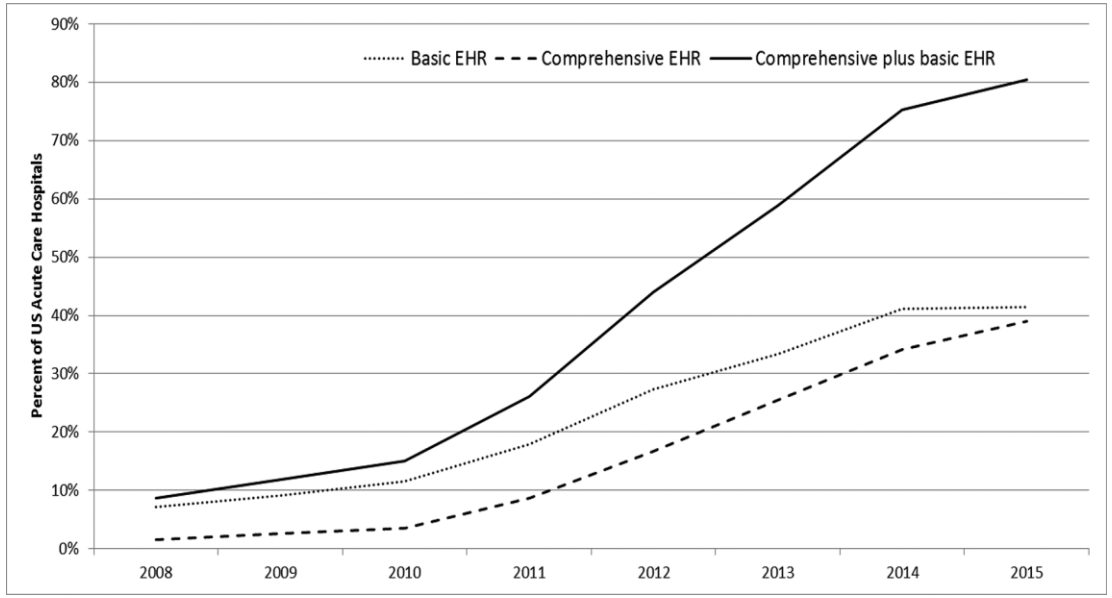
Leveraging RWD in a Multinational Trial: Results from the other eHARMONY (Harmony Outcomes EHR Ancillary study)

Sudha Raman, PhD
Bradley Hammill, DrPH
Lesley Curtis, PhD

Duke Clinical Research Institute | FROM THOUGHT LEADERSHIP TO CLINICAL PRACTICE

Way back when…



J Am Med Inform Assoc https://doi.org/10.1093/jamia/ocx080

Opportunities to use the EHR in clinical research

Pre-study
- Examine how high-performing sites use the EHR
- Assess usability of inclusion and exclusion criteria
- Examine cohort interaction profiles with health system
- Inform recruitment plan

Study Setup
- Identify local participants
- Embed encounter instructions and site content into EHR
- Embed pre-consent & study specific consent
- Model outcomes

Recruitment
- Incorporate screening criteria into EHR for
  - Scheduling subjects
  - Contacting subjects
  - Recruiting subjects
- Alert provider of patient eligibility
- EHR Health Portals
  - Patient opt in/out for types of studies

Study Conduct
- Data capture at care delivery
- Auto-populated CRFs fields from EHR
- Extract data to facilitate work of study coordinator
- Rules, Alerts & Checks
  - Data completeness
  - Quality compliance
  - Hospitalization/AEs
  - Event rates
- Patient retention and education


The NEW ENGLAND JOURNAL of MEDICINE

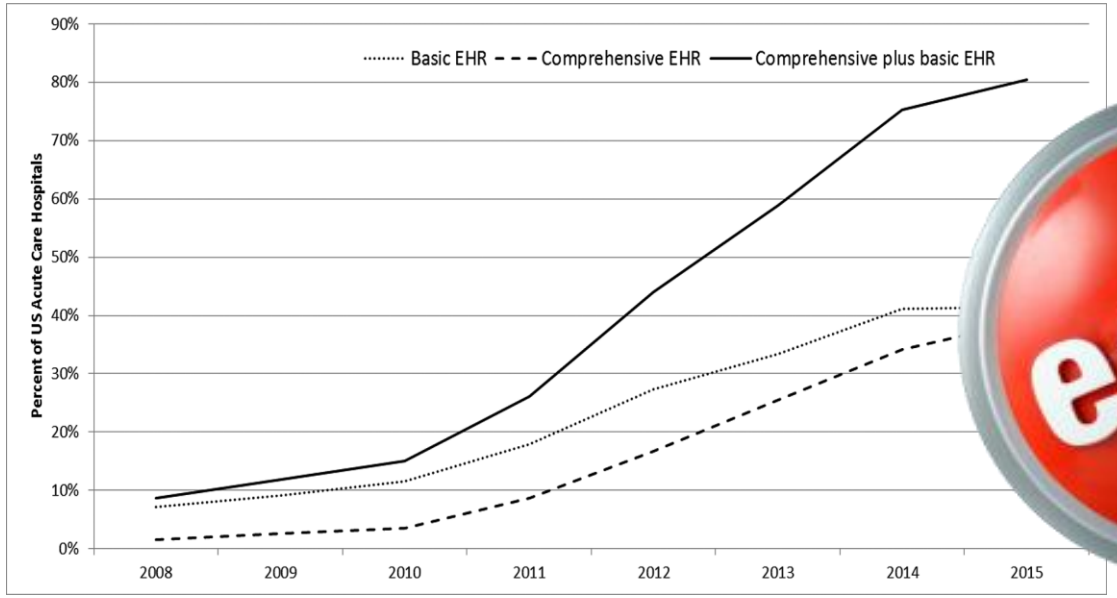
SOUNDING BOARD

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.

