Early Lessons from PCORnet Trials: ADAPTABLE

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Foreseeing the Future of Clinical Trials …

- Having 300,000 patients prequalified at ~30 sites
- Approaching 1000 patients in a week at single sites
- Having a 5 page consent form available as a video option
- Testing comprehension of the study before randomization
- Enrolling a patient when it is convenient *for them*
- Working with patients on the schedule of assessments *ahead of FPI*
- Collecting all follow-up data from the EHR

*Randomizing 20,000 patients at 30 sites over 24 months – achieving metrics never even considered with traditional trials!*
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

- ASA 81 mg QD
- ASA 325 mg QD

- Electronic follow-up: Every 3 or 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

† Participants without internet access will be consented and followed via a parallel system.
# Traditional Trials vs. ADAPTABLE

<table>
<thead>
<tr>
<th></th>
<th>Traditional</th>
<th>ADAPTABLE</th>
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</thead>
<tbody>
<tr>
<td>Inclusion/Exclusion criteria</td>
<td>Sample via monitor visit</td>
<td>EHR and CDM (Common Data Model)</td>
</tr>
<tr>
<td>check</td>
<td>Sample via monitor visit</td>
<td>EHR and CDM (Common Data Model)</td>
</tr>
<tr>
<td>Representative cohort</td>
<td>Narrow</td>
<td>Broad</td>
</tr>
<tr>
<td>Consent</td>
<td>In Person Facilitated</td>
<td>Patient-directed</td>
</tr>
<tr>
<td>Comprehension tested</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Format</td>
<td>Paper</td>
<td>Electronic (e-consent)</td>
</tr>
<tr>
<td>Data collection</td>
<td>Patient-reported</td>
<td>Patient-reported</td>
</tr>
<tr>
<td></td>
<td>Site-recorded</td>
<td>CDM</td>
</tr>
<tr>
<td>Source documents</td>
<td>Only seen by site</td>
<td>EHR data via CDM</td>
</tr>
<tr>
<td>Endpoint adjudication</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Patient involvement</td>
<td>Participants only</td>
<td>Protocol design, DSMB, analyses, dissemination</td>
</tr>
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</table>
Trial Cost Comparisons

ADAPTABLE: $850 per participant
- 20,000 participants
- $17M total cost (Directs + Indirects)

PROMISE* (pragmatic trial): $3,100 per participant
- 10,003 participants
- $27M total cost

BRIDGE**: $13,000 per participant
- 1,884 participants
- $23M total cost

*Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease

**Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

ClinicalTrials.gov: NCT02697916
Efficiencies in ADAPTABLE

Employs system-wide screening of EHRs using key indicators to identify patients to approach.

Eliminates data entry redundancies by obtaining information directly from EHRs via the Common Data Model (CDM):
- Medical History
- Endpoints (re-hospitalizations) and safety data
- Labs and Medications

Collects longitudinal patient-reported outcomes directly from participants via the Adaptable patient web portal.

Eliminates costly monitoring to verify data accuracy.
ADAPTABLE Main Trial Objectives

To compare the effectiveness and safety of two doses of aspirin (81 mg and 325 mg) in high-risk patients with atherosclerotic cardiovascular disease (ASCVD)

- **Primary effectiveness endpoint:** all causes of mortality, hospitalization for MI, or hospitalization for stroke
- **Primary safety endpoint:** Hospitalization for major bleeding

To compare the effects of aspirin in predefined key subgroups of ASCVD patients

- Age, diabetes, sex
- Race, P2Y12 inhibitor use
- Chronic kidney disease

To develop and refine the infrastructure for PCORnet to conduct multiple comparative effectiveness trials in the future
CDRNs and Health Care Systems Participating in ADAPTABLE

This map depicts the coverage of health systems within Clinical Data Research Networks (CDRN) participating in ADAPTABLE.
ADAPTOR Patient Investigators

- Patients involved in prioritization of the research topic, protocol design, and trial conduct
- ADAPTORS integral to empirical development of participant-centric consent form and comprehension assessment
- ADAPTORS working with CDRNs on the development of recruitment plans and materials
IRB Reviews and Approaches

Each CDRN has independent IRB review and approval of the protocol, trial web portal, and trial-related materials.

CDRNs are using different IRB approaches:

- **Traditional Approach** - each individual site within the network submits to their local IRBs for full review.
- **Research Alliance (multiple)** - lead site submits to their local IRB for full review. Sites within the network submit the lead IRB approval to their local IRBs for expedited review.
- **Research Alliance (single)** - participating sites agree to have a single lead site submit to their local IRB for review to cover all sites within the network.

