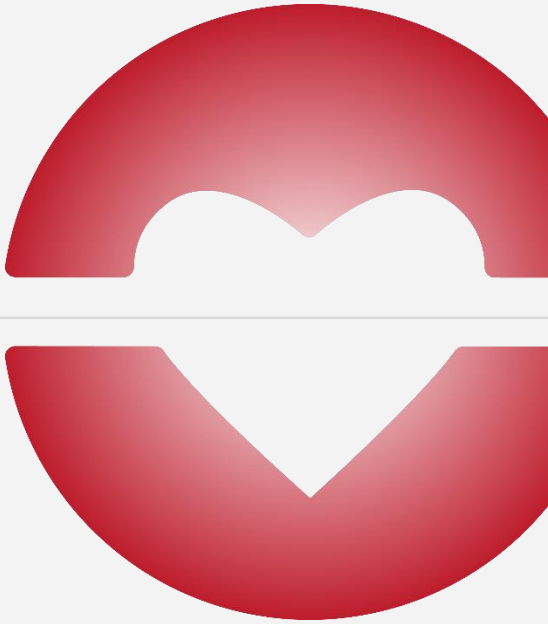
Please note that these slides were created during the earlier development phase.

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

PCORnet ADAPTABLE Data Strategy Discussion



Friday, December 11, 2015

Hosted by Lesley Curtis, PhD and Schuyler Jones, MD

Facilitated by Shelley Rusincovitch and Lisa Eskenazi

Adaptable

The Aspirin Study

Welcome & Overview

Prior meetings

- Phenotype working session on **September 4**
  - Slides, recording, and summary: https://pcornet.centraldesktop.com/p/ZgAAAAAAZgS3
- Data strategy session on **September 25**
  - Slides, recording, and summary: https://pcornet.centraldesktop.com/p/ZgAAAAAAZn7T
- Data strategy session on **October 30**
  - Slides, recording, and summary: https://pcornet.imeetcentral.com/p/ZgAAAAAAaMVO

Protocol and informed consent

- Protocol and consent are finalized as of October 22
  - Publically posted on PCORnet.org: http://www.pcornet.org/aspirin/
  - Protocol: www.pcornet.org/wp-content/uploads/2015/10/ADAPTABLE-Final-Protocol-Vers-1-Oct-22-2015.pdf
  - Consent: www.pcornet.org/wp-content/uploads/2015/04/ADAPTABLE-Consent-Form_2015-10-22-FINAL.pdf

Setting the stage for today's meeting

Our scope for today:

- Discuss the current status of development for the ADAPTABLE data components
- Outline considerations and areas needing further assessment

Setting the stage for today's meeting (2)

Important context:

- 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

Final caveat

- We'll be talking today about the *current* state of development
- These details may change during the iterative design, development, and implementation of the project

Data Sharing in ADAPTABLE

Language from ADAPTABLE Consent

6. We will get some information from other places. Taking part in ADAPTABLE does not require any special study visits or trips to your doctor. But to be sure we get a complete picture of your health:

   - We will get certain information from your medical records. Examples include information about your health problems, health care visits, hospital stays, medical procedures, and lab results. In some cases, we might need you to sign a form saying it is okay for us to get the information we need for the study.
   - We will ask for the last 4 digits of your Social Security number and health insurance ID numbers. We need these to check other sources (such as health insurance claims) for information about your health.

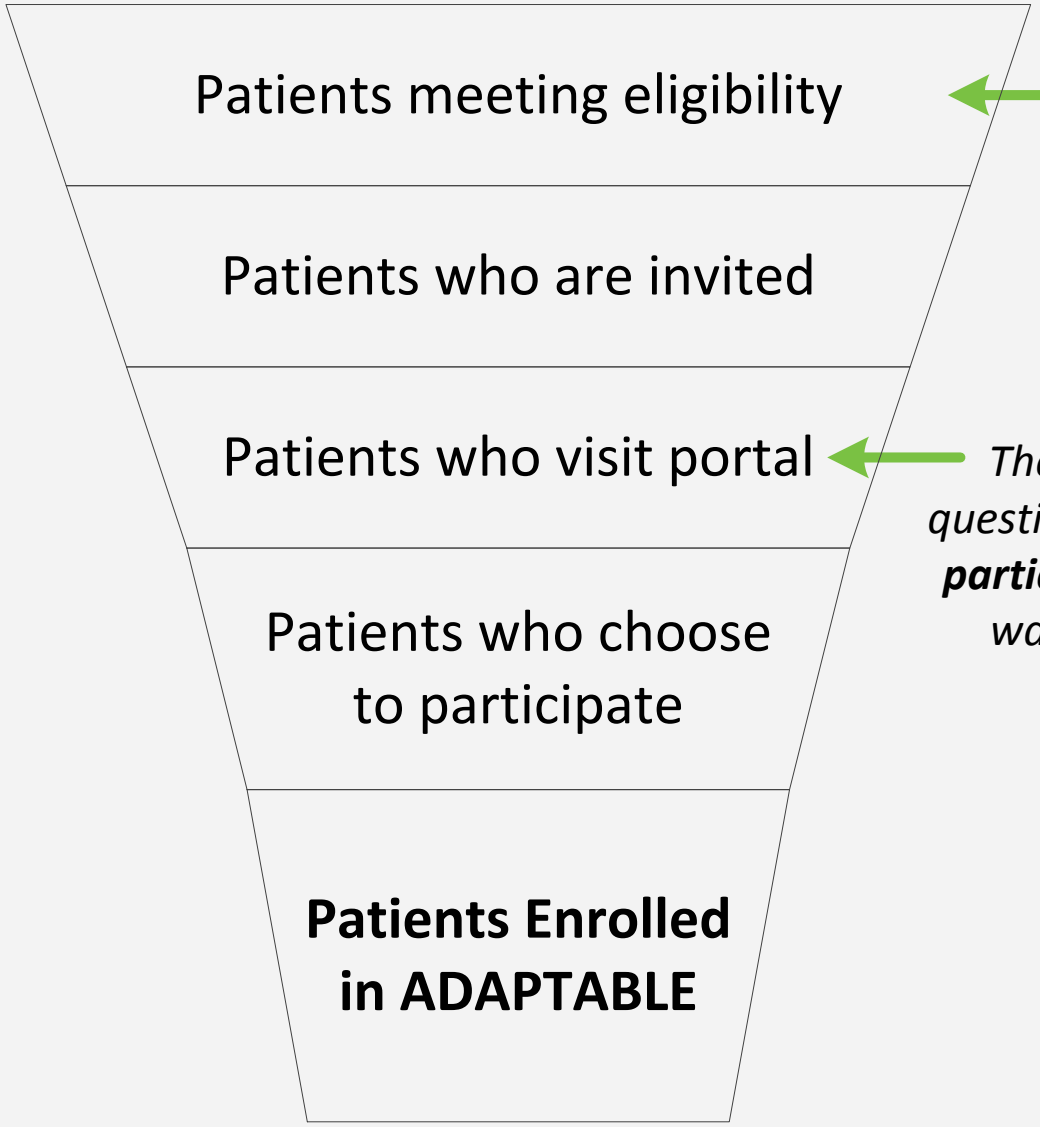
   We will get these kinds of information from time to time for as long as you are in the study.