N ENGL J MED 375;23 NEJM.ORG DECEMBER 8, 2016

Way back when…



J Am Med Inform Assoc https://doi.org/10.1093/jamia/ocx080

Opportunities to use the EHR in clinical research

Pre-study

- …e how high-…g sites use the
- …bility of …d exclusion
- …hort …profiles with …tem
- …ecruitment plan

Study Setup

- Identify local participants
- Embed encounter instructions and site content into EHR
- Embed pre-consent & study specific consent
- Model outcomes

Recruitment

- Incorporate screening criteria into EHR for
  - Scheduling subjects
  - Contacting subjects
  - Recruiting subjects
- Alert provider of patient eligibility
- EHR Health Portals
  - Patient opt in/out for types of studies

Study Conduct

- Data capture at care delivery
- Auto-populated CRFs fields from EHR
- Extract data to facilitate work of study coordinator
- Rules, Alerts & Checks
  - Data completeness
  - Quality compliance
  - Hospitalization/AEs
  - Event rates
- Patient retention and education

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.

N ENGL J MED 375;23 NEJM.ORG DECEMBER 8, 2016

Harmony Outcomes Trial

Trial objective

To determine the effect of albiglutide, when added to standard blood glucose lowering therapies, on major cardiovascular events in patients with type 2 diabetes mellitus

- 9,400 subjects
- Event-driven trial
- 28 countries
- 644 sites

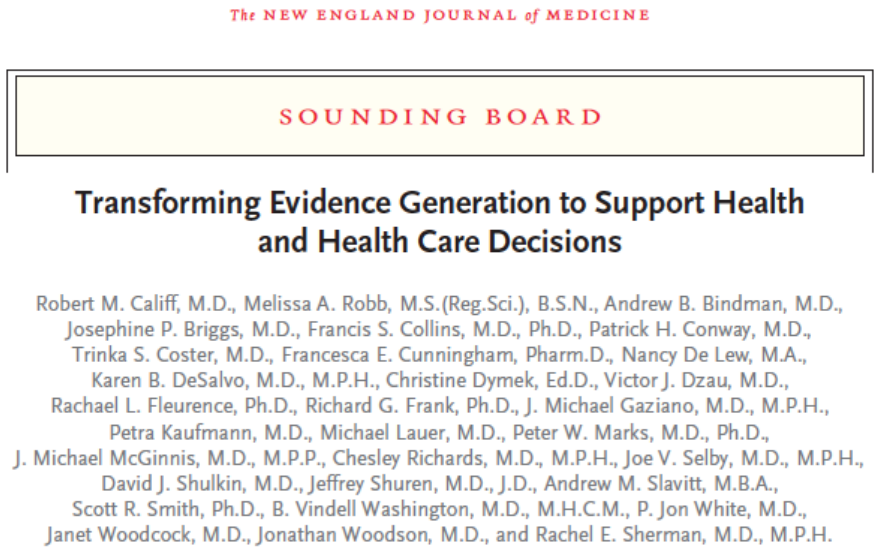
Harmony Outcomes EHR Ancillary Study

Guiding principle

The EHR is a rich source of clinical data that are increasingly used in pragmatic health research initiatives, but the assumption that EHR data are fit for use in high-quality clinical research has not been rigorously evaluated.

Goals

- To further our understanding of how EHR data can be organized to facilitate a more efficient, reliable, and cost-effective research process
- To identify ways to transform trial conduct, reducing personnel burden



Harmony Outcomes EHR Ancillary Study (Planned)

Timeline: Concurrent with main trial

Objective 1

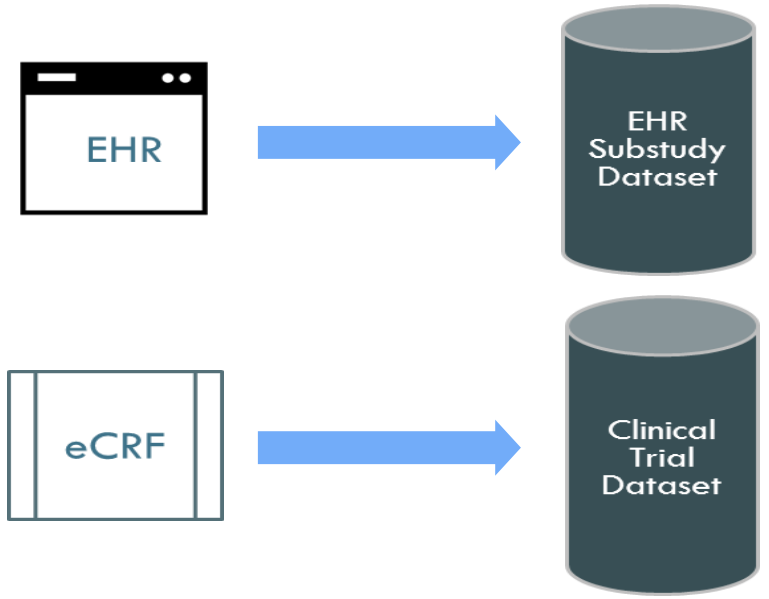
Understand how EHR data are used to facilitate trial recruitment and the barriers to that use

Objective 2

Evaluate the fitness of EHR data for use in populating baseline characteristics in the eCRF

Objective 3

Explore the use of EHR data to find events of interest during trial follow-up



Harmony Outcomes EHR Ancillary Study (Actual)

Timeline: Following main trial database lock

Objective 1

Understand how EHR data are used to facilitate trial recruitment and the barriers to that use.

