Design and Architecture of a Distributed Network Pragmatic Clinical Trial: The PCORnet ADAPTABLE Study

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S36: Infrastructure for Data-driven Translational Science

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The National Patient-Centered Clinical Research Network

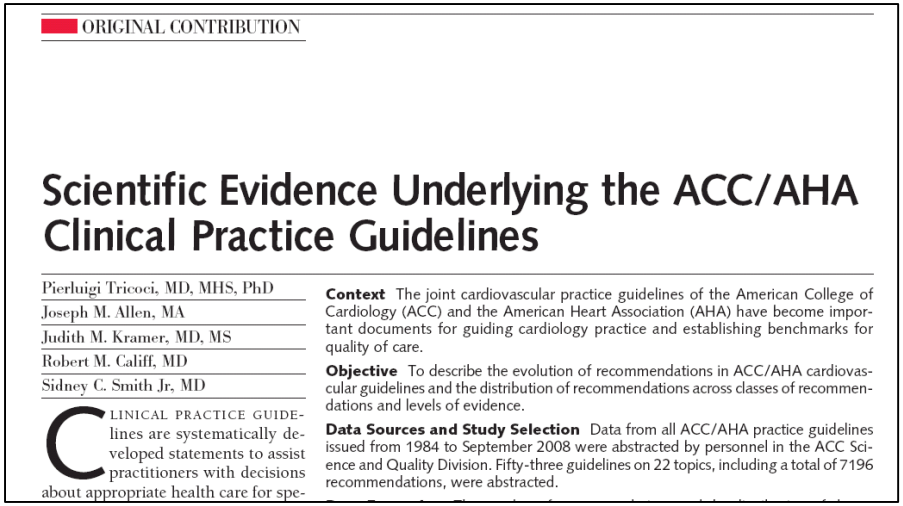
Disclosure

- Lesley Curtis receives research funding from AHA, NHLBI, FDA, PCORI, Boston Scientific, GlaxoSmithKline, Gilead, and Novartis and has received honoraria from Amgen.

Learning Objectives

- After participating in this activity, the learner should be better able to:
  - Understand the design drivers for the ADAPTABLE study database.
  - Evaluate how distributed research networks can provide reusable infrastructure for pragmatic clinical trials.
  - Understand the data flows required to support a pragmatic trial atop a distributed research network

What problem are we trying to solve?



ORIGINAL CONTRIBUTION

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

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Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.

CLINICAL PRACTICE GUIDElines are systematically developed statements to assist practitioners with decisions about appropriate health care for spe-

Lack of high-quality evidence to inform patients, providers, payers, policy makers

Inefficient clinical research system that favors disposable over reusable

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ADAPTABLE: The Aspirin Trial

ADAPTABLE has 3 objectives:

1. To compare the effectiveness and safety of two doses of aspirin (81 mg and 325 mg) in high-risk patients with coronary artery disease
   - **Primary effectiveness endpoint:** Composite of all-cause mortality, hospitalization for MI, or hospitalization for stroke
   - **Primary safety endpoint:** Hospitalization for major bleeding
2. To compare the effects of aspirin in predefined key subgroups of patients
   - Age, diabetes, sex
   - Race, P2Y12 inhibitor use
   - Chronic kidney disease
3. To develop and refine the infrastructure for PCORnet to conduct multiple comparative effectiveness trials in the future