ADAPTABLE Consent, Final Version 1.0, October 22, 2015. Page 2.
http://www.pcornet.org/wp-content/uploads/2015/04/ADAPTABLE-Consent-Form_2015-10-22-FINAL.pdf

Two areas of consideration

- **External linkage projects for ADAPTABLE** (which may include Medicare, private health claims with partners, and National Death Index) will be managed by the Coordinating Center
  - Patient-level linkage between ADAPTABLE patients and these external sources will also be performed by the Coordinating Center
- Transmitting information about **subject recruitment status** is a different process and will be covered in operational updates.

Review of Phenotype Context



Managed at site and/or network level

This is where the phenotype is situated

*The patient answers a few basic questions to **check for those unsafe to participate**, but full eligibility criteria was determined at the site level*

ADAPTABLE eligibility criteria

ADAPTABLE Protocol Final Version 1.0, October 22, 2015, section III.A.1., pages 16-17 (PDF pages 20-21).

[This image altered to remove page break.]

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 safety concerns or side effects considered to be related to aspirin, including
    a. No history of significant allergy to aspirin such as anaphylaxis, urticaria, or significant gastrointestinal intolerances
    b. No history of significant GI bleed within the past 12 months
    c. Significant bleeding disorders that preclude the use of aspirin
4. Access to the Internet. In the event that the CDRNs are notified that a cohort of patients without internet access can be included, then patient agreement will be obtained during the consent process to provide follow-up information by telephone contact with the DCRI Call Center.
5. Not currently treated with an oral anticoagulant – either warfarin or a novel anticoagulant (dabigatran, rivaroxaban, apixaban, edoxaban) – and not planned to be treated in the future with an oral anticoagulant for existing indications such as atrial fibrillation, deep venous thrombosis, or pulmonary embolism.
6. Not currently treated with ticagrelor and not planned to be treated in the future with ticagrelor.
7. Female patients who are not pregnant or nursing an infant
8. 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. Serum creatinine > 1.5 mg/dL
    c. Diabetes mellitus (Type 1 or Type 2)
    d. 3-vessel coronary artery disease
    e. Cerebrovascular disease and/or peripheral arterial disease
    f. Left ventricular ejection fraction (LVEF) < 50%
    g. Current cigarette smoker

Ticagrelor criterion was added as a result of protocol comment cycle

Adaptable

ADAPTABLE eligibility criteria contain both inclusions and exclusions

There will be no exclusions for any upper age limit, comorbid conditions, or concomitant medications other than oral anticoagulants and ticagrelor that are used at the time of randomization, or are planned to be used during the study follow-up.

Simple, inclusive eligibility criteria will make enrollment easier, and will render study results more generalizable to a broader population of patients. We will exclude pregnant or lactating women (because of concern for the fetus or child), patients taking oral anticoagulants or likely to require an oral anticoagulant during trial follow-up (because of complex drug interactions and a projected excessive risk of bleeding), and patients at relatively low risk for cardiovascular events (ie, no enrichment factor because of the large number of outcomes needed to detect a clinically meaningful difference with the available sample size).

ADAPTABLE Protocol Final Version 1.0, October 22, 2015, section III.A.1., page 17 (PDF page 21).

Screening and recruitment development

- Sites and/or networks are heterogeneous, and expected to have different processes for identifying, contacting, and inviting potential trial participants
  - "Base phenotype" (to be developed by ADAPTABLE CC) **will be modified by individual sites to best suit their processes**

Base phenotype customization is expected

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 developed by the DCRI Coordinating Center (based on the trial inclusion criteria) and customized by the CDRN for their own 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.

ADAPTABLE Protocol Final Version 1.0, October 22, 2015, section III.A.3.b. Page 21/PDF page 25.

In summary:

The ADAPTABLE eligibility phenotype will not be executed by the Coordinating Center.

Each network will run their phenotype at the local level, against their **own data sources**, and **using logic that best fits** their local **workflows and governance** for potential participant identification.