ClinicalTrials.gov: NCT02697916
Site Activation Timelines – Traditional Trials vs. ADAPTABLE

<table>
<thead>
<tr>
<th>Event</th>
<th>ADAPTABLE</th>
<th>Traditional</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDRN Contract Executed</td>
<td>125</td>
<td>200</td>
</tr>
<tr>
<td>IRB Approval</td>
<td>150</td>
<td>200</td>
</tr>
<tr>
<td>Initial CDRN Site Activation</td>
<td>250</td>
<td>250</td>
</tr>
<tr>
<td>Site Activation</td>
<td>225</td>
<td>250</td>
</tr>
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</table>
Optimizing Computable Phenotype for EHR Searches

Confirmation of coronary artery disease is nuanced
  - Previous events (MI) or procedures (PCI/CABG) may have been in other health systems or before the “look back” time period for EHR data searches
  - Angiographic data hard to access in CDM
  - Chronic CAD diagnosis codes key for confirmation

Difficulties in confirming some enrichment factors
  - Current smoking, known 3 vessel CAD, LVEF < 50%

Accuracy of patient identification with the CP has been evaluated in different ways across CDRN’s
  - What type of validation or verification is needed?
ADAPTABLE Inclusion Criteria – Computable Phenotype with Protocol Amendment

Known ASCVD
- Prior MI
  OR
- Prior revascularization (PCI or CABG)
  OR
- Prior angiogram showing significant CAD
  OR
- History of chronic ischemic heart disease, CAD, or ASCVD

≥ 1 enrichment factor:
- Age ≥ 65 years
- Creatinine ≥ 1.5 mg/dL
- Diabetes mellitus
- Known 3-vessel CAD
- Cerebrovascular disease
- Peripheral arterial disease
- Current smoker
- Known LVEF < 50%
- Chronic systolic or diastolic heart failure
- SBP ≥ 140 (within past 12 mos)
- LDL ≥ 130 (within past 12 mos)

Electronic patient outreach

ClinicalTrials.gov: NCT02697916
Recruitment approach (1)

- 8 CDRNs are participating
  - Total planned enrollment: 20,000 patients
- Electronic, computable phenotype used to query CDRN EHR data to facilitate widespread screening of large numbers of potentially eligible patients

Patient Outreach

- Direct Mail and Email (messages locally customized)
- Facilitated “In Clinic” Recruitment (EHR Alerts to clinic teams, Tablet-based recruitment app, etc)
- CDRN customized outreach strategies

Potential patients are directed to the web portal for confirmatory screening and electronic informed consent
Recruitment approach (2)

- A subset of participants who do not have internet access will be enrolled at each CDRN
  - Consented in the clinic using the patient web portal
  - Sites will facilitate entry of the baseline information in the portal for participants
  - Follow-up will occur by the DCRI call center every 4 months

- Patient engagement through the ADAPTORS patient group being used to enhance and refine recruitment approaches

- Only individuals who receive their health care within the participating CDRNs are eligible to participate
**Web-Based Patient Portal Enrollment**

1. **Watch Introduction Video**
   - 5 minutes

2. **Read Study Information**
   - 15 minutes

3. **Review the Informed Consent**
   - 5 minutes

4. **Confirm Key Eligibility Criteria**
   - 3 minutes

5. **Create Personal Profile**
   - 15 minutes

6. **E-sign Consent**
   - 5 minutes

7. **Obtain Randomization Assignment**
   - 5 minutes

8. **Consent and Assignment emailed to Participant**

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Site Activation and Enrollment Update

Enrollment began in April, 2016
- First patient enrolled at Vanderbilt (Mid-South CDRN)

20 Sites Currently Activated (as of 11.10.16)
- 14,430 patients approached through all methods
- 1191 Golden Tickets entered into the patient web portal (8.3% of approached patients have Golden Tickets entered)
- 509 Subjects Randomized (3.5% of approached patients randomized)

Enrollment metrics dynamic during study start up
- 12 sites have started enrolling patients
- Total approached patients per site ranges from 140 to 5,500
- Site enrollment averaging between 7-36 patients/site/month
Currently focusing upon bending enrollment curve upward.
Early Lessons Learned from ADAPTABLE

- Widespread screening of EHRs requires flexibility and creative approaches to successfully recruit patients
  - Optimal methods for patient outreach being determined
  - Key factors for successful randomization after initial outreach and contact of eligible patients remain uncertain
  - Large numbers of patients need to be approached to achieve enrollment goals

- Patient engagement is a key attribute of the trial and a defining feature of ADAPTABLE

- Further experience will be gained with pragmatic approaches for patient follow up and endpoint ascertainment in ADAPTABLE