→ ***Site survey***

Objective 2

Evaluate the fitness of RWD data for use in populating baseline characteristics in the eCRF

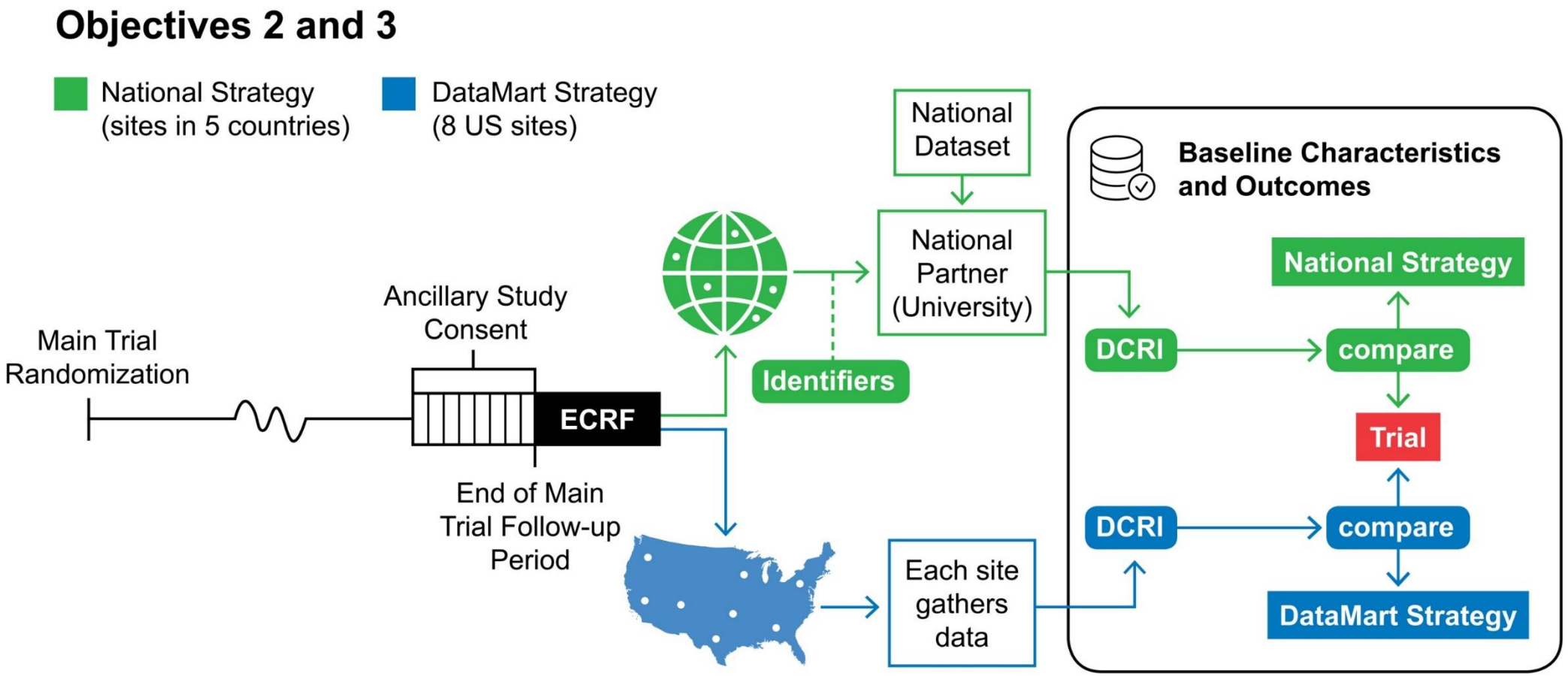
Objective 3

Evaluate the fitness of RWD data for use