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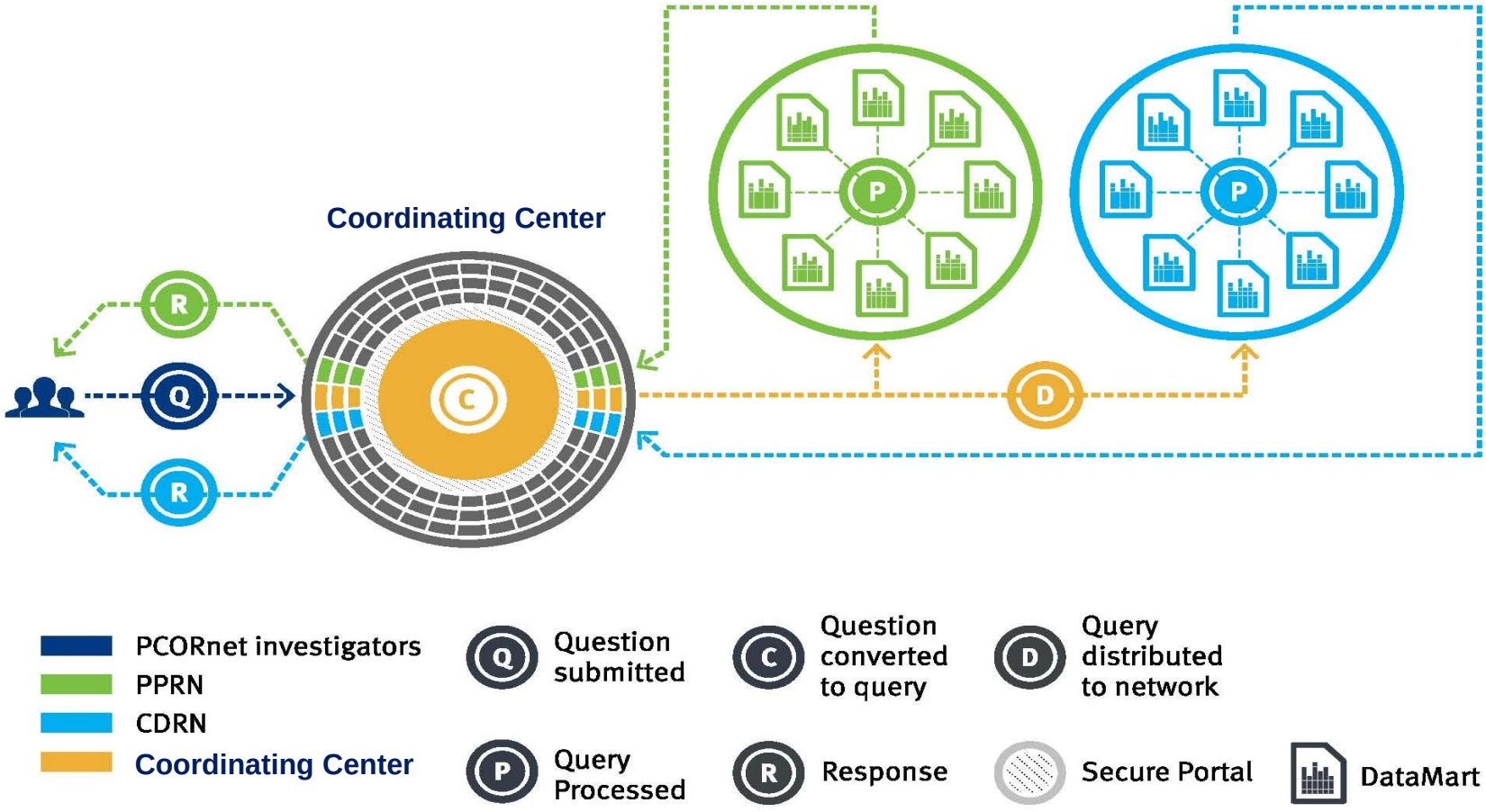
PCORnet Distributed Research Network



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The 15 PCORnet CDM Domains, v3.0

CONDITION v2.0

A condition represents a patient's diagnosed and self-reported health conditions and diseases. The patient's medical history and current state may both be represented.

DEATH v3.0

Reported mortality information for patients.

DEATH_CAUSE v3.0

The individual causes associated with a reported death.

DEMOGRAPHIC v1.0

Demographics record the direct attributes of individual patients.

DIAGNOSIS v1.0

Diagnosis codes indicate the results of diagnostic processes and medical coding within healthcare delivery.

DISPENSING v2.0

Outpatient pharmacy dispensing, such as prescriptions filled through a neighborhood pharmacy with a claim paid by an insurer. Outpatient dispensing is not commonly captured within healthcare systems.

ENROLLMENT v1.0

Enrollment is a concept that defines a period of time during which all medically-attended events are expected to be observed. This concept is often insurance-based, but other methods of defining enrollment are possible.

ENCOUNTER v1.0

Encounters are interactions between patients and providers within the context of healthcare delivery.

HARVEST v3.0

Attributes associated with the specific PCORnet datamart implementation

LAB_RESULT_CM v2.0

Laboratory result Common Measures (CM) use specific types of quantitative and qualitative measurements from blood and other body specimens. These standardized measures are defined in the same way across all PCORnet networks.

