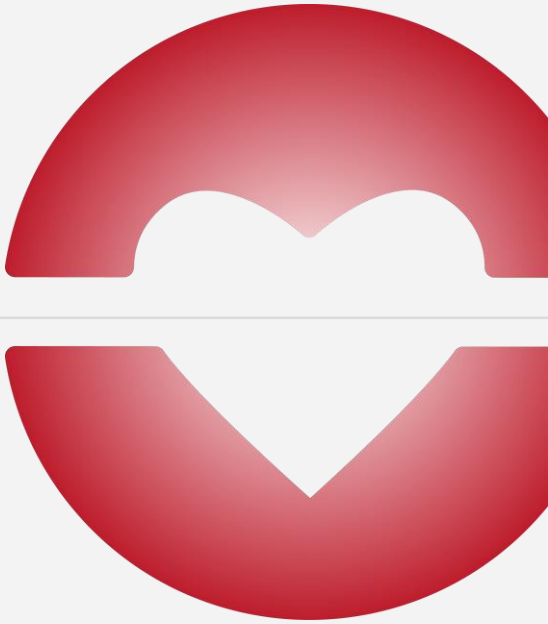
Please note that these slides were created during the earlier development phase.

Details are subject to change and should not be applied without confirmation.

ADAPTABLE Phenotyping Working Session



Friday, September 4, 2015

Hosted by Lesley Curtis, PhD and Schuyler Jones, MD

Facilitated by Shelley Rusincovitch

Adaptable

The Aspirin Study

Welcome & Overview

Setting the stage for today's meeting

Our scope for today:

- Open the discussion about phenotyping in ADAPTABLE
- Begin recognizing experiences and best practices
- Outline considerations and areas needing further assessment

Setting the stage for today's meeting (2)

Important context:

- The trial protocol is not yet formally finalized
- Contracting is not yet executed
- Given this state, today's conversation is not intended to assign tasks or effort for networks; however, networks may choose to "work ahead" if they feel appropriate

Setting the stage for today's meeting (3)

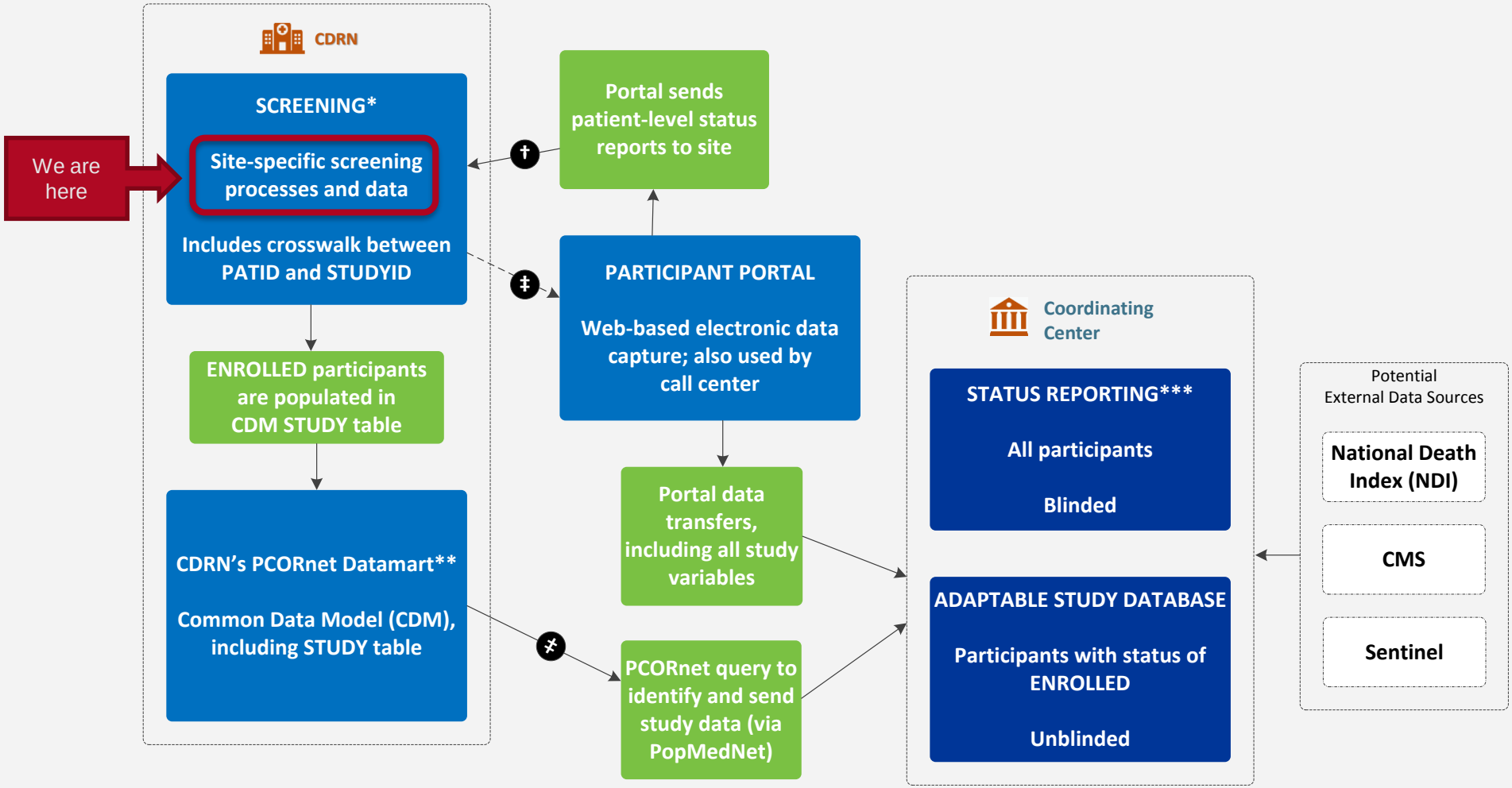
Out of scope for today:

