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REAL WORLD EVIDENCE ISSUES AROUND THE WORLD

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TECHNICAL FELLOW

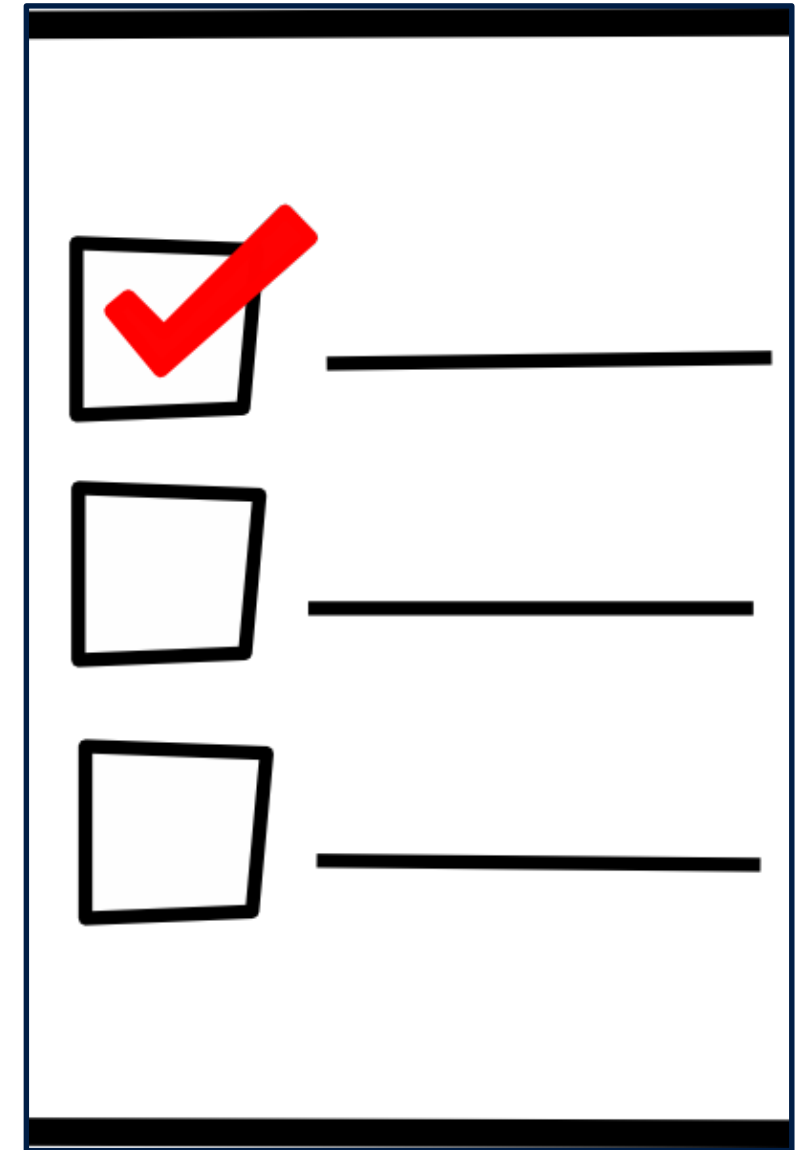
SENIOR DIRECTOR, CORPORATE BIOSTATISTICS



Medtronic
Further, Together

OUTLINE OF PRESENTATION

- **Real World Evidence as External Evidence**
- **RWE to satisfy French reimbursement questions**
- **Relevant aspects of recent IMDRF work**
- **3830 His-bundle pacing example**
- **RWE for Micra**
- **Registries, randomized registries, and quality concerns**
- **Closing**



EXTERNAL EVIDENCE

- In context of a clinical trial, **external evidence** refers to data *generated* outside the current trial, but *analyzed* together with the current trial data
 - Separation of data generation and data analysis processes is an important concept
- Can include RWE/RWD from registries, claims, EHR
 - Not restricted to such data
- Examples of external evidence include:
 - Historical trial data matched to current study data via propensity scoring
 - Historical trial data used as an informative prior together with new data
 - Virtual patient data (generated through modeling and simulation) combined with new real patient observations
 - OPC or PG values determined from literature to be used a benchmark against new clinical data

Leveraging External Data to
Generate Evidence: A Case Study

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Example #1

- Investigational device – Left Ventricular Assist Device
- Study design – Prospective comparative study for pre-market approval
- External data source - Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)
- Use of external data – Concurrent control group
- Statistical method - Propensity score stratification

US Food and Drug Administration. Summary of safety and effectiveness data – HeartWare® ventricular assist device. Section X. Summary of primary clinical study. Available at:

http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100047b.pdf. Accessed August 29, 2016.