in identifying clinical endpoints

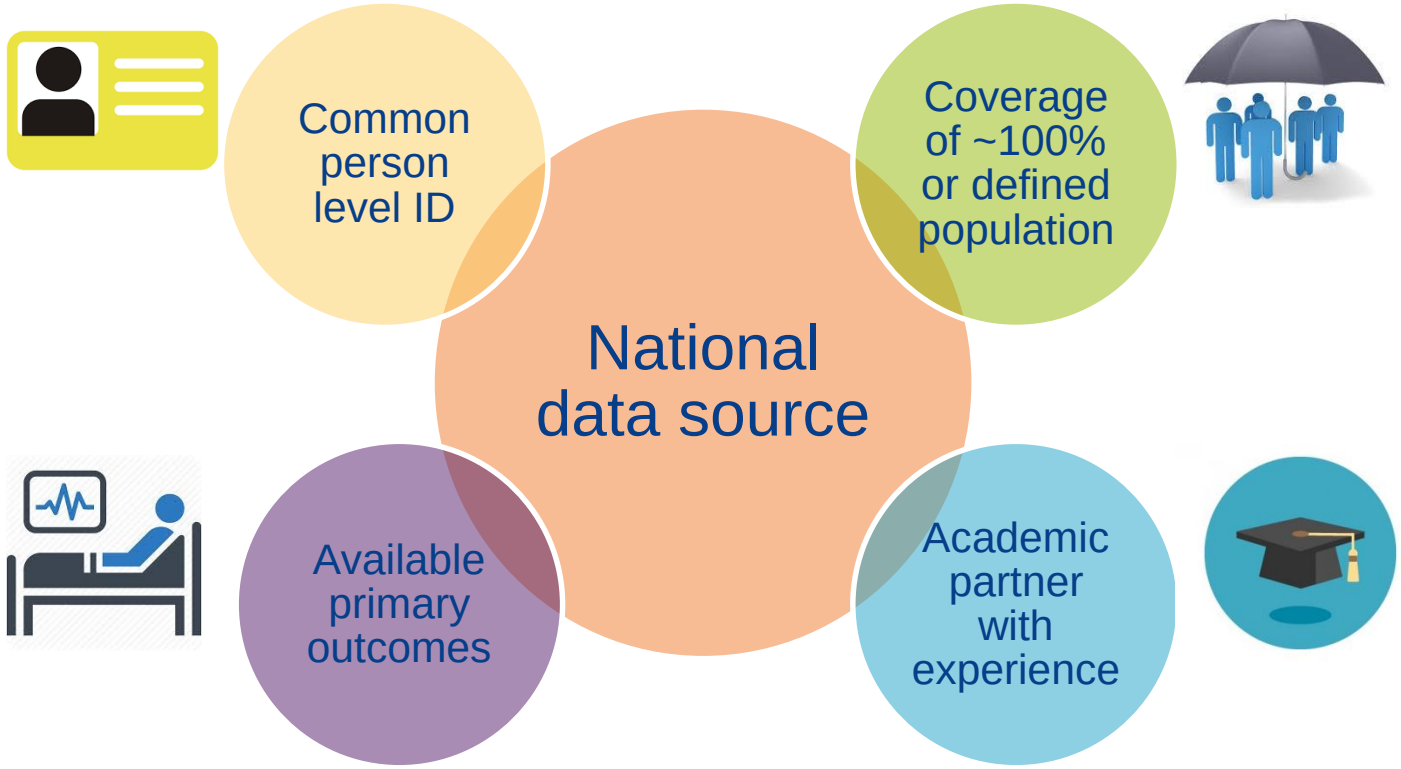
→ ***DataMart Strategy***

→ ***National Strategy***

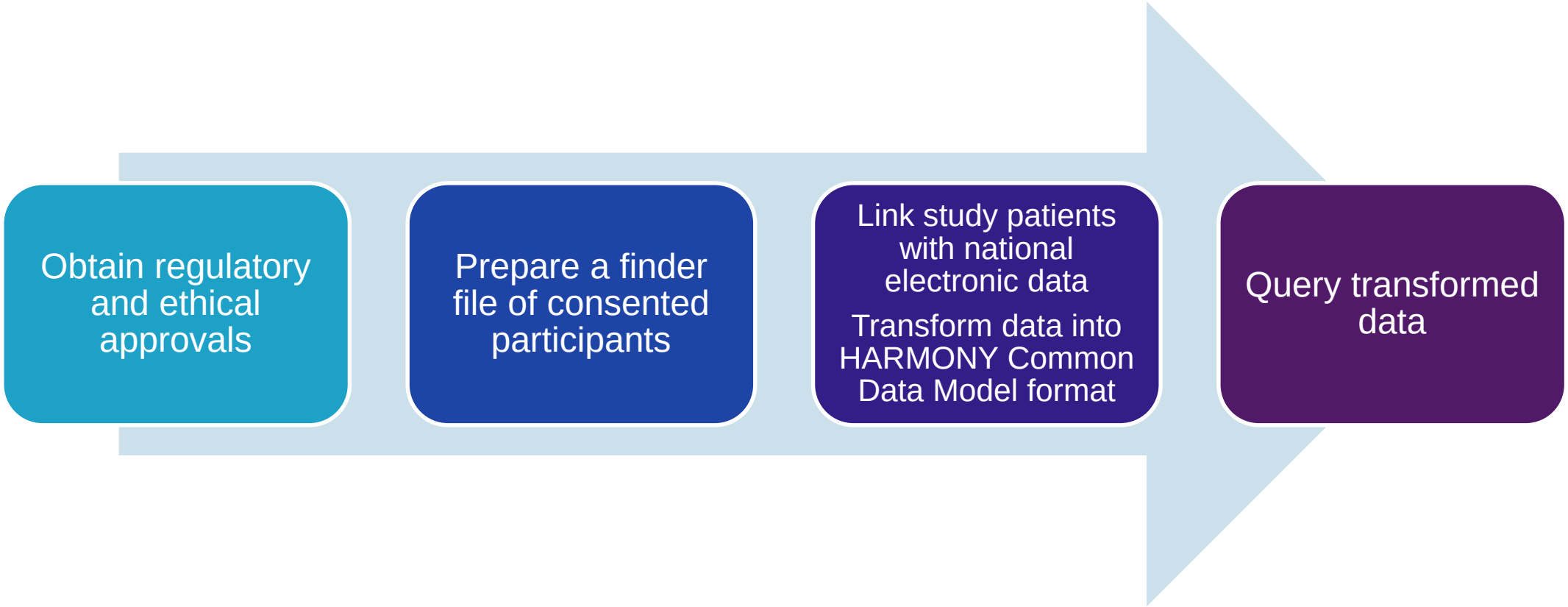
Harmony Outcomes EHR Ancillary Study Data Flows