PCORNET_TRIAL v3.0

Patients who are enrolled in PCORnet clinical trials.

PRESCRIBING v3.0

Provider orders for medication dispensing and/or administration.

PRO_CM v2.0

Patient-Reported Outcome (PRO) Common Measures (CM) are standardized measures that are defined in the same way across all PCORnet networks. Each measure is recorded at the individual item level: an individual question/statement, paired with its standardized response options.

PROCEDURES v1.0

Procedure codes indicate the discreet medical interventions and diagnostic testing, such as surgical procedures, administered within healthcare delivery.

VITAL v1.0

Vital signs (such as height, weight, and blood pressure) directly measure an individual's current state of attributes.

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ADAPTABLE Study Design

Patients with known ASCVD + ≥ 1 "enrichment factor"*

Identified through EHR (computable phenotype) by CDRNs
(PPRN patients that are already a part of a CDRN are eligible to participate.)

Patients contacted with trial information and link to e-consent;†
Treatment assignment will be provided directly to patient

Exclusion criteria

- Age <18 years
- ASA allergy or contraindication (including pregnancy or nursing)
- Significant GI bleed within past 12 months
- Significant bleeding disorder
- Requires warfarin, direct oral anticoagulant, or ticagrelor

ASA 81 mg QD | ASA 325 mg QD

Electronic follow-up: Every 3–6 months
Supplemented with EHR/CDM/claims data

Duration: Enrollment over 24 months; maximum follow-up of 30 months

Primary endpoint:
Composite of all-cause mortality, hospitalization for MI, or hospitalization for stroke

Primary safety endpoint:
Hospitalization for major bleeding

***Enrichment factors**

- Age >65 years
- Creatinine >1.5 mg/dL
- Diabetes mellitus (type 1 or 2)
- Known 3-vessel CAD
- Current CVD or PAD
- Known EF <50% by echo, cath, nuclear study
- Current smoker

† A subset of participants who do not have internet access may be consented and followed via a parallel system.

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Enabling and testing pragmatic research: e-data collection and e-follow-up

N=20,000

ADAPTABLE enrollee

Baseline data

mytrus

mytrus

Web portal follow-up
- *Randomized to 3 vs 6 mos contact*
- *Patient-reported hospitalizations*
- *Medication use*
- *Health outcomes*

DCRI call center
- *Patients who miss 2 contacts*
- *Patient-reported hospitalizations*
- *Medication use*
- *Health outcomes*

6 | 12 | 18 | 24 | 30

PCORnet Coordinating Center follow-up
- *Via Common Data Model*
- *Validated coding algorithms for endpoints*

CMS and private health plans follow-up
- *Longitudinal health outcomes*
- *Validated coding algorithms for endpoints*

Death ascertainment

National Death Index (NDI) & Social Security Database

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Validated endpoint coding algorithms (1)

Efficacy endpoints

- **Hospitalization for MI:** ICD-9-CM* diagnosis codes 410.x0–410.x1 in the principal or primary position.
- **Hospitalization for ischemic stroke:** ICD-9-CM* diagnosis codes 430.x, 431.x, 433.x1, 434.x1, 435.x, 436, and 362.3 in the principal or primary position.
- **Hospitalization for hemorrhagic stroke:** ICD-9* diagnosis codes 431 and 432 in the principal or primary position.
- **Coronary revascularization** includes all coronary revascularization procedures (PCI/CABG) performed during the study. These will be identified using procedure codes 3610–3617, 3619, 0066, 3606, 3607, 3609.*