- Specific mechanics of the invitation to the potential participant
- Other specific systems-level details (although it will be helpful for us to recognize where more assessment is needed)

We're scheduling a follow-up "data strategy" session to discuss more on the data flows.

Phenotyping Objectives

Draft Data Flow



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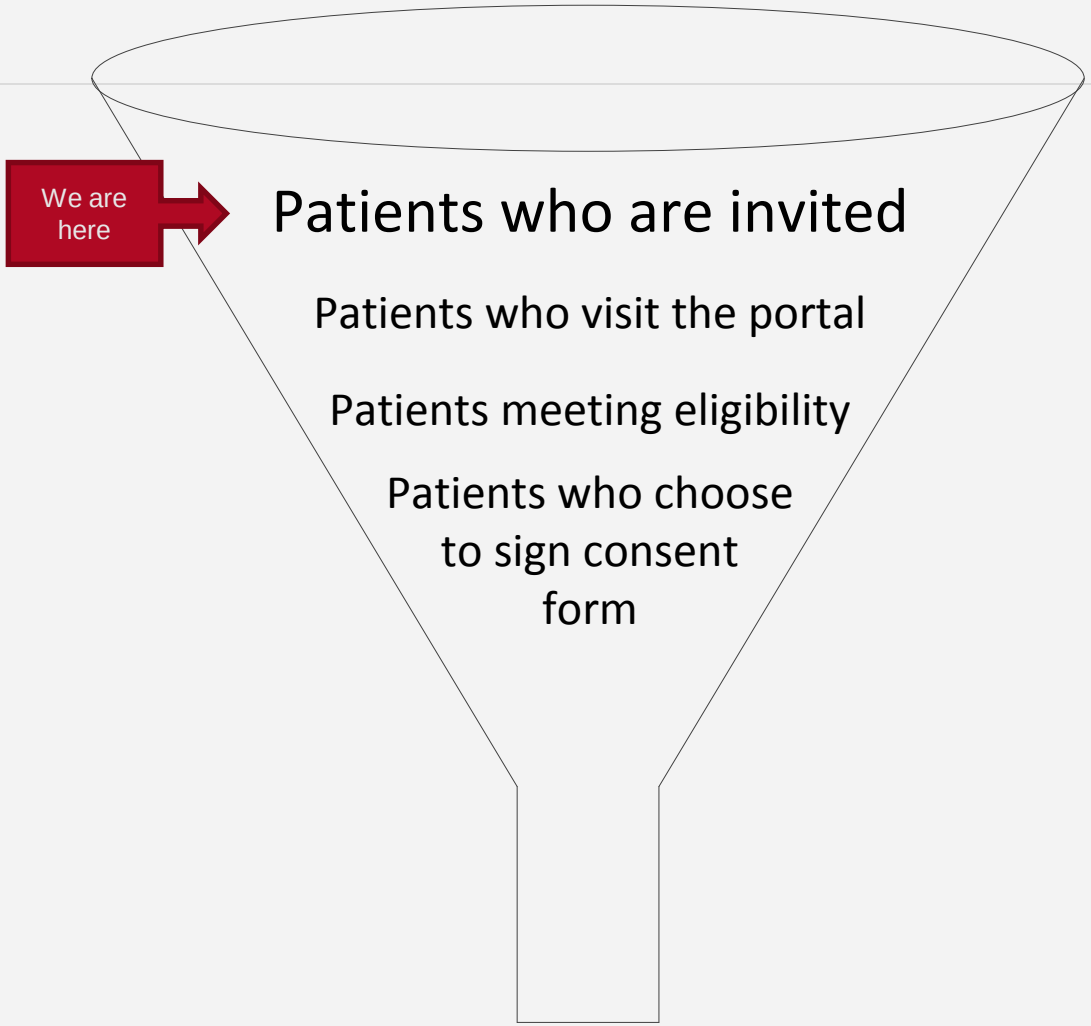
Potential Participant Pool