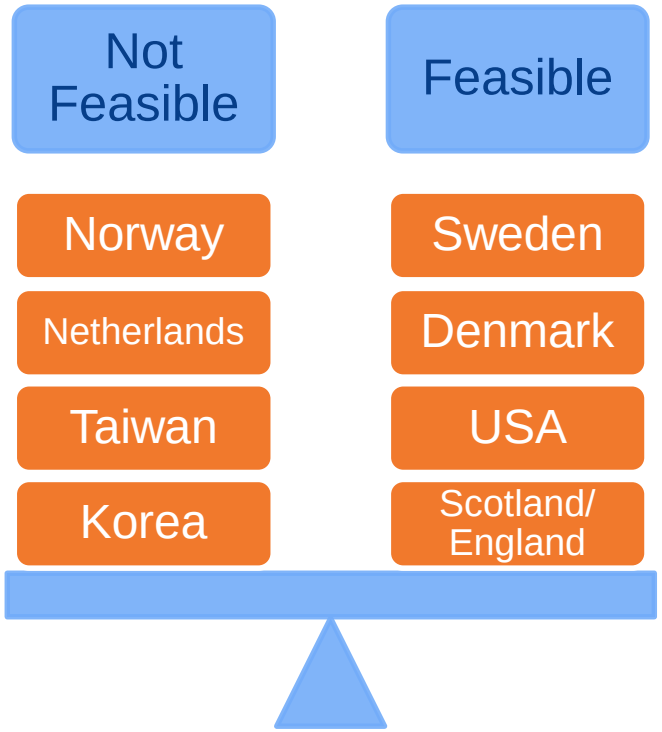
Key Requirements for National Partners



National Strategy



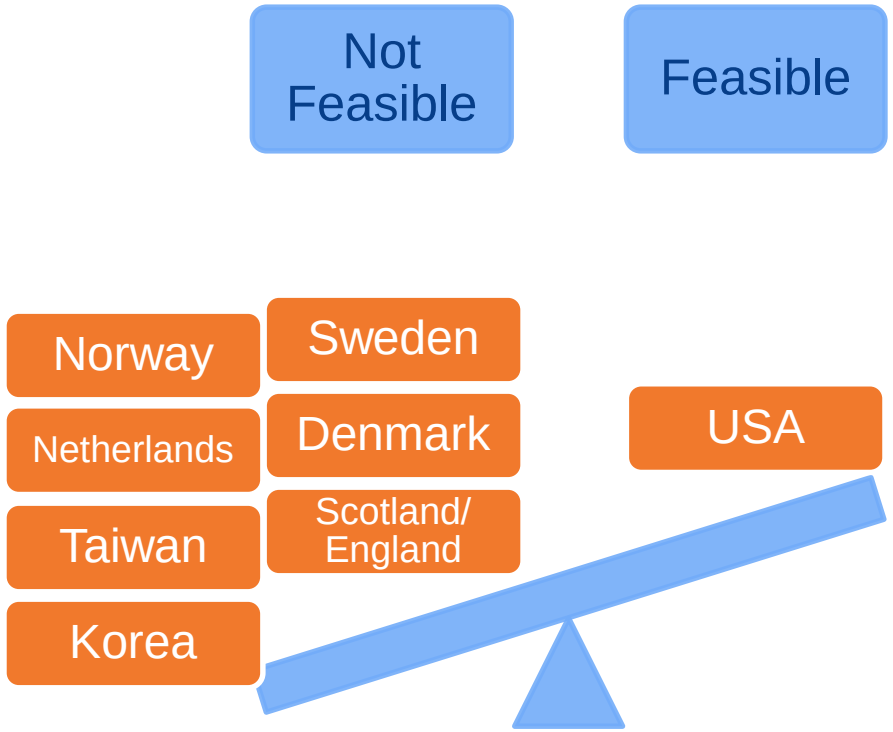
National Partners



Data Sources

- National Hospital Discharge registry (Sweden)
- National Health Service Register (Denmark)
- Medicare insurance claims data (US)
- National Health Service hospital discharge data (UK)