Example #2

- Investigational device – Transcatheter Aortic Heart Valve
- Study design – Comparative study for indication expansion with historical control
- External data source – The surgery arm of a completed randomized clinical trial
- Use of external data – Historical control group
- Statistical method - Propensity score stratification

EXTERNAL EVIDENCE

- Easy cases
 - Merging in mortality information for all subjects from Social Security Death Index for a US study
 - Merging in hospital costs for all subjects
 - Data generated during study, but captured without regular site staff
- Harder cases
 - Using only historical data for the control arm, and only current data for the experimental arm
 - Especially hard if data capture mechanism differ substantively between arms
 - Working with a novel virtual patient model derived from M&S
 - Unclear what level of validation is appropriate



LEVERAGING THE PLATFORM: SUPPORTING GEOGRAPHY-SPECIFIC NEEDS

Deep Brain Stimulation (DBS)



- **Product/Therapy**
 - Implantable stimulator for the treatment of movement disorders such as Parkinson's Disease and Essential Tremor
 - FDA-approved labeling for MRI head scans under specific conditions
 - Reversible and adjustable via non-invasive clinician programmer
- **Issue/Barrier**
 - French health authority (HAS) reimbursement levels dependent on outcomes and reporting
 - France HAS requirement for France-exclusive data that makes gathering suitable sample sizes challenging (would require upwards of 21 new French sites contributing data)

LEVERAGING THE PLATFORM: SUPPORTING GEOGRAPHY-SPECIFIC NEEDS

- **PAN Solution for French HAS DBS Requirement**
 - Proposed utilization of global standardized PAN protocol and platform, complement of patients from existing EU sites to contribute clinical evidence
- **Status/Result**
 - French HAS accepted proposal; only 5 French sites needed, with remainder of patients contributing from existing EU sites already on PAN platform (20 total sites)
 - Fulfilled geographic requirements, accelerated data collection via existing active sites, avoided costs associated with opening new sites for a single study requirement.

REAL WORLD EVIDENCE INTERPRETATION

OPPORTUNITIES FOR DATA

- Positive ongoing collaborations across countries to share information from multiple medical device registries
- Consider Vision of IMDRF Registry Working Group
 - We **envision international harmonization** of medical device registries analytical methodologies via international Coordinated Registry Networks (iCRNs) **based on demonstrated best practices**
 - While not all countries will contribute registry data to every device evaluation, **all countries will benefit from the global collaboration**
 - The collaboration should be based on a **systematic agreed upon process** for sharing and evaluating data/findings from medical device registries
 - All registries will agree on **pre-specified analyses and collaborative sharing** of the outputs with each other and the regulators
- Structured sharing can enable better and quicker understanding of device performance without undue delay by country/region
 - Interpret region specific findings in context of all relevant evidence





- Sets as a default the position that foreign data can be accepted
 - Foreign data can still be challenged on a case by case basis
 - Earlier stance (in some jurisdictions) was that acceptance of foreign data always needed to be justified
- Note that this is bilateral
 - Speaks to both data import and data export
- Possibly the most impactful change to previous documents

IMDRF MDCE WG (PD2)/N56 (formerly GHTE/SG5/N2R8:2007)

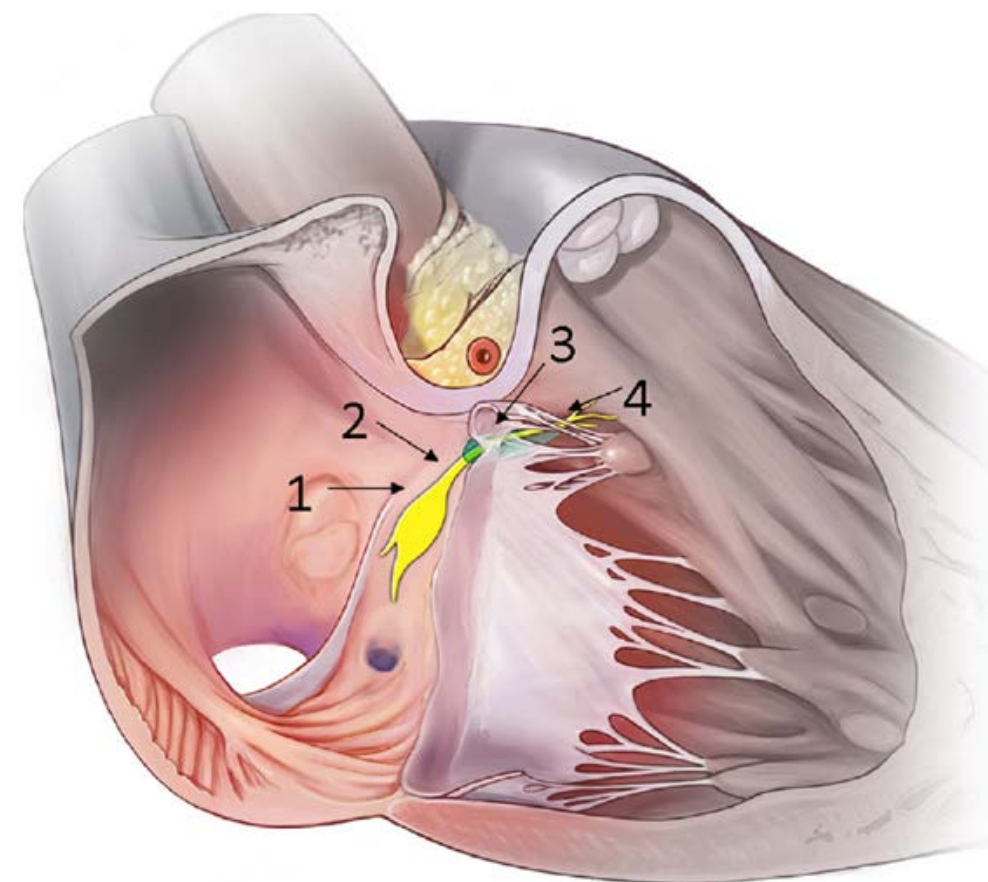
**Appendix D: Considerations for the Application of Clinical Data Generated from
Different Jurisdiction(s)**