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Phenotyping is a broad activity

- ADAPTABLE scope: identifying **potential participants** to approach for trial
- Different from a phenotype use case with outcomes

Process of Recruitment (please note: draft version of protocol!)

IV.A.1.d. Recruitment and Informed Consent

Each CDRN will develop a recruitment process that will work best within their organization, utilizing the tools they have available and their local infrastructure. Prior to cohort identification, site investigators will be asked to endorse the protocol, and depending upon their preference, they will either determine each patient's eligibility or will give permission for the CDRN, through its integrated health system members, to identify and contact potentially eligible patients. In the latter case, patients who meet criteria for secondary prevention after a cardiovascular event will be identified using search algorithms unique to each network from their aggregated EHR systems. Broad agreement from both cardiovascular specialists and primary care physicians will be sought. In this trial, we believe that most systems will agree that prior screening by the relevant clinician will be needed and useful since these patients will be at high-risk for death or a major disabling event. While it is unlikely that a medical reason for ineligibility will be found, most of these patients are close to their clinicians whose confidence in and support of the trial will be important for promoting adherence to the study medication and treatment of the inevitable clinical events. Patients will be enrolled after providing electronic informed consent.

Page 45, draft study protocol version 6.2/June 5, 2015, posted for public comment on June 26, 2015.

Cohort Identification (please note: draft version of protocol!)

III.A.3.b. Cohort Identification

Local site investigators within the CDRNs will be asked to endorse the protocol. They will then be asked to give their permission for the CDRN, through its integrated health system members, to identify and contact potentially eligible patients.

In the latter case, patients who meet criteria for secondary prevention after a cardiovascular event will be identified using search algorithms unique to each network (based on the trial inclusion criteria) from their EHR systems. Broad agreement from both cardiovascular specialists and primary care physicians will be sought. In this trial, we believe that most systems will agree that prior approval of the relevant clinician will be needed and useful since these patients will be at high-risk for death or a major disabling event. Although it is unlikely that a medical reason for ineligibility will be found, most of these patients are close to their clinicians, whose confidence in and support of the trial will be important for patient engagement, both in terms of participation as well as promoting adherence to the study medication and treatment of the inevitable clinical events.

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Page 23, draft study protocol version 6.2/June 5, 2015, posted for public comment on June 26, 2015.