Phenotype Feedback Cycle

Feedback cycle for base phenotype specification

- Feedback cycle November 3-20
- **89 discreet comments received from 6 networks**
  - With many thanks!
- Comments classified into 16 thematic categories, responses added, and posted:
  - https://pcornet.imeetcentral.com/adaptabletrial/file/43196859/

16 thematic categories

Tag
AGE
ALLERGY
AUTHORITATIVE_SOURCE
BLEED
COHORT_BASIS
ENRICHMENT
FUTURE_TX
GLOBAL
LOOK_BACK
MEDS
MI
MORTALITY
NET_ACCESS
PREGNANCY
SITE_PLANNING
SMOKING

Enrichment factors (eligibility #8)

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 safety concerns or side effects considered to be related to aspirin, including
   a. No history of significant allergy to aspirin such as anaphylaxis, urticaria, or significant gastrointestinal intolerances
   b. No history of significant GI bleed within the past 12 months
   c. Significant bleeding disorders that preclude the use of aspirin
4. Access to the Internet. In the event that the CDRNs are notified that a cohort of patients without internet access can be included, then patient agreement will be obtained during the consent process to provide follow-up information by telephone contact with the DCRI Call Center.
5. Not currently treated with an oral anticoagulant – either warfarin or a novel anticoagulant (dabigatran, rivaroxaban, apixaban, edoxaban) – and not planned to be treated in the future with an oral anticoagulant for existing indications such as atrial fibrillation, deep venous thrombosis, or pulmonary embolism.
6. Not currently treated with ticagrelor and not planned to be treated in the future with ticagrelor.
7. Female patients who are not pregnant or nursing an infant
8. 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. Serum creatinine > 1.5 mg/dL
   c. Diabetes mellitus (Type 1 or Type 2)
   d. 3-vessel coronary artery disease
   e. Cerebrovascular disease and/or peripheral arterial disease
   f. Left ventricular ejection fraction (LVEF) < 50%
   g. Current cigarette smoker

Only "**one or more**" enrichment factor is required

8. 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 OR
   b. Serum creatinine > 1.5 mg/dL OR
   c. Diabetes mellitus (Type 1 or Type 2) OR
   d. 3-vessel coronary artery disease OR
   e. Cerebrovascular disease and/or peripheral arterial disease OR
   f. Left ventricular ejection fraction (LVEF) < 50% OR
   g. Current cigarette smoker

Some networks expressed concern about reliability of certain factors in their data (such as current smoking status).

However, the "one or more" requirement means that **sites have discretion** about which enrichment factor(s) to implement.

Adaptable

Overlap with baseline CRF

In the portal, the potential participant will answer a few basic questions to check for those unsafe to participate.

The basic questions are expected to include:

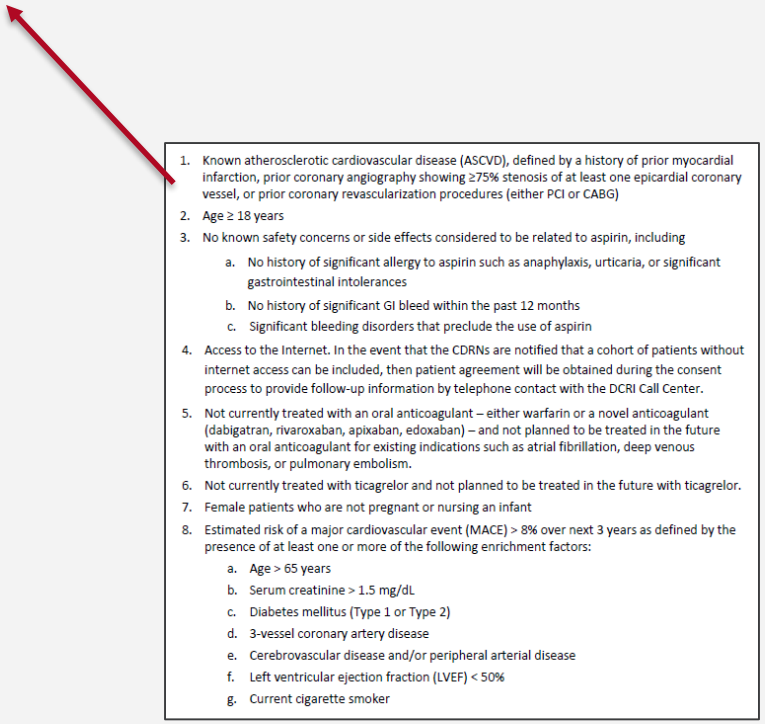
1. Aspirin allergy
2. History of severe bleeding
3. Oral anticoagulant use
4. Pregnancy

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 safety concerns or side effects considered to be related to aspirin, including
    a. No history of significant allergy to aspirin such as anaphylaxis, urticaria, or significant gastrointestinal intolerances
    b. No history of significant GI bleed within the past 12 months
    c. Significant bleeding disorders that preclude the use of aspirin
4. Access to the Internet. In the event that the CDRNs are notified that a cohort of patients without internet access can be included, then patient agreement will be obtained during the consent process to provide follow-up information by telephone contact with the DCRI Call Center.
5. Not currently treated with an oral anticoagulant – either warfarin or a novel anticoagulant (dabigatran, rivaroxaban, apixaban, edoxaban) – and not planned to be treated in the future with an oral anticoagulant for existing indications such as atrial fibrillation, deep venous thrombosis, or pulmonary embolism.
6. Not currently treated with ticagrelor and not planned to be treated in the future with ticagrelor.
7. Female patients who are not pregnant or nursing an infant
8. 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. Serum creatinine > 1.5 mg/dL
    c. Diabetes mellitus (Type 1 or Type 2)
    d. 3-vessel coronary artery disease
    e. Cerebrovascular disease and/or peripheral arterial disease
    f. Left ventricular ejection fraction (LVEF) < 50%
    g. Current cigarette smoker

Adaptable

Known Atherosclerotic Cardiovascular Disease

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)