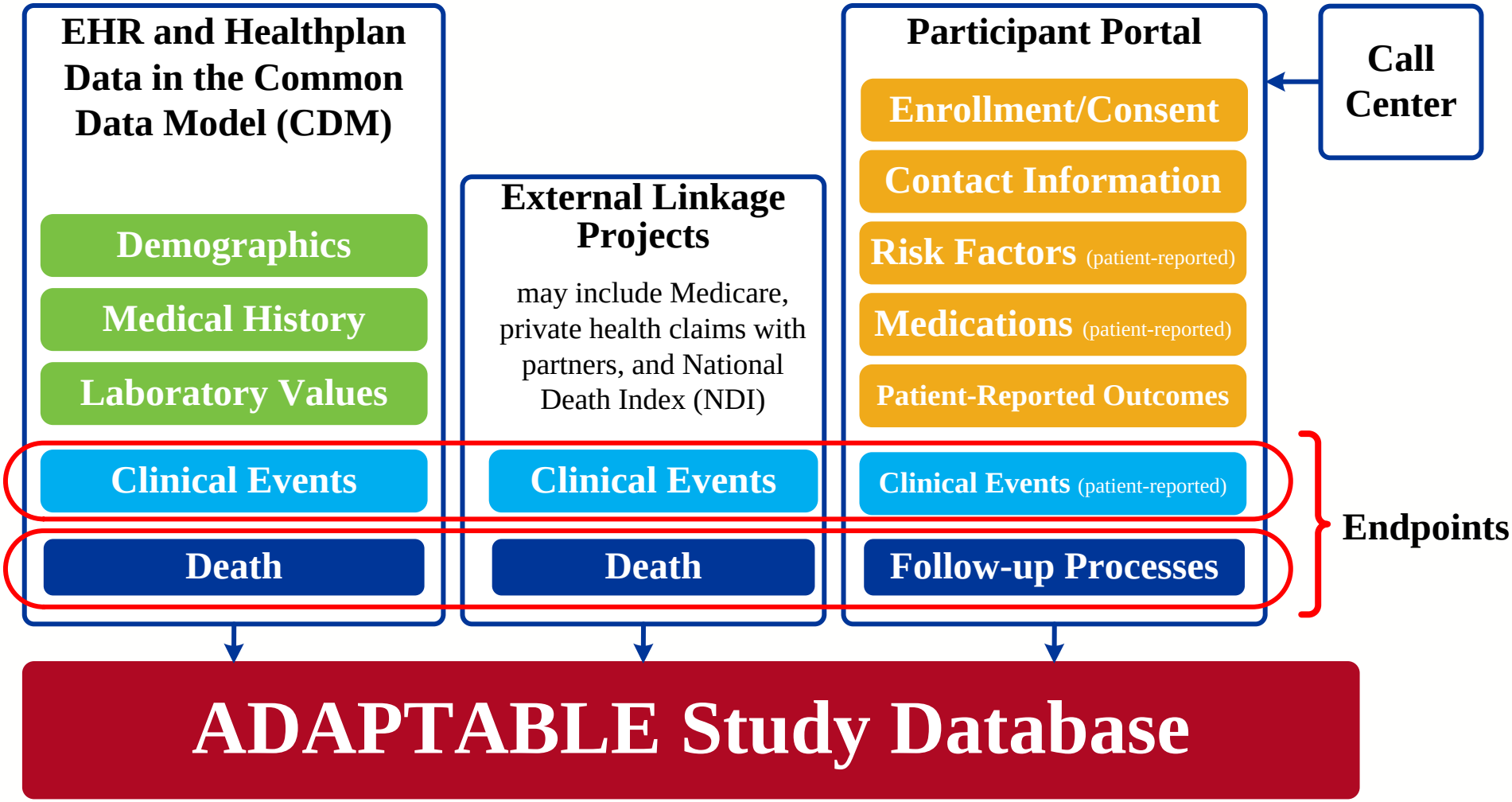
**Will be updated to ICD-10 coding algorithms*

Validated endpoint coding algorithms (2)