Open Discussion: Process Related

- Broadly, how has your network considered the **use of EHR data for potential participant identification** with ADAPTABLE?
- What can we all learn from your experiences from generating **prep to research** metrics for ADAPTABLE?
- What can we all learn from your experiences and lessons learned from **other projects**?

Phenotyping Criteria

Inclusion/ Exclusion Criteria (please note: draft version of protocol!)

Page 20, draft study protocol version 6.2/June 5, 2015, posted for public comment on June 26, 2015.

Adaptable

III.A.1. Enrollment and Eligibility

Importantly, these criteria are intended to reflect the best judgment of clinicians in practice and to reflect the general "uncertainty principle"—in patients for whom aspirin is indicated to reduce recurrent events, the clinician is uncertain about the best dose and the patient is interested in participation, randomization should be offered as an approach to care.

1. Known atherosclerotic cardiovascular disease (ASCVD), defined by a history of prior myocardial infarction, prior coronary angiography showing ≥75% stenosis of at least one epicardial coronary vessel, or prior coronary revascularization procedures (either PCI or CABG)
2. Age ≥ 18 years
3. No known intolerance to an aspirin dose of ≤ 325 mg/day (intolerance includes a true allergic reaction or a side effect, including gastrointestinal issues, that may preclude using aspirin at a dose of 325 mg/day)
4. Access to the Internet or agreement to collect follow-up information by the DCRI Call Center from patients without Internet access and for Spanish-speaking patients
5. Not currently using an oral anticoagulant – either warfarin or a novel anticoagulant (dabigatran, rivaroxaban, apixaban, edoxaban)
6. Female patients who are not pregnant or nursing an infant
7. Estimated risk of a major cardiovascular event (MACE) > 8% over next 3 years as defined by the presence of at least one or more of the following enrichment factors:
    a. Age > 65 years
    b. Known serum creatinine > 1.5 mg/dL
    c. Diabetes mellitus
    d. Known 3-vessel coronary artery disease
    e. Known cerebrovascular disease and/or peripheral arterial disease
    f. Known left ventricular ejection fraction (LVEF) < 50%
    g. Current cigarette smoker.
8. Able and willing to provide informed consent and agreeing to be followed through the Internet and/or through calls by the DCRI Call Center for the duration of the trial (maximum expected follow-up of 30 months)

There will be no exclusion for any upper age limit or comorbid conditions.

A lesson learned

- It may be helpful to consider how results will be triaged or filtered
- Techniques for filtering down thousands (or tens of thousands) of results may benefit from non-clinical elements
- May also assist in responsiveness to enrollment foci and targeted recruitment groups

Ideas for non-clinical data elements

- Are they a “current” patient? Do they receive their routine care here?
  - If not an explicit flag in the system, are there potential indirect indicators?
    - For example: do they live in this state?
    - When was their last encounter?
    - When is their next scheduled appointment?

Ideas for non-clinical data elements (2)

- How are they receiving their care?
  - Does the patient have a PCP?
  - Specialty care association?
  - Registry flag?
- Are they alive?
  - If mortality data are known to be incomplete, can last encounter data be helpful?

Open Discussion: Phenotype Criteria

- What **clinical** data domains and elements do you feel are most important for your ADAPTABLE phenotyping?
- What components of the ADAPTABLE **inclusion/exclusion criteria** may be difficult to translate for your network?
- What **non-clinical** data domains and elements do you feel may be important for your processes?

Phenotyping Logistics

Possible Considerations

- Potential data sources may include:
  - Data transformed to CDM
  - Other non-CDM sources
- Logistics may include:
  - Latency of source data
  - Frequency of refreshes
  - Tracking previously contacted patients, including those who decline

Open Discussion: Phenotype Logistics

- What logistics do you think will be most important for your processes? Some examples may include:
  - Selection of **potential data sources**
  - Considering **structured** data elements vs. **unstructured/narrative** content
  - **Latency** considerations of source data and also associated **refreshes** and **transformation** processes

Wrapping Up

Next Steps

- High-level “data strategy” overview meeting tentatively planned for week of September 21 (scheduling in process)
- More specific and targeted technical meetings to follow