When clinical investigations are conducted ethically in accordance with applicable Good Clinical Practice (GCP), the clinical data should be accepted for consideration in any jurisdiction. However, the applicability of the clinical data may be dependent on differences in regulatory requirements, intrinsic and extrinsic factors.

INDICATION EXPANSION

USING EXISTING INFORMATION

- In March 2018, FDA informed us that use of Medtronic systems for His-bundle pacing was off label
- FDA recommended PMA-S submission via Real-World Evidence to update 3830 labeling to include His-bundle pacing
 - Leverage Medtronic's meta-analysis as the foundation of the Clinical assessment
 - Update 3830 Instructions for Use
- An expedited submission was encouraged
 - Medtronic set an internal target for April, 2018



INDICATION EXPANSION

USING EXISTING INFORMATION

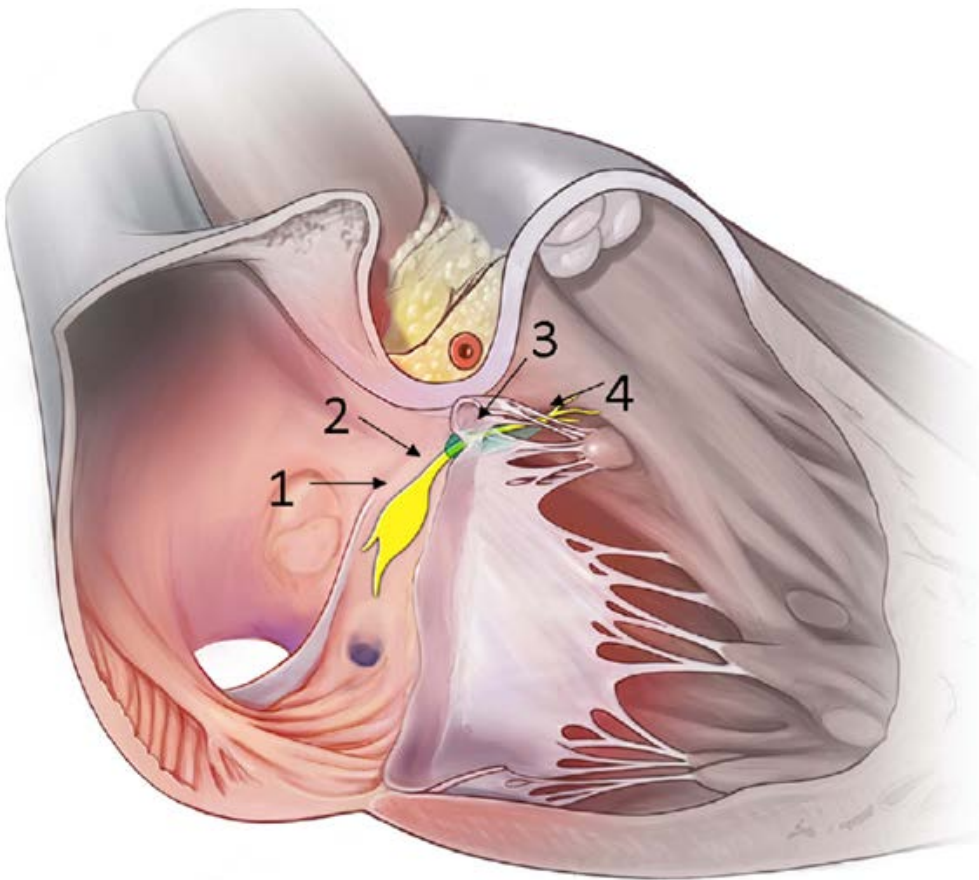
Aim: Submit Real-World Evidence Assessment and PMA-S to update 3830 labeling for His-bundle Pacing

Data Used

- Literature: Systematic review and Meta-analysis
- Clinical: Product Surveillance Registry
- Big data: Device Registration and CareLink

Milestones Achieved

- ✓ Real-World Evidence Assessment and PMA-S submitted within 4 weeks from FDA notification
- ✓ Completed 3 rounds of deficiencies
- ✓ FDA approved labeling in June 2018