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 safety concerns or side effects considered to be related to aspirin, including
    a. No history of significant allergy to aspirin such as anaphylaxis, urticaria, or significant gastrointestinal intolerances
    b. No history of significant GI bleed within the past 12 months
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6. Not currently treated with ticagrelor and not planned to be treated in the future with ticagrelor.
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8. 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. Serum creatinine > 1.5 mg/dL
    c. Diabetes mellitus (Type 1 or Type 2)
    d. 3-vessel coronary artery disease
    e. Cerebrovascular disease and/or peripheral arterial disease
    f. Left ventricular ejection fraction (LVEF) < 50%
    g. Current cigarette smoker

Other important areas (1 of 2)

- Cohort basis, including consideration of “loyalty cohorts”
- Practices of date obfuscation within a datamart (such as shifting all birth dates by a random number of days)
- Concern for reliability of smoking data (enrichment factor)

Other important areas (2 of 2)

- Does the presence of an e-mail address serves as a proxy measure for Internet access
- Confirmation of future treatment issue
- Global: Development processes

Draft SAS code and specification for eligibility phenotype

https://github.com/ADAPTABLETRIAL

Caveats:

- **This is a draft.**
- This is the “base” phenotype, but is not customized for your site (see slide 13). People should feel free (and are encouraged!) to use and modify.

Operational Updates

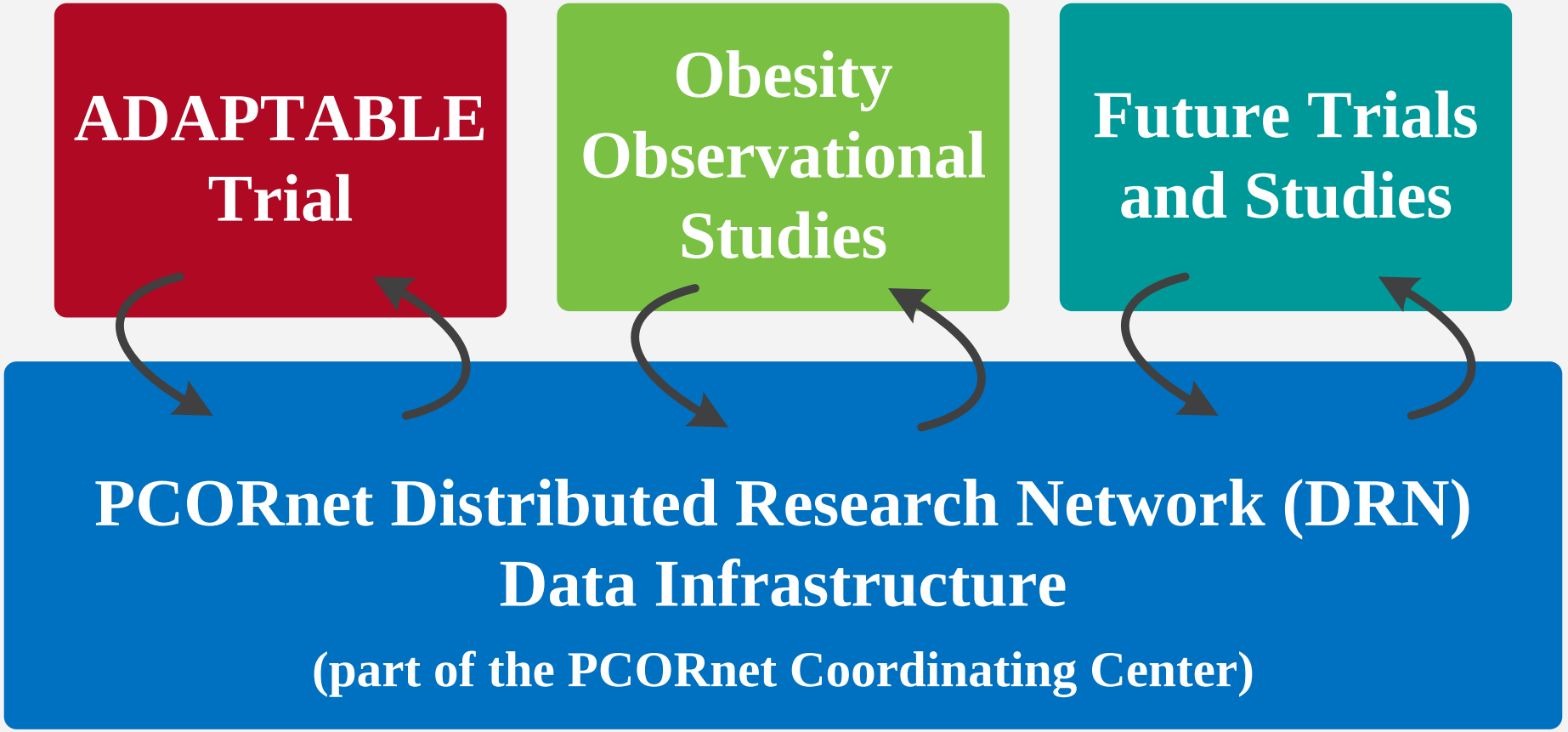
Next steps

- Materials from this meeting to be posted and shared
  - PCORnet weekly updates (Monday e-mails) will be important mechanism to monitor
  - DRNOC and Workgroups blog: https://pcornet.centraldesktop.com/drnoc-workgroups/blog/
- Contracting, site operations, and startup
  - Biweekly CDRN Calls, Mondays at 2 PM

Reference Slides

Abbreviations

- CDM = Common Data Model (http://pcornet.org/resource-center/pcornet-common-data-model/)
- DCRI = Duke Clinical Research Institute, the ADAPTABLE Coordinating Center
- DRN = Distributed Research Network
- DSMB = Data and Safety Monitoring Board
- DSSNI = Data Standards, Security, and Network Infrastructure
- LTFU = Lost to Follow-up
- RDBMS = Relational Database Management System (for example, Oracle, SQL Server, PostgreSQL, MySQL)



The ADAPTABLE trial is based upon the foundation of the PCORnet DRN data infrastructure. PCORnet trials and studies form a continuous cycle of improvement in data infrastructure development.