Reference Slides

Main Objectives of the ADAPTABLE Trial

- 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, nonfatal MI, nonfatal stroke
  - **Primary Safety Endpoint:** Major bleeding complications
- To compare the effects of aspirin in subgroups of patients:
  - Women vs men
  - Older vs younger
  - Racial and ethnic minorities vs. whites
  - Diabetics vs. nondiabetics
  - Chronic kidney disease (CKD) vs. not
  - Internet users vs. not
  - P2Y12 inhibitor users vs. not
- To develop and refine the infrastructure for PCORnet to conduct multiple comparative effectiveness trials in the future

Implementation of v3.0

- v3.0 expected to be in place at beginning of Phase II, per PFA
- Phase II expectations for CDM versioning are in development, and not part of this current discussion

Page 13 of the Phase II PFA (highlight added) www.pcori.org/sites/default/files/PCORI-PFA-CDRN.pdf

Slide from CDM Stakeholder meetings on April 28 and 29, 2015.

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Goal 2. Phase I Data Infrastructure and Analysis-Ready Data Requirements

Applicant CDRNs should provide evidence of meeting Phase I requirements for analysis-ready data and for the ability to rapidly query the data, as described below. New applicants must explain and demonstrate that the network will be able to achieve this goal within six-months of the contract award.

The application should describe the data infrastructure in place at the time of the application and describe how it:

- Includes the full range of quality-checked data for a population of one million individuals, transformed into the PCORnet CDM Version 2.1[3] or current version; for this one million-person population, provide criteria to indicate how they were included in the core population (e.g., enrollment information if health plan data are available, a certain number of visits to the health system, or other indicators that characterize the defined population); in cases where this total has not been met, or where the data are missing certain tables or fields for structural reasons, describe reasons for missing data and plans to collect the data if applicable or feasible.
- The status of the CDRNs analysis-ready data set in the appropriate template
- Includes activities to complete the capture of longitudinal data for the CDRN's core population of at least one million persons; PCORI recognizes that some linkages may be feasible only for IRB-approved research studies and will accept evidence of agreements with suitable partners in lieu of complete data on the one million-person core population
- Includes the ability to execute data queries against the PCORnet CDM, including queries provided by the PCORnet coordinating center that are written in Statistical Analysis System (SAS) code and able to run without modification against the CDRN's data; for existing CDRNs, this capability must be in place at the time of the award; for new CDRNs, this capability must be in place within six months of receiving the award; CDRN applicants are expected to be able to return simple query results within one week of receipt
- Includes the capacity to continue development of the CDRN data resource consistent with PCORnet CDM v 2.1 and subsequent versions.
- Includes policies and practices to ensure data security and patient privacy and confidentiality, including policies about who may access the data, under what conditions, and how the CDRN

[3] Available at http://www.pcornet.org/resource-center/pcornet-common-data-model/

PCORnet Common Data Model v3.0

New to v3.0

DEMOGRAPHIC
PATID
BIRTH_DATE
BIRTH_TIME
SEX
HISPANIC
RACE
BIOBANK_FLAG

Fundamental basis

ENROLLMENT
PATID
ENR_START_DATE
ENR_END_DATE
CHART
ENR_BASIS

DISPENSING
DISPENSINGID
PATID
PRESCRIBINGID (optional)
DISPENSE_DATE
NDC
DISPENSE_SUP
DISPENSE_AMT

DEATH
PATID
DEATH_DATE
DEATH_DATE_IMPUTE
DEATH_SOURCE
DEATH_MATCH_CONFIDENCE

DEATH_CONDITION
PATID
DEATH_CAUSE
DEATH_CAUSE_CODE
DEATH_CAUSE_TYPE
DEATH_CAUSE_SOURCE
DEATH_CAUSE_CONFIDENCE

Data captured from processes associated with healthcare delivery

VITAL
VITALID
PATID
ENCOUNTERID (optional)
MEASURE_DATE
MEASURE_TIME
VITAL_SOURCE
HT
WT
DIASTOLIC
SYSTOLIC
ORIGINAL_BMI
BP_POSITION
SMOKING
TOBACCO
TOBACCO_TYPE