P830061/S157	06/28/2018	N - Normal 180 Day	CAPSURE SENSE MRI SURESCAN LEAD AND CAPSURE SENSE MRI SURESCAN LEAD	MEDTRONIC CARDIAC RHYTHM DISEASE MANAGEMENT	Approval for an update to the indications for use to include pacing at the bundle of His. The device, as modified, will be marketed under the trade name SelectSecure MRI SureScan Lead Model 3830 and is indicated for: The Model 3830 lead is intended for pacing and sensing in the atrium or right ventricle. It is also intended for pacing and sensing at the bundle of His as an alternative to right ventricular pacing in a single or dual chamber pacing system.
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COVERAGE WITH EVIDENCE DEVELOPMENT

MICRA (LEADLESS PACEMAKER)

- **Longitudinal Coverage With Evidence Development Study on Micra Leadless Pacemakers (Micra CED)**

- ClinicalTrials.gov Identifier: NCT03039712

- Detailed Description:

- Micra CED study is a study of the Medicare beneficiary population implanted with single-chamber ventricular pacemakers, and will be executed by analyzing administrative claims data. The study consists of two primary objectives: estimate the: (1) acute overall complication rate and (2) the **2-year survival rate** of patients implanted with a Micra leadless pacemaker. As part of the secondary objectives of the study, a comparative analysis of Micra leadless pacemakers to single-chamber ventricular transvenous pacemakers will be conducted.
- The analysis will be in CMS claims data and is subject to a central IRB. However, individual hospitals are not engaged in research and local IRB oversight is not necessary.

- Estimated Enrollment : 37000 participants

- **Micra Transcatheter Pacing System Post-Approval Registry**

- ClinicalTrials.gov Identifier: NCT02536118

- Detailed Description:

- The Micra Registry is a global, prospective, observational, multi-site registry. Patients enrolled in the Micra Registry will be **prospectively followed for a minimum of 9 years** post-implant or until registry closure, patient death, patient exit from the registry (i.e., withdrawal of consent), or unless patient is participating in an acute performance sub-study of the Micra Registry*.
- Enrolled patients will have scheduled follow-up visits at least annually or as prompted by reportable adverse events; however, all Micra system follow-up patient visits are to be reported. Therefore, if more frequent scheduled visits occur per a provider's standard care practice, those visits are reported. The total estimated registry duration is 11 years.

- Estimated Enrollment : 3100 participants

LEADLESS PACEMAKER NATIONAL COVERAGE DETERMINATION (NCD)

- Final NCD issued January 18, 2017 by Centers for Medicare & Medicaid Services (CMS)
 - Covers leadless pacemakers consistent with FDA labeling
 - Requires coverage with evidence development (CED), including prospective longitudinal studies (i.e., those using administrative Medicare claims data)
- Medtronic is conducting two studies that meet CED requirement for leadless pacemakers

Micra CED Study (NCT03039712)

- Approved by CMS on March 9, 2017
- Focuses on outcomes reliably measured in Medicare claims data
- Tracks all Medicare beneficiaries with claims linked to Micra implants
- Includes comparative analysis to transvenous pacemakers

Micra TPS Post Approval Study (PAS) (NCT02536118)

- Approved by CMS on February 9, 2017
- FDA-required post-market registry
- 9-year follow-up
- Addresses questions of interest to CMS such as hemodynamic affects and battery longevity

THE MICRA CED STUDY

SUMMARY OF OUTCOME MEASURES



Acute Complication Rate (30 days)

- Single-chamber ventricular pacemaker system and/or procedure related complications at 30 days.
- Acute complications include embolism/thrombosis, event at the puncture site, cardiac effusion/perforation, device-related complication, or other complications following the implantation of a single-chamber ventricular pacemaker system.



2-Year Survival Rate

- Estimate the 2-year survival rate of patients implanted with a Micra leadless pacemaker.

Chronic Complication Rate (6 months)

- Chronic complications are a subset of acute complications that may also occur within six months following the implantation of a single-chamber ventricular pacemaker.
- Single-chamber ventricular pacemaker system and/or procedure related complications at six months.

Device-Related Re- Intervention Rates

- Device-related re-interventions are procedures associated with the insertion/replacement, revision, or removal of either a leadless or transvenous pacemaker system or components following the index implantation of a single-chamber ventricular pacemaker.
- Device-related re-intervention rates will be reported at six month intervals for two years following the index implantation of a single-chamber ventricular pacemaker.

★ Primary Objectives

REPORTING OF ACUTE COMPLICATIONS IN MICRA STUDIES

KEY DISTINCTIONS BETWEEN IDE, PAS, AND CED IN MEASUREMENT & REPORTING

Micra IDE

- Collected serious and all cardiovascular events regardless of relatedness to procedure or system
- Independent physician-adjudication committee classified relatedness and severity

Micra PAS

- PAS collects events related to the procedure or system as determined by the center
- Independent physician-adjudication committee classified relatedness and severity

Micra CED Study

- A priori definition of outcomes
- An outcome/event is counted if a procedure/diagnosis code occurs on or after the Micra implant procedure date regardless of relatedness

-
- Rates included in results from Micra IDE, PAS and CED are unadjusted
 - Event rates reflect number of unique patients

