fitbit and other multi-sensor consumer devices


Genomics, Proteomics

Disease risk assessment

Economic, Clinical, and Humanistic Outcomes (ECHO)

Cost-effectiveness
Budget impact
Cost of hospitalization
Payback period
Number needed to treat
Clinic workflow and HCRU



Mortality
Hospitalization and length-of-stay
Disease progression
Therapy usage and effectiveness

Quality of life
Patient satisfaction
Patient preference
Willingness-to-pay

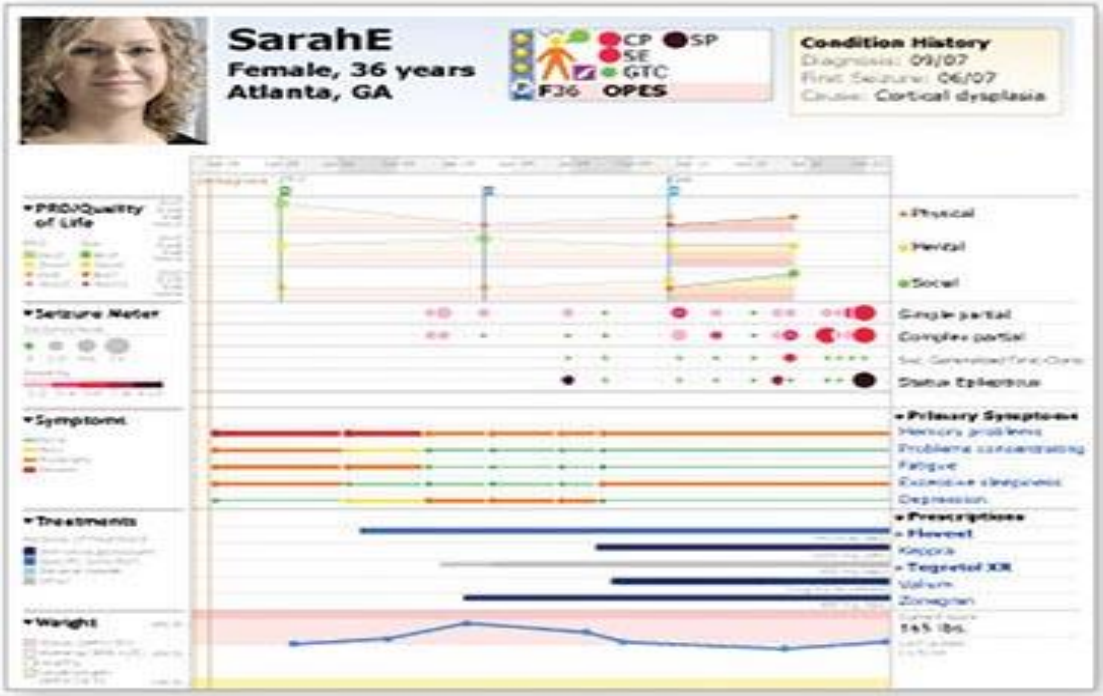
patientslikeme®

Live better, together.™

patientslikeme®

join a free online community for patients with epilepsy.

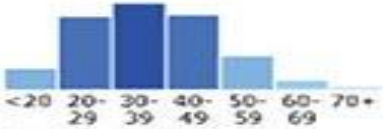
Share Your Health Profile



Find Patients Like You

You can search by epilepsy type, seizure type, symptoms, gender and age to more easily connect with patients like you.