CONDITION
CONDITIONID
PATID
ENCOUNTERID (optional)
REPORT_DATE
RESOLVE_DATE
ONSET_DATE
CONDITION_STATUS
CONDITION
CONDITION_TYPE
CONDITION_SOURCE

PRO_CM
PRO_CM_ID
PATID
ENCOUNTERID (optional)
PRO_ITEM
PRO_LOINC
PRO_DATE
PRO_TIME
PRO_RESPONSE
PRO_METHOD
PRO_MODE
PRO_CAT

Data captured within multiple contexts: healthcare delivery, registry activity, or directly from patients

ENCOUNTER
ENCOUNTERID
PATID
ADMIT_DATE
ADMIT_TIME
DISCHARGE_DATE
DISCHARGE_TIME
PROVIDERID
FACILITY_LOCATION
ENC_TYPE
FACILITYID
DISCHARGE_DISPOSITION
DISCHARGE_STATUS
DRG
DRG_TYPE
ADMITTING_SOURCE

DIAGNOSIS
DIAGNOSISID
PATID
ENCOUNTERID
ENC_TYPE (replicated)
ADMIT_DATE (replicated)
PROVIDERID (replicated)
DX
DX_TYPE
DX_SOURCE
PDX

PROCEDURES
PROCEDURESID
PATID
ENCOUNTERID
ENC_TYPE (replicated)
ADMIT_DATE (replicated)
PROVIDERID (replicated)
PX_DATE
PX
PX_TYPE
PX_SOURCE

LAB_RESULT_CM
LAB_RESULT_CM_ID
PATID
ENCOUNTERID (optional)
LAB_NAME
SPECIMEN_SOURCE
LAB_LOINC
PRIORITY
RESULT_LOC
LAB_PX
LAB_PX_TYPE
LAB_ORDER_DATE
SPECIMEN_DATE
SPECIMEN_TIME
RESULT_DATE
RESULT_TIME
RESULT_QUAL
RESULT_NUM
RESULT_MODIFIER
RESULT_UNIT
NORM_RANGE_LOW
NORM_MODIFIER_LOW
NORM_RANGE_HIGH
NORM_MODIFIER_HIGH
ABN_IND

PRESCRIBING
PRESCRIBINGID
PATID
ENCOUNTERID (optional)
RX_PROVIDERID
RX_ORDER_DATE
RX_ORDER_TIME
RX_START_DATE
RX_END_DATE
RX_QUANTITY
RX_REFILLS
RX_DAYS_SUPPLY
RX_FREQUENCY
RX_BASIS
RXNORM_CUI

Data captured from healthcare delivery, direct encounter basis

PCORNET_TRIAL
PATID
TRIALID
PARTICIPANTID
TRIAL_SITEID
TRIAL_ENROLL_DATE
TRIAL_END_DATE
TRIAL_WITHDRAW_DATE
TRIAL_INVITE_CODE

Associations with PCORnet clinical trials

HARVEST
NETWORKID
NETWORK_NAME
DATAMARTID
DATAMART_NAME
DATAMART_PLATFORM
CDM_VERSION
DATAMART_CLAIMS
DATAMART_EHR
BIRTH_DATE_MGMT
ENR_START_DATE_MGMT
ENR_END_DATE_MGMT
ADMIT_DATE_MGMT
DISCHARGE_DATE_MGMT
PX_DATE_MGMT
RX_ORDER_DATE_MGMT
RX_START_DATE_MGMT
RX_END_DATE_MGMT
DISPENSE_DATE_MGMT
LAB_ORDER_DATE_MGMT
SPECIMEN_DATE_MGMT
RESULT_DATE_MGMT
MEASURE_DATE_MGMT
ONSET_DATE_MGMT
REPORT_DATE_MGMT
RESOLVE_DATE_MGMT
PRO_DATE_MGMT
REFRESH_DEMOGRAPHIC_DATE
REFRESH_ENROLLMENT_DATE
REFRESH_ENCOUNTER_DATE
REFRESH_DIAGNOSIS_DATE
REFRESH_PROCEDURES_DATE
REFRESH_VITAL_DATE
REFRESH_DISPENSING_DATE
REFRESH_LAB_RESULT_CM_DATE
REFRESH_CONDITION_DATE
REFRESH_PRO_CM_DATE
REFRESH_PRESCRIBING_DATE
REFRESH_PCORNET_TRIAL_DATE
REFRESH_DEATH_DATE
REFRESH_DEATH_CAUSE_DATE

Process-related data

http://www.pcornet.org/pcornet-common-data-model/

Bold font indicates fields that cannot be null due to primary key definitions or record-level constraints.