INCORPORATING MECHANISMS FOR OUTCOME VALIDATION IN MICRA CED

ANALYSIS OF MICRA PAS PATIENT SUBSET IN CED STUDY

- Micra CED Study relies on RWE to characterize patient population and measure outcomes
 - Patient demographics, comorbidities and outcomes are defined using procedure and diagnosis coding
 - Outcomes were derived from outcomes reported in landmark pacing clinical trials and the Micra IDE and PAS
 - An independent Micra CED committee developed the outcome definitions a priori and reviewed individual complicated cases
- Challenges with event attribution
 - Contacting patients or providers to validate outcomes observed in claims data **is prohibited**
 - In contrast, Micra PAS study is based on traditional case report forms and clinical adjudication of events
- Micra CED Study included an outcome validation analysis to compare Micra PAS and Micra CED
 - Outcome validation analysis assessed subset of patients enrolled in both the Micra PAS and the Micra CED Study
 - We measured whether outcomes from adjudicated PAS case reports can be found using Medicare claims

MICRA CED AND PAS ACUTE COMPLICATION OUTCOME VALIDATION ANALYSIS

RELIABLE IDENTIFICATION OF CLINICALLY MEANINGFUL EVENTS

- Outcomes validation study included >200 patients enrolled in both Micra PAS and Micra CED studies
- PAS
 - Collects events related to the procedure or system as determined by the center
 - Independent physician-adjudication committee classified relatedness and severity: major; minor; observations
- Outcome validation analysis assessed whether the same outcomes are measured in the same patients
 - Outcomes: embolism/thrombosis, effusion/perforation, events at groin/puncture site, device dislodgement, and infection

Results of Outcome Validation Analysis

- 100% of the acute major or minor complication events in the PAS were identified using claims data in the Micra CED study data
 - i.e., all major and minor events seen in PAS were seen in CED
- Evidence that the CED has a higher potential for false positives
 - 8 additional patients with major and/or minor events seen in CED did not have events in PAS

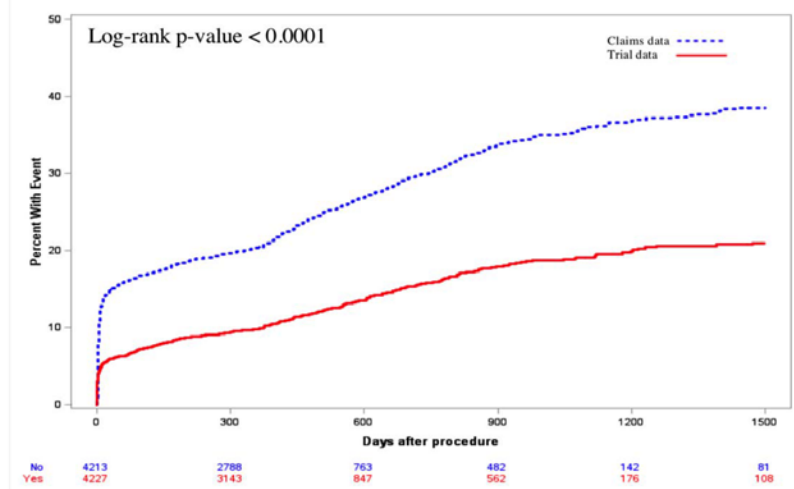
* Major: Complications related to the Micra procedure or system that resulted in hospitalization, prolonged hospitalization ≥ 48 hours, permanent loss of device function, system revision or death; Minor: Events clinically-adjudicated as related and requiring invasive therapy, but not meeting criteria of a major complication; Observation: related events with no invasive intervention required

EXTENSIONS

INVESTIGATING DIFFERENCES IN DATA SOURCES

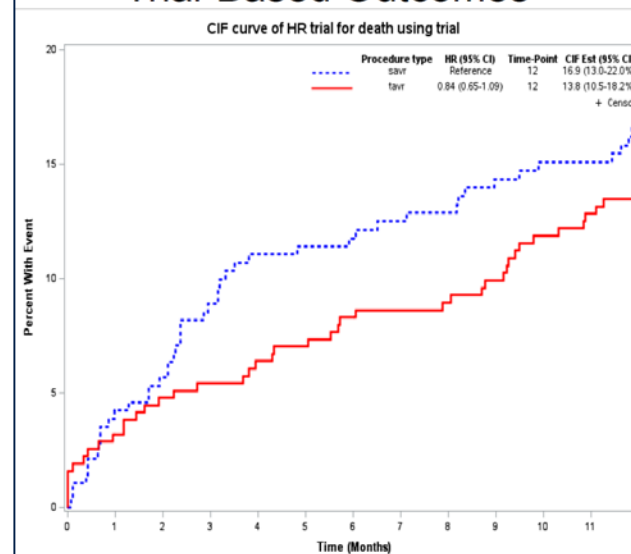
Inclusive Set of Stroke Claims Overcounts and Undercounts Stroke

- 631 trial adjudicated strokes. 395 with a corresponding claim
- Also, a large number of excess stroke codes in claims not adjudicated as strokes