Safety endpoint

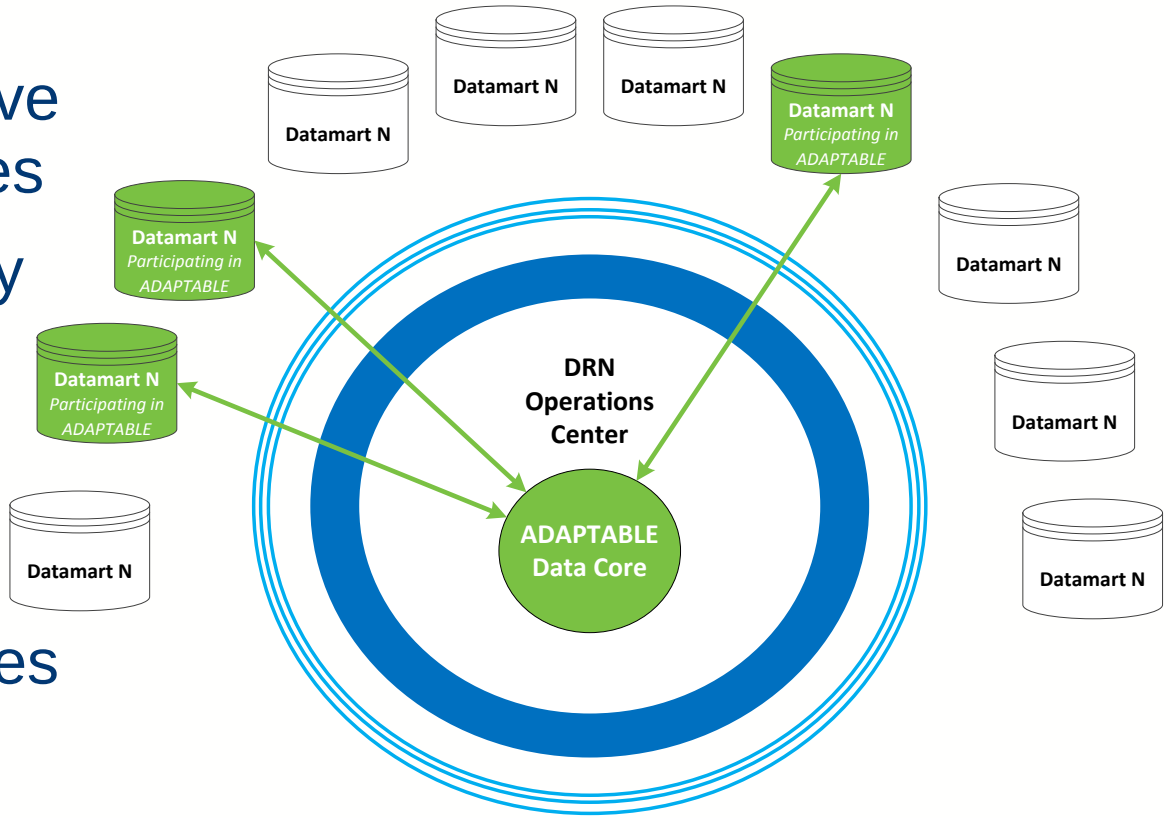
- **Hospitalization for major bleeding:** Major bleeding at any location will be ascertained using ICD-9-CM* diagnosis codes for
  a) intracranial bleeding
  b) gastrointestinal bleeding
  c) bleeding at another location or physician service code for GI hemorrhage (CPT code 43255 or ICD-9 procedure code 44.4x)
- Major bleeding requires an above code plus a CPT code 36430 for any blood product transfusion during the same hospitalization

**Will be updated to ICD-10 coding algorithms*


EHR and Healthplan Data in the Common Data Model (CDM)
Demographics
Medical History
Laboratory Values
Clinical Events
Death
External Linkage Projects
may include Medicare, private health claims with partners, and National Death Index (NDI)
Clinical Events
Death
Participant Portal
Enrollment/Consent
Contact Information
Risk Factors (patient-reported)
Medications (patient-reported)
Patient-Reported Outcomes
Clinical Events (patient-reported)
Follow-up Processes
Call Center
Endpoints
ADAPTABLE Study Database

ADAPTABLE Distributed Querying

- Not all PCORnet datamarts will receive ADAPTABLE queries
- Only analysis-ready datamarts will populate the ADAPTABLE study database
- ADAPTABLE queries will be performed in SAS