Slide from 2015-09-25 ADAPTABLE data strategy session

Why are “sites” different from “datamarts”?

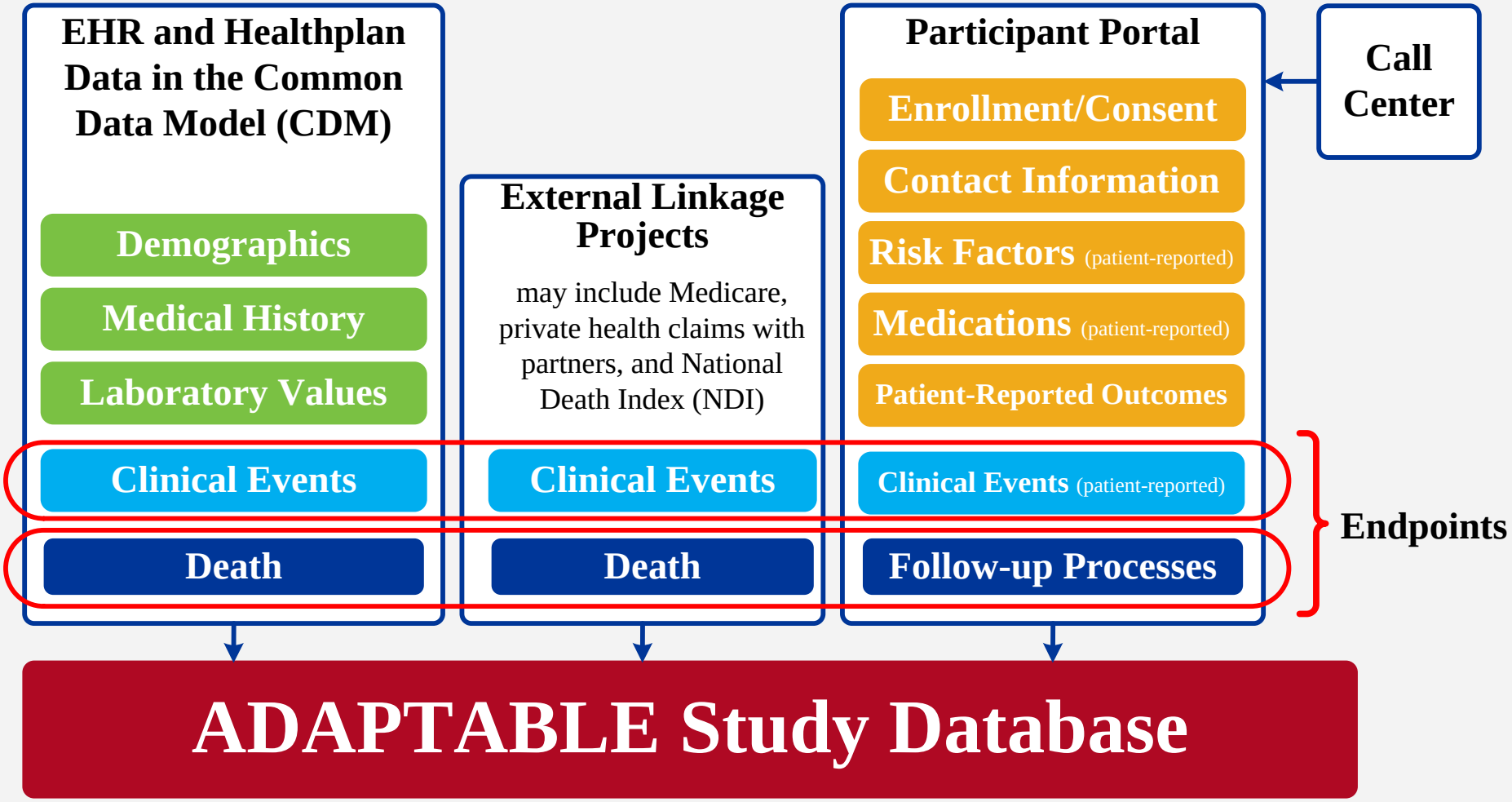
Working definitions:

Sites = **Organization of people** for clinical and patient-facing purposes.

Datamarts = **Organization of data** for distributed querying activity.

- Existing CDRNs have different network typologies (ie, different configurations for their datamarts)
  - One datamart may include more than one site
- Sites participating in ADAPTABLE will likely be smaller components of larger networks

How it all comes together for analysis (draft version)



Adaptable

Please note: The CRF is not yet finalized.

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/resource-center/pcornet-common-data-model/