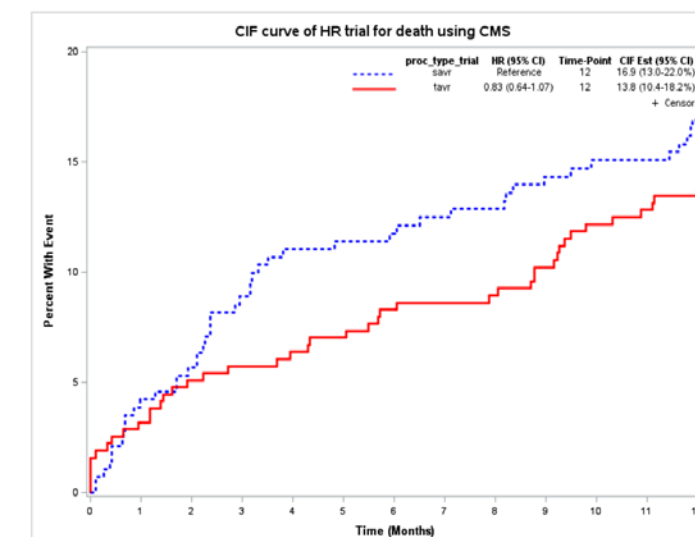


Treatment Effect Comparisons – Death at 1 year, CoreValve High Risk Pivotal

Trial-Based Outcomes



Claims-Based Outcomes



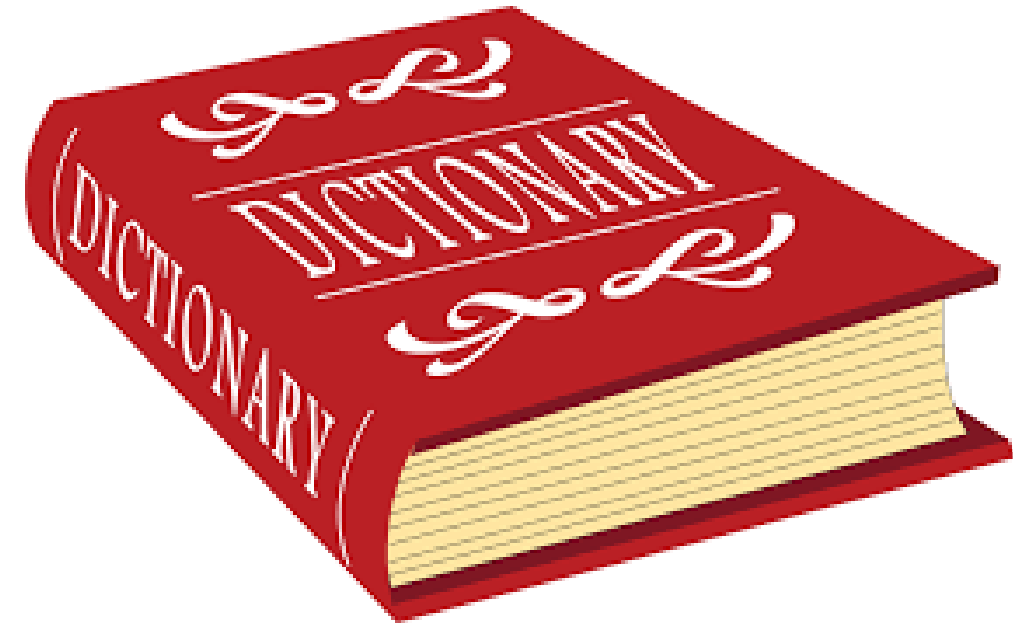
THE EXTEND STUDY: LINKING MEDTRONIC COREVALVE PIVOTAL TRIAL DATA TO CMS CLAIMS

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Beth Israel Deaconess Medical Center
Medical Director of Trial Design, Baim Institute for Clinical Research
Associate Professor of Medicine, Harvard Medical School

DEFINITIONS

A **Registry** is an organized system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure. At their core, registries are data collection tools created for the purpose of generating clinically usable information and evidence. Entry in a registry is generally defined either by diagnosis of a disease (disease registry) or prescription of a drug, device, or other treatment (exposure registry). *(Adapted version of the European Medicines Agency's definition of "registry")*

A **randomized registry trial** is a randomized trial embedded in a registry. Much emphasis may be placed on minimizing the additional infrastructure (above that of the registry) that is needed to perform randomization.



DESIGNING A NEW REGISTRY

WITH THE CAPABILITY OF EMBEDDING A CLINICAL TRIAL

Requirements	Practical Considerations
The quality of the data should be evaluated; assured across multiple dimensions	The data must be contemporaneous, accurate, legible, consistent, complete, and reliable



REAL WORLD EVIDENCE INTERPRETATION

FDA GUIDANCE ON USE OF REAL WORLD EVIDENCE

IV. Regulatory context in which RWE may be used

A. General considerations for the use of RWE

FDA will consider the use of RWE to support regulatory decision-making for medical devices when it concludes that the clinical data contained within RWD source(s) used to generate the RWE are of sufficient quality to provide confidence in the analyses necessary to inform or support the regulatory decision throughout the total product life cycle. The threshold for sufficient quality will depend on the specific regulatory use of the evidence. For example, a specific patient registry might be informative for postmarket surveillance, but not adequate for a premarket determination of safety and effectiveness, while another patient registry may be suitable to address both pre- and postmarket evidence requirements.