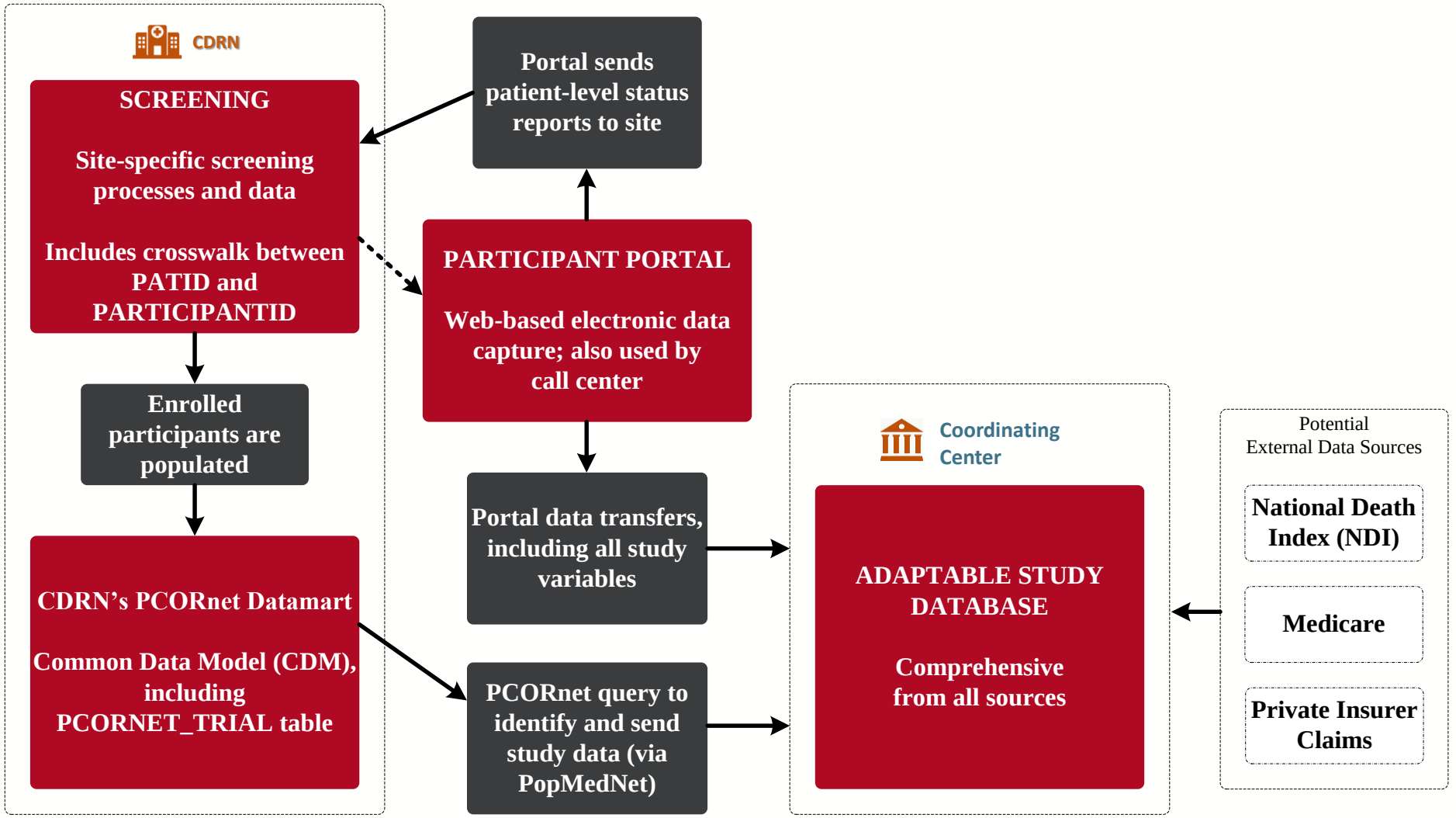


DRN Query Tool with Secure Portal (PopMedNet)

Network topology is used to direct ADAPTABLE queries to ADAPTABLE-participating datamarts

Linkage with external data sources

- Current pilot projects with GPC's Kansas University Med Ctr and Mid-South's Vanderbilt
  - Important work for developing efficient processes
- All ADAPTABLE sites will be expected to contribute patient-level identifiers for external linkage
  - These identifiers will not be exposed through the CDM; instead this will be a separate process
  - Exact details will be based upon experiences with the pilot projects



Data stores are indicated in red, and data exchange processes are indicated in gray.

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The views, statements, and opinions presented in this work are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee or other participants in PCORnet.

The PCORnet Team

Links and further reading

The ADAPTABLE fact sheet: http://www.pcori.org/sites/default/files/PCORI-Aspirin-Trial-Fact-Sheet.pdf

The ADAPTABLE: The Aspirin Study website: http://theaspirinstudy.org/

Hernandez AF, Fleurence RL, Rothman RL. The ADAPTABLE Trial and PCORnet: Shining Light on a New Research Paradigm. Ann Intern Med 2015;163(4):635-636. http://annals.org/article.aspx?articleid=2430210

“Why PCORnet Exists”: http://www.pcornet.org/why-pcornet-exists/

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