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

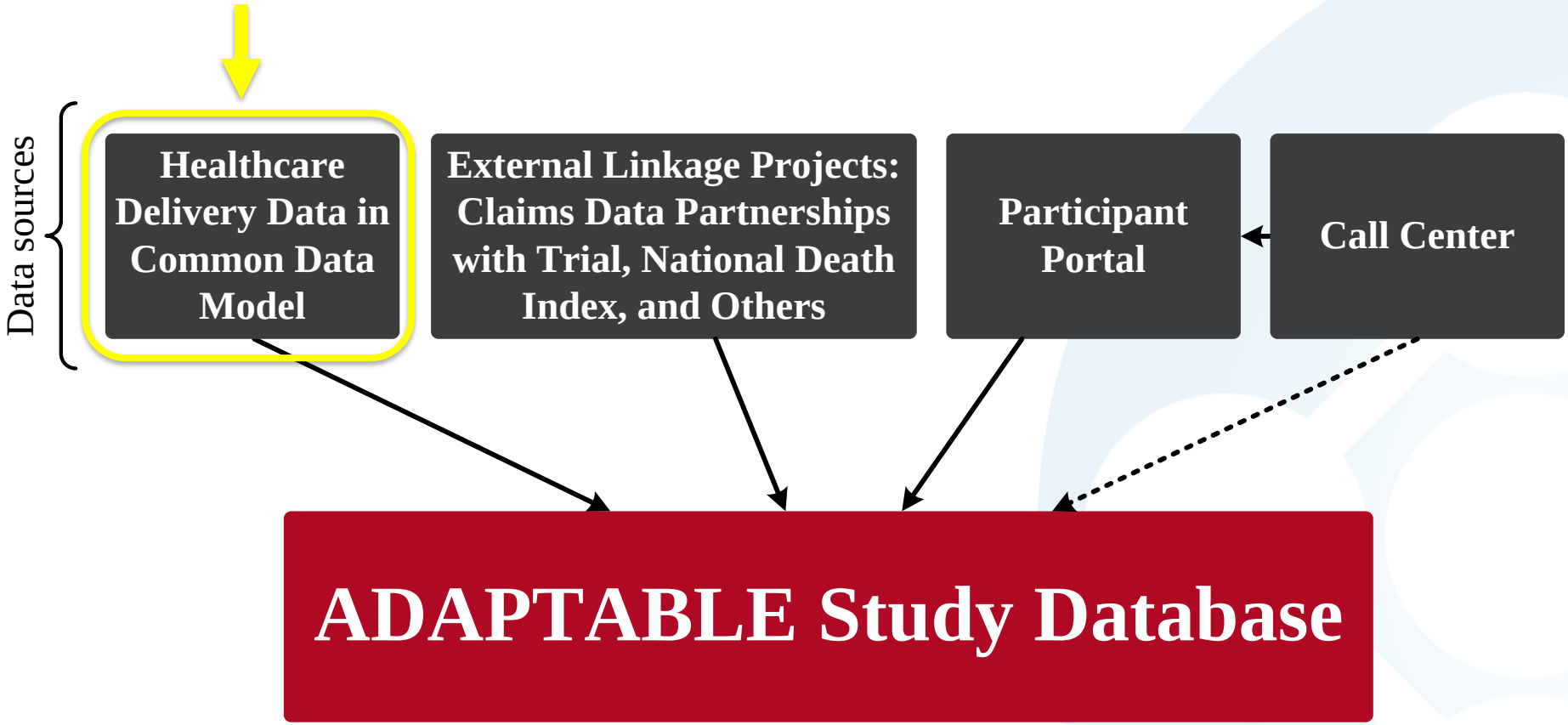
pcornet

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

ADAPTABLE RDBMS and SAS Platform Basis (from October 30 session)

pcornet

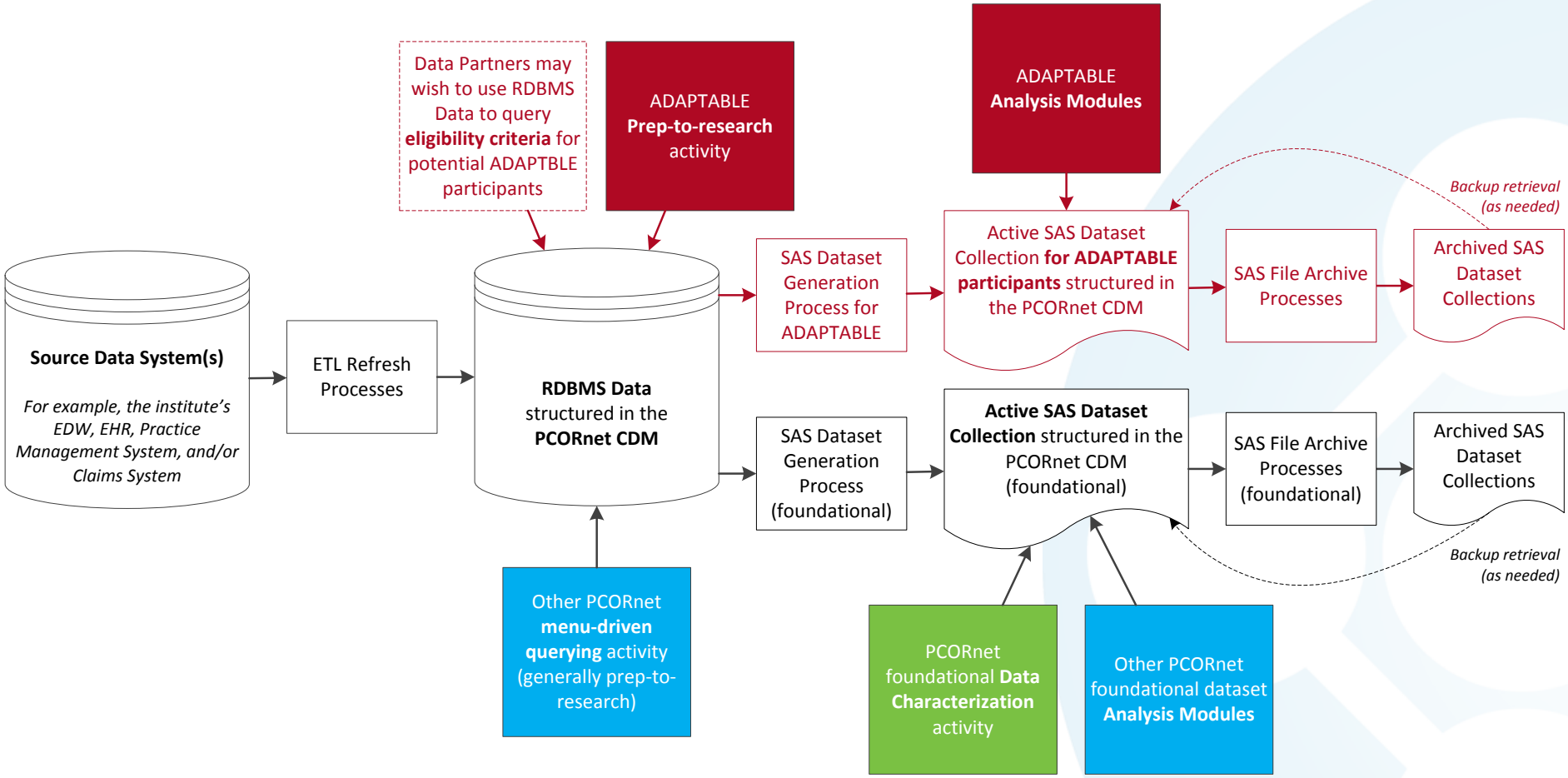
Modules of the data landscape amalgamate into the study database