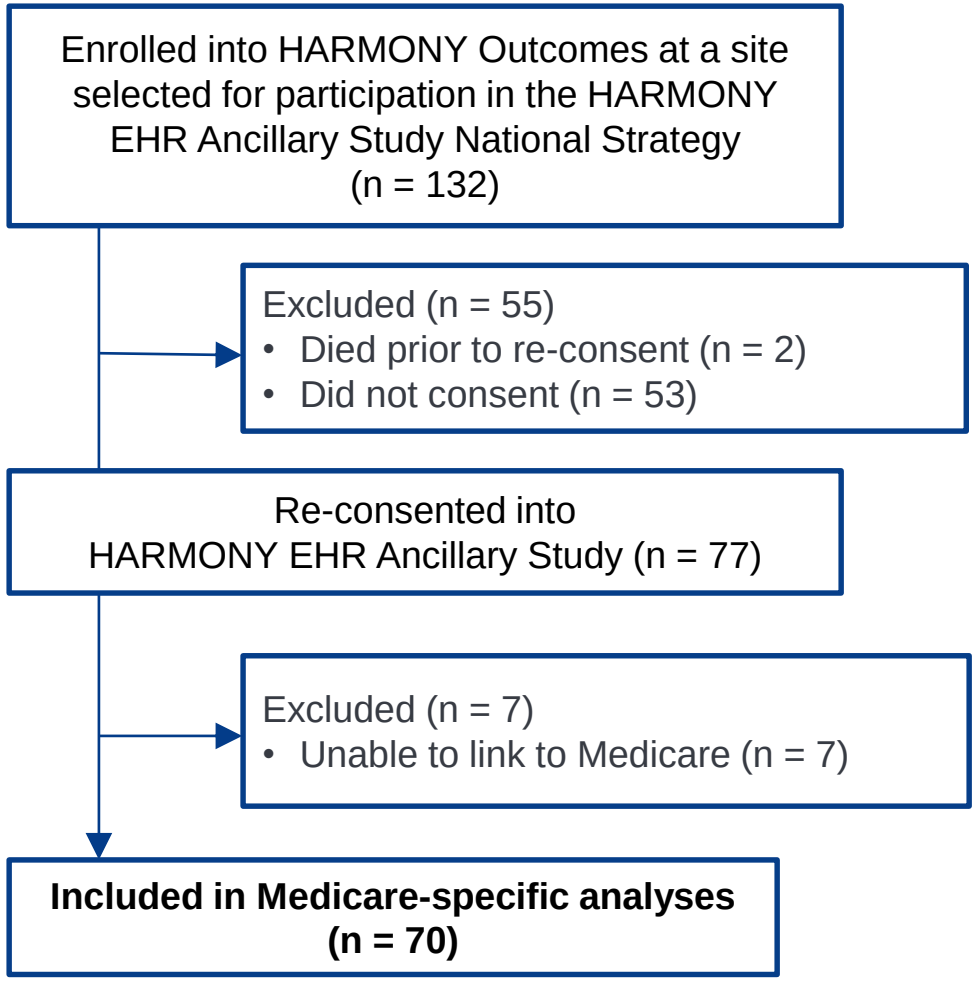
National Partners



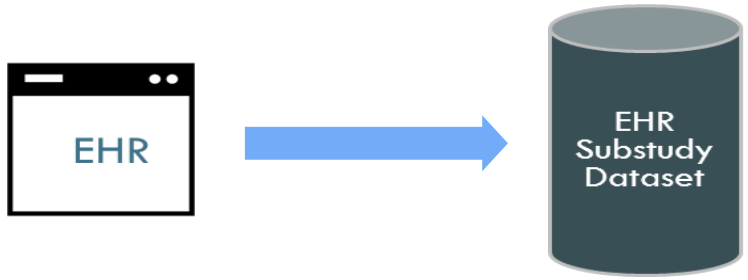
- General Data Protection Regulation (2018)
- GDPR controls movement of individual level outside of the EU
- Proposed another data flow solution which involved moving trial data and RWD to a common EU location
- Ultimately, applying the new rules to a novel situation proved too difficult

National Strategy, Medicare population

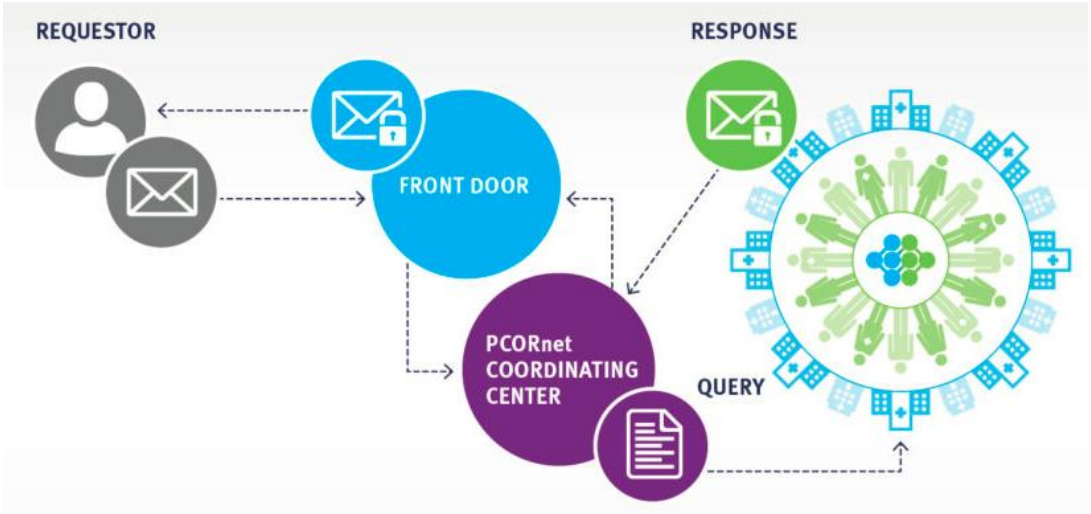
- Contracted: 9 sites with 132 participants
- Linked to Medicare: 70 participants
- Analysis-specific populations
  - n = 70 for demographics
  - n = 38 for medical history (enrolled in Parts A/B)
  - n = 53 for medications (enrolled in Part D)



DataMart Strategy



- Select U.S. sites only
- Planned for ~12 sites with ~200 participants
- PCORnet-like DataMart and querying
- Evaluation of baseline characteristics and endpoints from coded data