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The PCORnet CDM lives at
http://pcornet.org/pcornet-common-data-model/

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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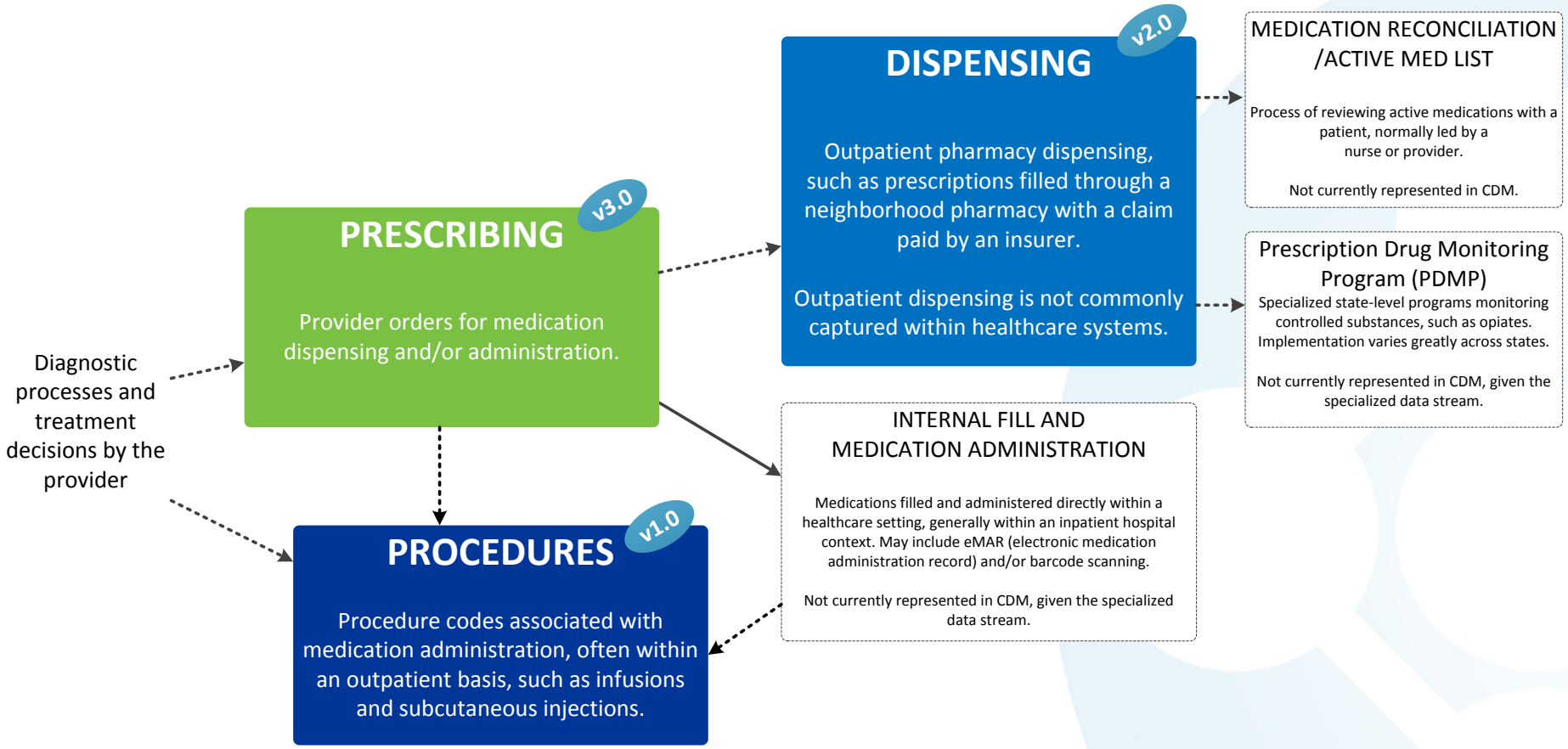
The PCORnet CDM lives at
http://pcornet.org/pcornet-common-data-model/