- Interpretation (and application) will be determined case-by-case
 - Should be done in the context of other relevant information
- Potential applications include:
 - Expanded indications for use
 - Postmarket surveillance studies
 - Control group
 - Supplementary data
- “Sufficient quality” is a key concern

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

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on July 27, 2016.



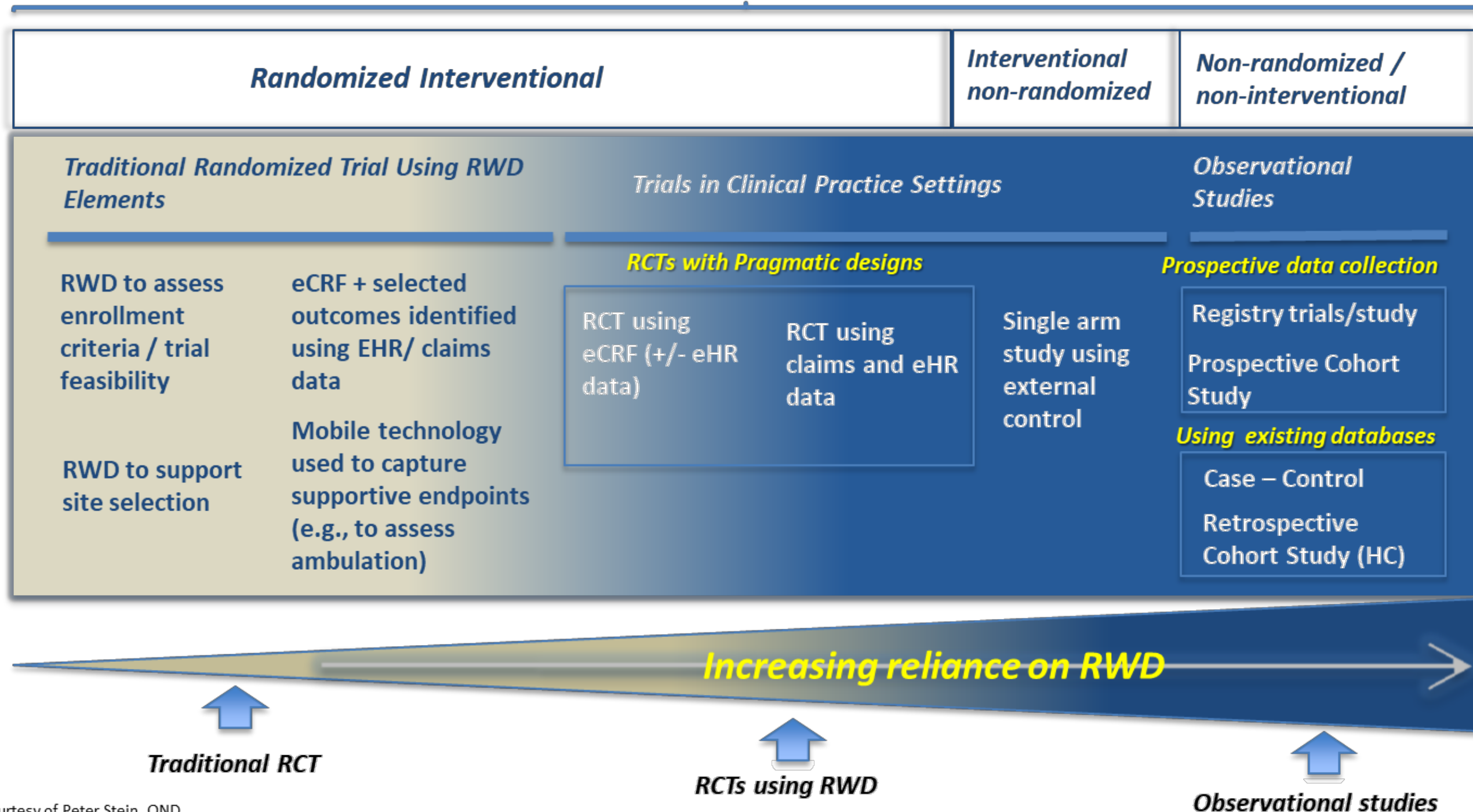
REGISTRIES AND RCTS

SOMETIMES DISTINCT, SOMETIMES EQUIVALENT

- RCT (randomized controlled trial) label only indicates treatment assignment mechanism and presence of comparator
 - Doesn't actually say anything about overall quality of the study
 - Need more nuance in evaluating levels of evidence