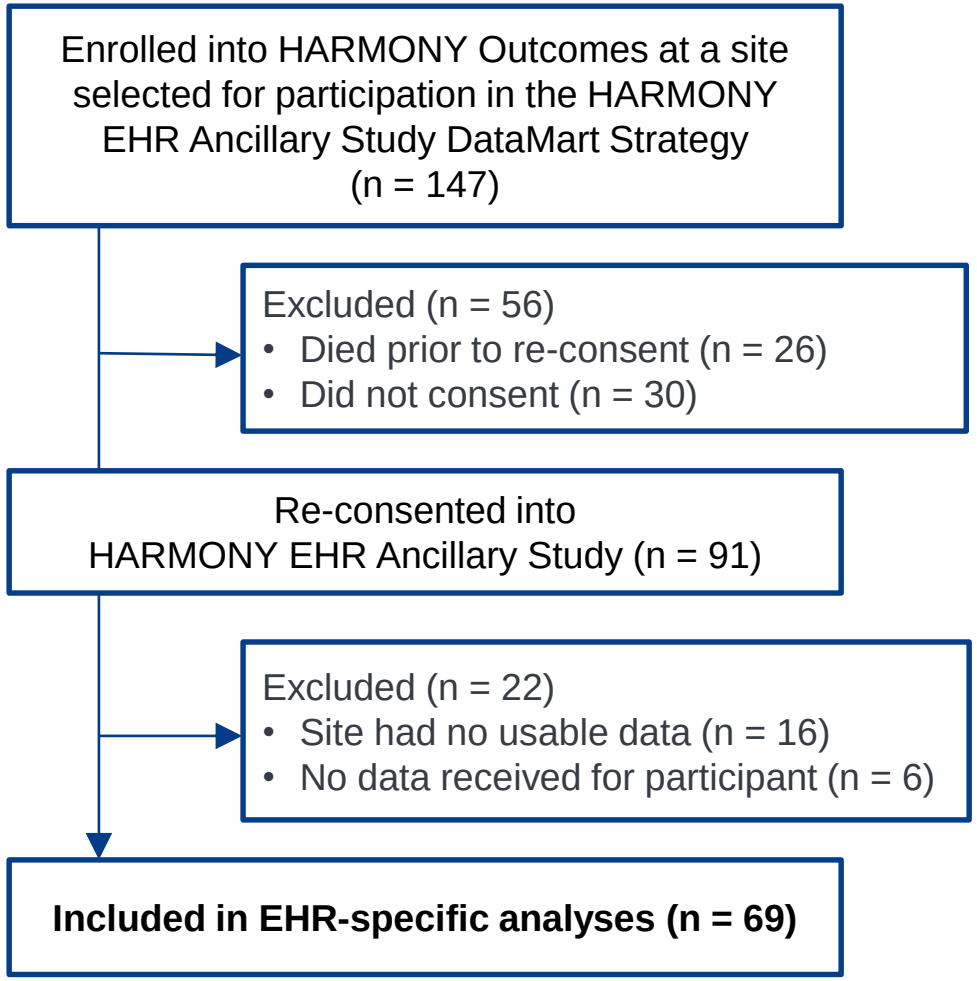


DataMart Strategy Site Requirements

- A data warehouse based on EHR data
- Ability to organize EHR data into a common data format
  - Appropriate technical staff
  - Appropriate data
- An integrated clinical, operational, and technical team

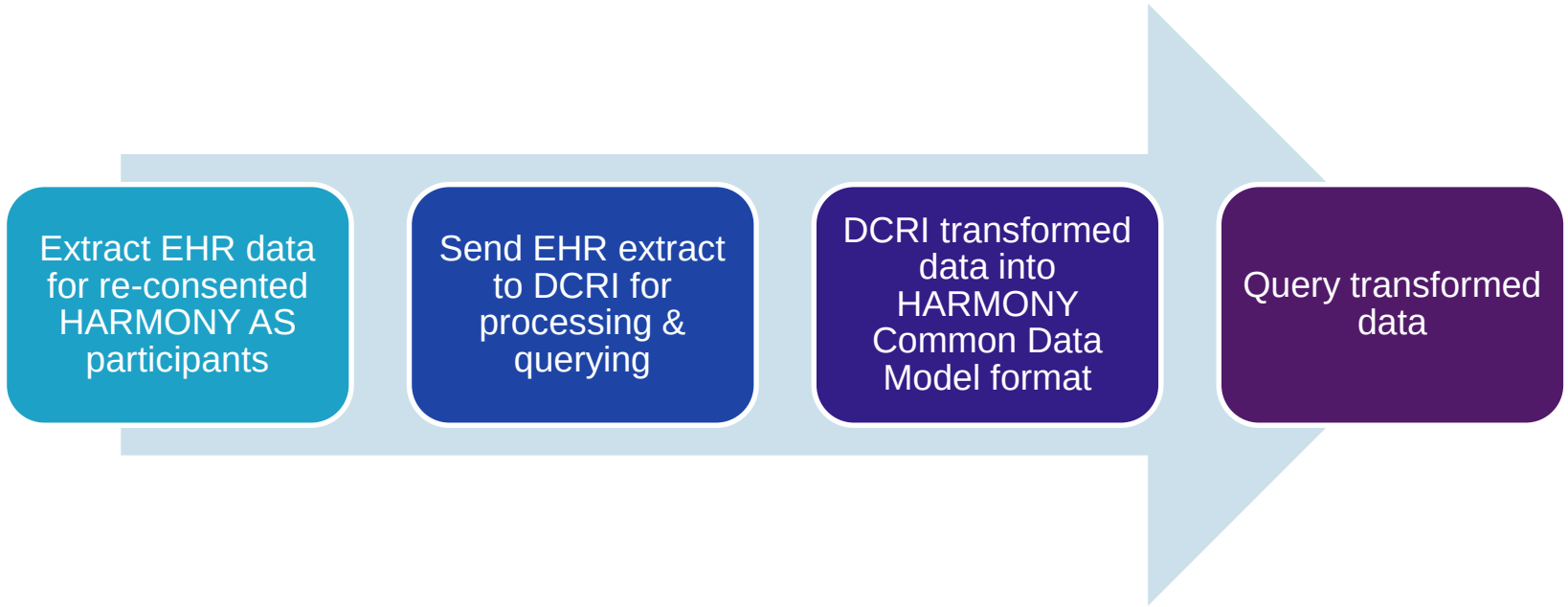
DataMart Strategy Study Population

- Planned for ~12 sites with ~200 participants
  - Contracted: 8 sites with 147 participants
  - Data from 69 participants from 7 sites



DataMart Strategy, Actual Data Flow

- PCORnet-like DataMart and querying
  - Worked as planned at 1 PCORnet site
  - Other sites, or their EHR vendor, sent data extracts to Duke for processing
    - Limited assessment of EHR data fitness prior to data extract receipt