pcornet

Recommended setup* for ADAPTABLE data partners - DRAFT

* Please note that data partners are known to be heterogeneous in their technical configurations and processes.

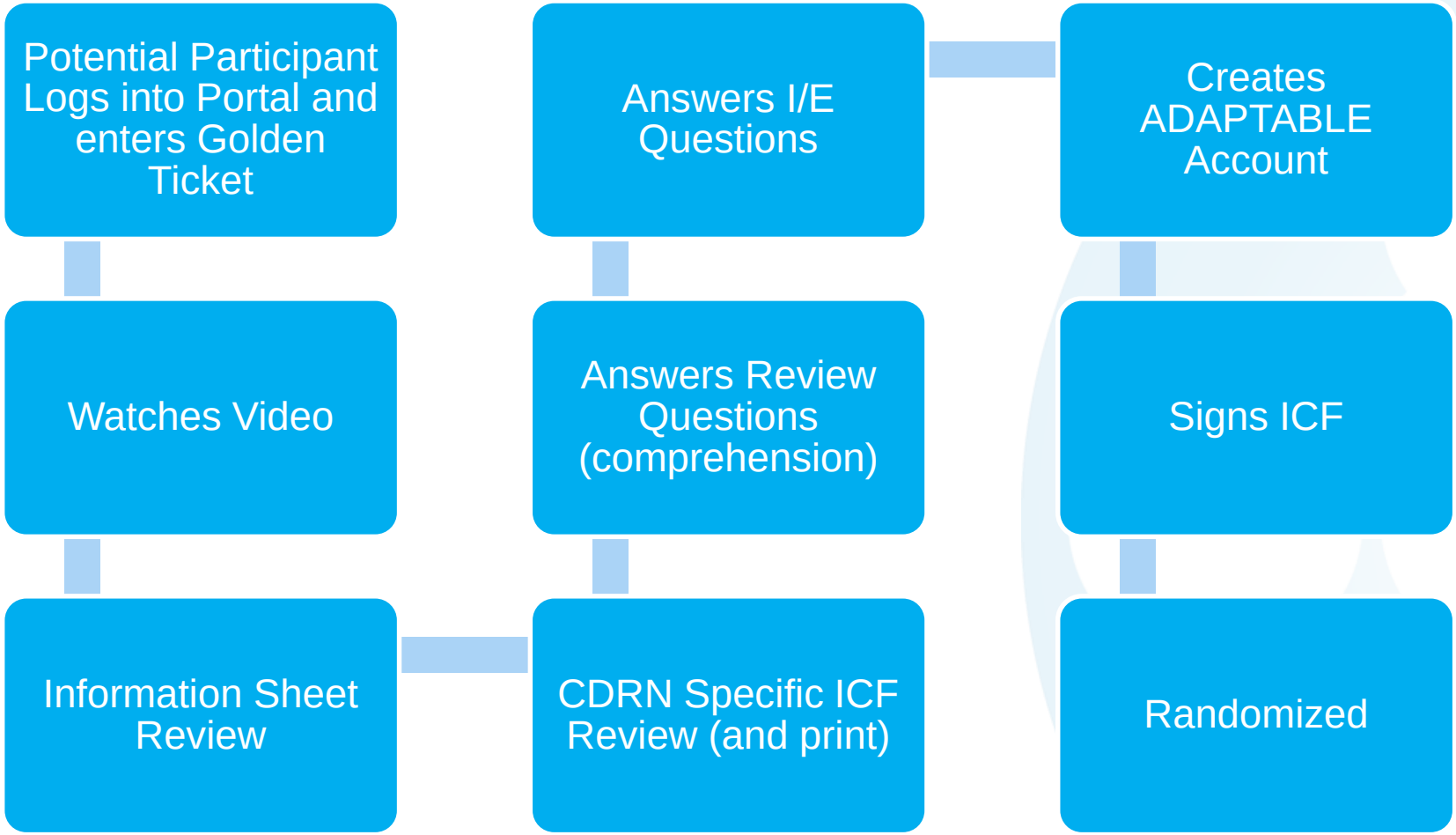


Data Flow Development between Patient Portal and Sites

(from October 30 session)