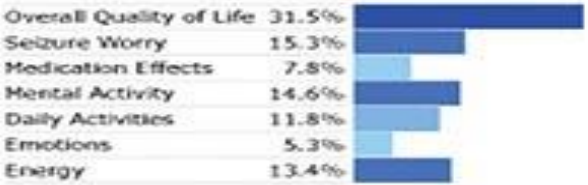
2,354 total patients



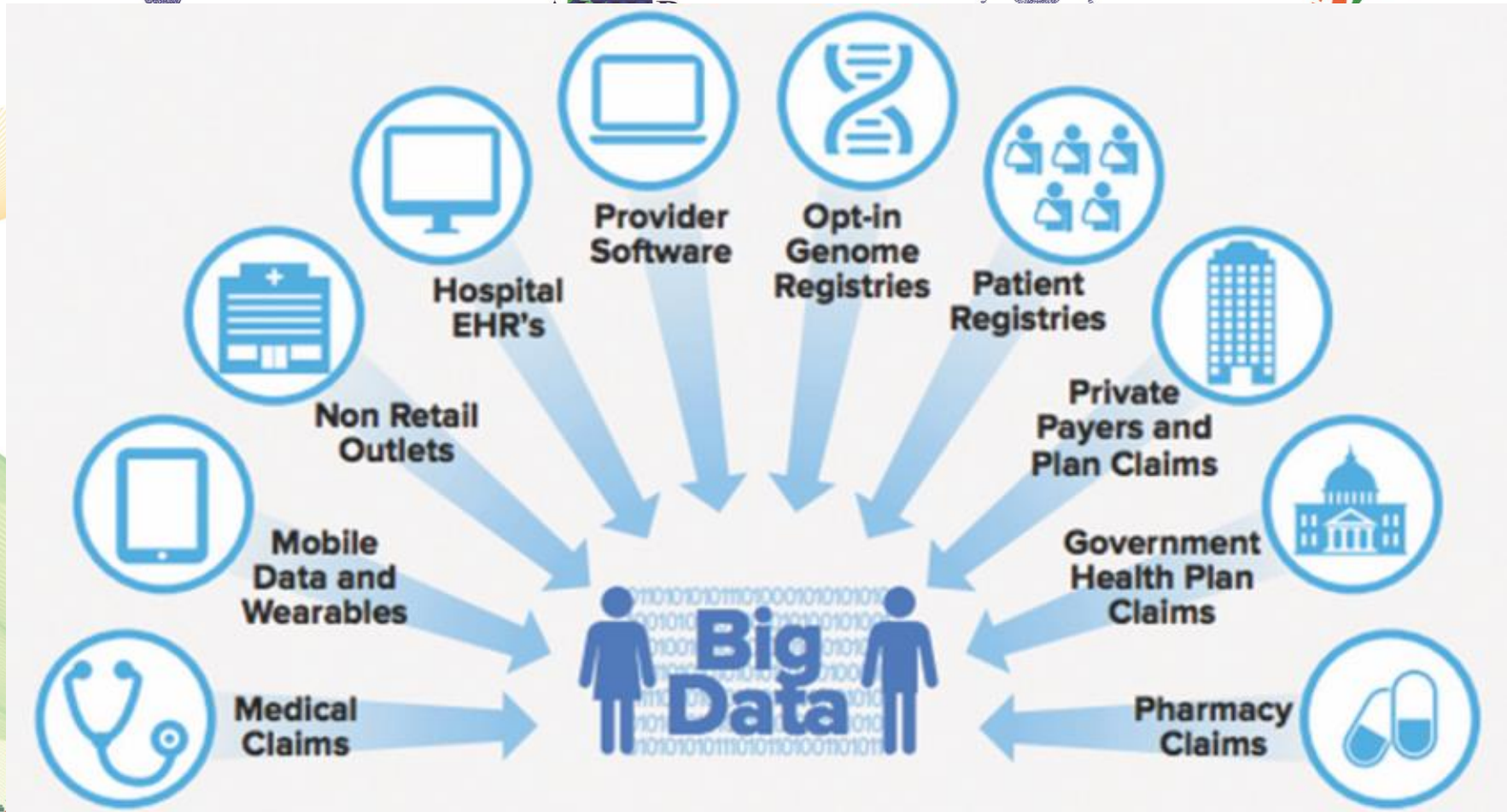
Age

Gender

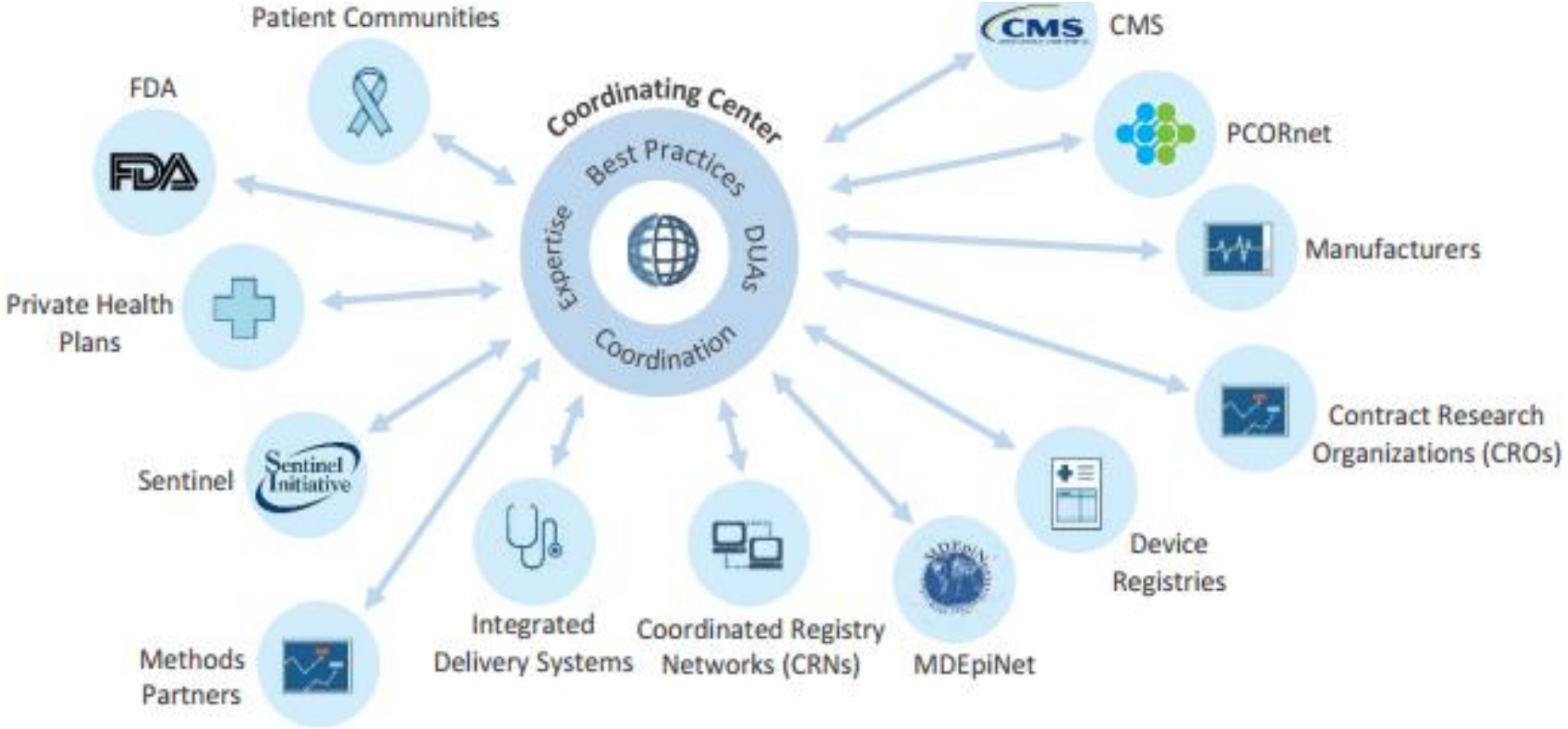
The issues that are most important to our patients:



Learn From Real World Patient Experiences


Provider Software
Opt-in Genome Registries
Hospital EHR's
Patient Registries
Non Retail Outlets
Private Payers and Plan Claims
Mobile Data and Wearables
Government Health Plan Claims
Big Data
Medical Claims
Pharmacy Claims

FDA Outlines Future Medical Device Coordinating Center



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Map: 2018 Health Insurance Exchanges Issuer County Map

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Ministry of Health & Family Welfare
Government of India

Asian Harmonization Working Party
WORKING TOWARDS MEDICAL DEVICE HARMONIZATION IN ASIA

Suggestions

Harmonized Guidance Development on RWE

Ministry of Health & Family Welfare
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