The Continuum of Clinically-related Medication Data Domains



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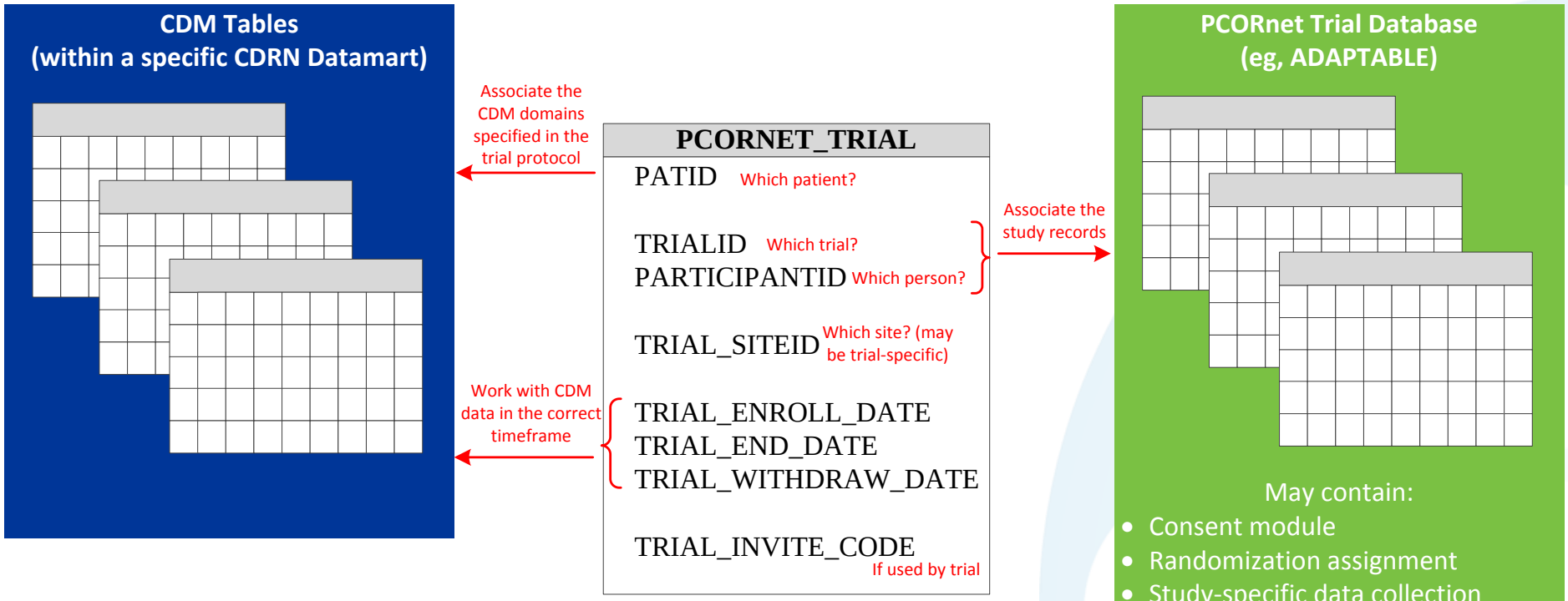
Section 3.4 of the PCORnet CDM v3.0
http://pcornet.org/pcornet-common-data-model/

The PCORNET_TRIAL table serves as a connector and filter for CDM data within the parameters of a given trial protocol:



Any given PCORnet datamart may contain data from a large number of patients. The PCORNET_TRIAL table assists the ADAPTABLE Data Core in knowing ***which of these patients have consented and been enrolled*** *in the ADAPTABLE trial for querying purposes.*

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Small modifications from the slide used with the CDM Stakeholder meetings on April 28 and 29, 2015.