pcornet

Steps to Randomize Participants

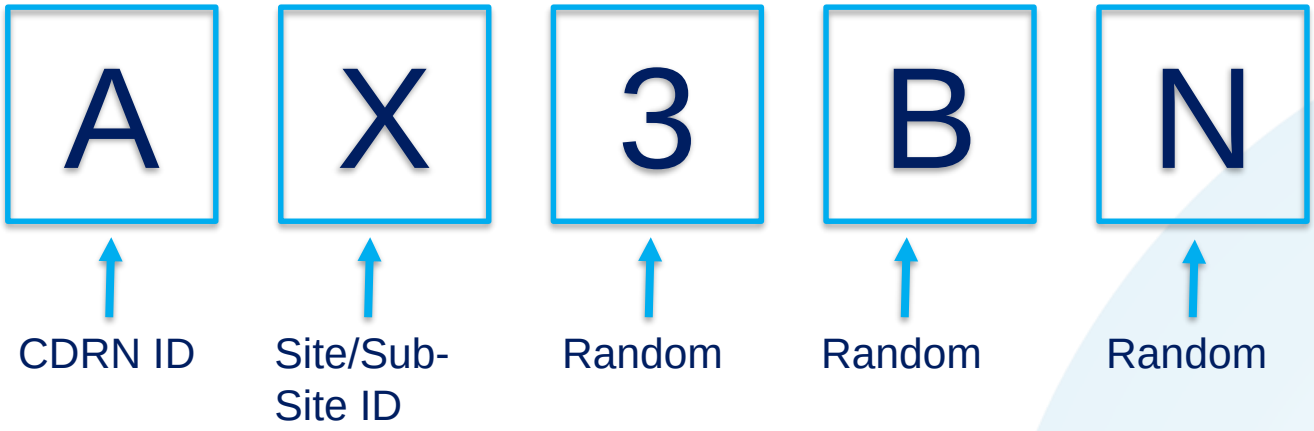


CDRN Responsibilities

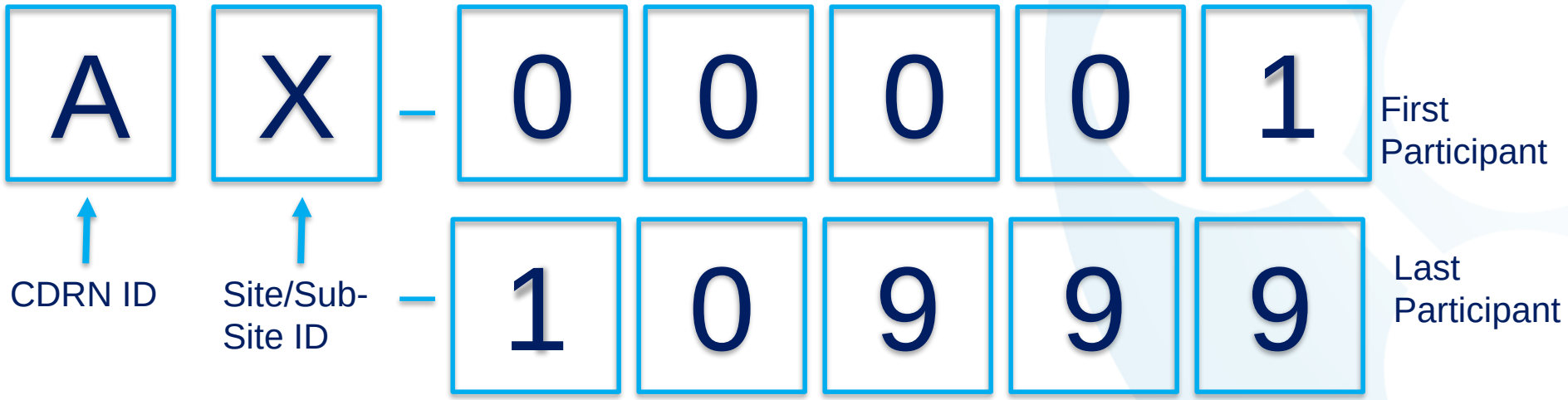
- CDRNs request “Golden Ticket” codes through Mytrus
- CDRNs invite potential participants and provide each a “Golden Ticket”
- CDRNs track “Golden Ticket” assignments
- Mytrus provides “Golden Ticket” status for those entered into Mytrus
- CDRNs reconcile “Golden Ticket” to patient identifiers
- CDRNs update PCORNET_TRIAL (including the PARTICIPANTID and TRIAL_INVITE_CODE)

pcornet

Golden Ticket



Mytrus Subject ID



pcornet

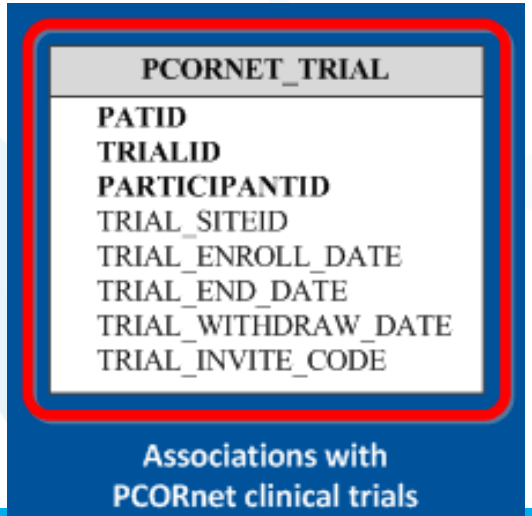
Participant Identifiers

ID	Origin	Trigger	Description
Golden Ticket	Mytrus	CDRNs request through Mytrus	CDRNs request as bulk and receive download that can be used for mail merges
Mytrus Subject ID	Mytrus	Upon randomization	Unique system generated study number assigned at randomization and sequential
PATID	PCORNET CDM	Present in the CDM	The unique subject identifier in the PCORNET CDM that CDRNs populate in PCORNET_TRIAL
PARTICIPANTID	PCORNET_TRIAL	CDRN Populates	The ADAPTABLE randomized participant identifier that links the Mytrus randomized participants to the PCORNET CDM
TRIAL_INVITE_CODE	PCORNET_TRIAL	CDRN Populates	The ADAPTABLE invited participant identifier captured in PCORNET_TRIAL

pcornet

Mytrus Reports

- Entered “Golden Ticket” Codes
- I/E Dropped Out *(aggregate)*
- Completed Account Creation
- Signed Consent
- Randomized
- Key Participant Identifiers (e.g. Name, DOB, Gender, Race)
- Other fields needed for PCORNET_TRIAL



pcornet