Concepts for comparison

Demographics
Sex
Race
Hispanic ethnicity
Age (at enrollment)

Medical History
Myocardial infarction
Coronary artery disease
Stroke
Transient ischemic attack
Carotid artery disease
Heart failure
Valvular heart disease
Atrial fibrillation
Hypertension
Hyperlipidemia
Diabetic eye disease
Diabetic neuropathy

Medications
ACE inhibitor
Angiotensin receptor blocker (ARB)
P2Y12 inhibitor
Anti-hyperglycemic meds
DPP-IV inhibitor

Laboratory Results
HbA1c
Serum creatinine

Events
Death
Myocardial infarction
Hospitalization for heart failure
Ischemic stroke
Hemorrhagic stroke
Transient ischemic attack
Coronary revascularization

Concepts for comparison

Demographics
Sex
Race
Hispanic ethnicity
Age (at enrollment)

Medical History
Myocardial infarction
Coronary artery disease
Stroke
Transient ischemic attack
Carotid artery disease
Heart failure
Valvular heart disease
Atrial fibrillation
Hypertension
Hyperlipidemia
Diabetic eye disease
Diabetic neuropathy

Medications
ACE inhibitor
Angiotensin receptor blocker (ARB)
P2Y12 inhibitor
Anti-hyperglycemic meds
DPP-IV inhibitor

Laboratory Results
HbA1c
Serum creatinine

Events
Death
Myocardial infarction
Hospitalization for heart failure
Ischemic stroke
Hemorrhagic stroke
Transient ischemic attack
Coronary revascularization

For the other domains

- Demographics
  - EHR and claims information consistently agreed with eCRF
- Lab results
  - EHR lab results were often missing, but agreed with the eCRF when present
- Events
  - Very small number of events in the ancillary study population
  - EHR data had low sensitivity and high specificity
  - Claims data had substantially higher sensitivity than EHR

Medical history, Ancillary study participants

Medical History	Harmony eCRF
Myocardial infarction	69 (49.6%)
Coronary artery disease	125 (89.9%)
Stroke	17 (12.2%)
Carotid artery disease	13 (9.4%)
Heart failure	29 (20.9%)
Atrial fibrillation	20 (14.4%)
Hypertension	127 (91.4%)
Hyperlipidemia	122 (87.8%)
Diabetic neuropathy	51 (36.7%)

Medical history, RWD performance metrics

Medical History	EHR Data		Medicare Data	
	Sensitivity	Specificity	Sensitivity	Specificity
Myocardial infarction	23.7	93.5	61.1	85.0
Coronary artery disease	49.2	80.0	80.0	100.0
Stroke	44.4	100	25.0	94.1
Carotid artery disease	0.0	98.5	44.4	82.8
Heart failure	53.3	96.3	87.5	90.0
Atrial fibrillation	55.6	96.7	66.7	90.6
Hypertension	54.7	100	81.8	40.0
Hyperlipidemia	49.2	50.0	78.8	60.0
Diabetic neuropathy	41.4	82.5	15.4	88.0

- Inconsistent results, but RWD often had low sensitivity and high specificity

Baseline medications, Ancillary study participants

Medication	Harmony eCRF (n = 139)
ACE inhibitor	75 (54.0%)
Angiotensin receptor blocker	45 (32.4%)
P2Y12 inhibitor	48 (34.5%)
Anti-hyperglycemic	139 (100%)
DPP-IV inhibitors	16 (11.5%)

Baseline medications, RWD performance metrics

Medication	EHR Data (n = 69) Sensitivity	EHR Data (n = 69) Specificity	Medicare (n = 53) Sensitivity	Medicare (n = 53) Specificity
ACE inhibitor	31.7	100	73.1	74.1
Angiotensin receptor blocker	33.3	96.1	82.4	88.9
P2Y12 inhibitor	52.0	100	94.4	80.0
Anti-hyperglycemic	46.4	--	92.5	--
DPP-IV inhibitors	33.3	83.3	83.3	72.3

- EHR data: Low sensitivity and high specificity
- Claims data: Substantially higher sensitivity than EHR data

Lessons we learned the hard way

- Each strategy required ongoing feasibility assessment
- Standalone clinical research sites have very little (extractable) EHR data about patients
- Some EHR data was more readily available than other EHR data
  - Diagnosis codes, procedure codes, and encounter dates were relatively easy to get
  - Lab results and medications were either not extractable or not mapped to a useful terminology

Lessons we learned the hard way

- Assessing data quality / fitness-for-use of a site's EHR data was often not possible
  - We could only see data for the few enrolled participants at most sites
  - We did know the data quality at one study site participating in PCORnet
- Pre-processing EHR data into a DataMart was difficult for trial sites
  - Many sites did not participate because they knew they could not perform this work
  - Many sites, who promised to do this work, could not deliver
  - Study site participating in PCORnet performed well

How can we realize the potential of RWD in clinical trials?

- Consider the real world when planning the trial!
  - Target populations with more complete data
    - Recruit sites affiliated with large health systems
    - Perform the trial within specified insurance populations (e.g., Medicare FFS)
  - Define history and event concepts to be more RWD-friendly
    - Prevalent disease (e.g., cerebrovascular disease, coronary artery disease) is easier to identify than historical clinical events (e.g., stroke, MI)
    - Focus on what's available in structured data (e.g., hospitalization with primary dx of MI)
  - Data governance processes are often opaque and dynamic. Ongoing due-diligence is essential.

How can we realize the potential of RWD in clinical trials?

- Contribute to the evidence base for evidence generation in the real world
  - Commit to evaluate new approaches
  - Report what works AND what doesn't