Spectrum of Potential Uses of RWD

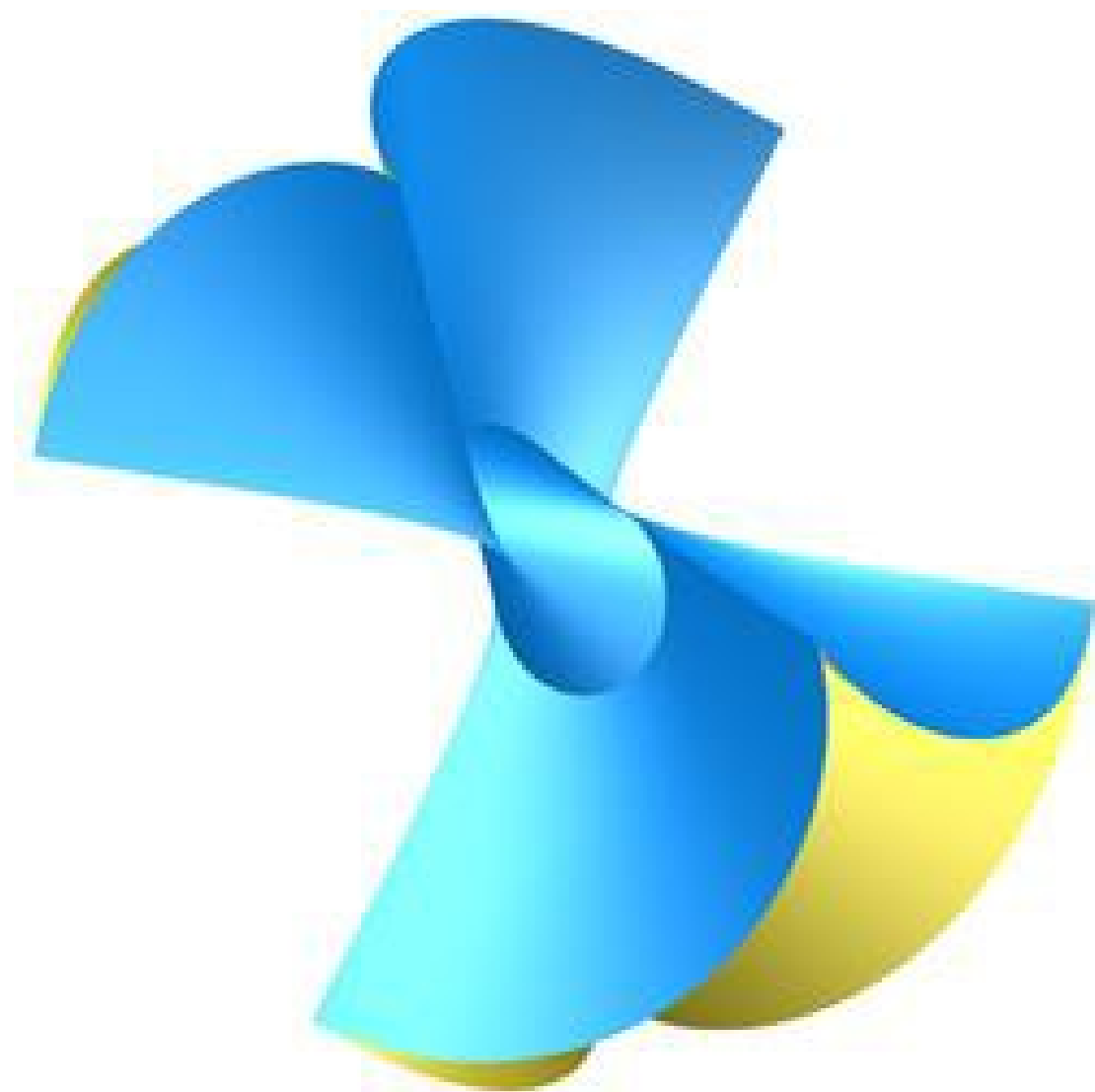


FDA Framework for Device Oversight



The FD&C Act provides a flexible framework that takes into account that all medical devices inherently carry some risk, recognizes that “safe and effective” does not mean “risk free,” and requires that FDA tailor its oversight of devices to the degree of risk presented to provide a “reasonable assurance” of safety and effectiveness rather than an “absolute assurance”

Medical Device Innovation



Innovation and Safety
are not polar opposites but
rather two sides of the
same coin

CLOSING

- Real world data/evidence (RWD/RWE) is increasingly of interest
 - Vital to ability to **generalize** findings beyond specialized clinics, researchers
- Diverging views as to proper role of RWE
 - Use existing infrastructure to capture new data settings?
 - Or push clinical trial infrastructure, auditing, etc. out to new data settings?
 - Only use when data is pristine?
 - Or make allowances when alternatives are challenging (e.g., small populations)?
 - Supplement or replacement to trial data?
 - Lots of intermediate options
- “Average patient” not likely to be in a study
 - **Only considering “research grade” RWE for all regulatory decision making could severely skew our understanding of real world usage**
- Organizations such as MDIC, CTTI, and IMDRF will be instrumental in building consensus around these and related issues



THANK YOU!

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