MHIF FEATURED STUDY: AEGIS 2

DESCRIPTION:
CSL112 is being developed for use in patients with ACS (diagnosed with either STEMI or NSTEMI and exclusive of unstable angina) to reduce the risk of CV death, MI, and stroke upon delivery of CSL112. Evidence from the Apo-I Event Reducing in Ischemic Syndromes-I (AEGIS-I) study has demonstrated that administration of apoA-I increases cholesterol efflux in MI patients.

CRITERIA LIST/QUALIFICATIONS:

Inclusion
Positive Troponin with at least 50% stenosis on > 1 epicardial artery or prior cath with at least 50% stenosis on > 1 epicardial artery or prior CABG
Additional risk factor: DM, > 65 y.o., prior hx of MI or PAD

Exclusion
- EF < 30%
- ALT > 3 x ULN
- GFR< 30
- Body weight < 50 kg
- Allergy to soy beans or peanuts
- Plan for CABG

CONDITION: Acute Coronary Syndrome
PI: Thomas Knickelbine, MD
RESEARCH CONTACT: Stephanie Ebnet
SPONSOR: CSL Behring

OPEN AND ENROLLING: Please Refer Patients to Steph!

Please Refer Patients to Steph!
I am not a clinical trialist.

I did not design the studies we will discuss.

My interest in PCORNet relates to the underlying framework for clinical research.
Objectives

- **Why** PCORnet was created
- **What** PCORnet will do for research
- **How** it (is intended to) works
- **Lessons** learned along the way
Our national clinical research system is well-intentioned but flawed

- High percentage of decisions not supported by evidence*
- Current system is:
  - Too slow
  - Too expensive
  - Unreliable
  - Doesn’t answer questions that matter most to patients
  - Unattractive to clinicians & administrators

We are not generating the evidence we need to support the healthcare decisions that patients and their doctors have to make every day.

PCORnet: the National Patient-Centered Clinical Research Network

An innovative initiative funded by the Patient-Centered Outcomes Research Institute (PCORI), PCORnet is a large, highly representative, national patient-centered clinical research network.

Our vision is to support a learning U.S. healthcare system and to enable large-scale clinical research conducted with enhanced quality and efficiency.

Our mission is to enable people to make informed healthcare decisions by efficiently conducting clinical research relevant to their needs.

Overall objectives of PCORnet: achieving a single functional research network

- **Create** a secure national research resource that will enable teams of health researchers, patients, and their partners to work together on researching questions of shared interest
- **Utilize** multiple rich data sources to support research, such as electronic health records, insurance claims data, and data reported directly by patients
- **Engage** patients, clinicians & health system leaders throughout the research cycle from idea generation to implementation
- **Support** observational and interventional research studies that compare how well different treatment options work for different people
- **Enable** external partners to collaborate with PCORI-funded networks
- **Sustain** PCORnet resources for a range of research activities supported by PCORI and other sponsors
Why is Traditional Clinical Research Slow and Costly?

Data is collected in care delivery
Not long ago, this data was only collected on paper.

Paper is OK, until....

...you want to start looking at many patients at once.

- Can’t find patterns, trends, outcomes
- Can’t make complex comparisons
- Can’t identify patients for important questions
What can we do with Electronic Health Records?

Using EHRs to find the right patients to answer a question

Developing a “computable phenotype”

Can you pull data from our EHR that will show me all patients between ages _____ and _____, who have been diagnosed with ________, with visits in the ______________ clinic over the past year?

I also need to know if they’re taking _____________ and have had any blood pressure readings over ___ or ___ lab values over ___ in the past year.
Now, what if you wanted to look at many patients at different health systems across the country?

But it can be hard...

- Data structure designed for local needs, not for collaboration
- Multi-site regulatory process is daunting and confusing
Objectives

• Why PCORnet was created
• What PCORnet will do for research
• How it (is intended to) works
• Lessons learned along the way

How Clinical Data Research Networks (CDRN) Work
CDMs allow data across sites to be compared.

- Allina’s data is optimized and coded for our organization. But what if we want to share it?
- If we just try to combine our data with the data from another care system, we’d have...

![Apple and Orange](close enough)

CDMs allow data across sites to be compared.

- CDMs emphasize a common data structure...
- ...as a result, we now have data that’s sharable in a number of ways

![Apple and Apple](close enough)
CDMs allow data across sites to be compared.

<table>
<thead>
<tr>
<th>SITE 1</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
</tr>
<tr>
<td>Multiple Race</td>
<td></td>
</tr>
<tr>
<td>Blank</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SITE 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>101</td>
<td></td>
</tr>
<tr>
<td>201</td>
<td></td>
</tr>
<tr>
<td>300</td>
<td></td>
</tr>
<tr>
<td>401</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td></td>
</tr>
<tr>
<td>600</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SITE 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td></td>
</tr>
<tr>
<td>American Indian</td>
<td></td>
</tr>
<tr>
<td>Asian American</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

Common Data Model Value Set

- 01 = American Indian or Alaska Native
- 02 = Asian
- 03 = Black or African American
- 04 = Native Hawaiian or Other Pacific Islander
- 05 = White
- 06 = Multiple Race
- 07 = Refuse to Answer
- NI = No Information
- UT = Unknown
- OT = Other

Types of Data

- Biospecimen & Genomic Data
- Prescribing
- Condition
- Encounters
- Procedures
- Patient Satisfaction
- Lab Results
- Claims
- Demographic
- Vital Status
Data federation allows for controlled data sharing

Data stored locally

Database 1  Database 2  Database 3  Database 4

Common data model

Data stored locally

Database 1  Database 2  Database 3  Database 4
Data federation allows for controlled data sharing.

Query for counts across sites

Common data model

Data stored locally

Federated Query Tool (Web-based)

- Database 1
- Database 2
- Database 3
- Database 4

CDRNs

- ADVANCE: Accelerating Data Value across a National Community Health Center Network (ADVANCE)
  - Oregon Community Health Information Network (OCHIN)
- CRAPiCORN: Chicago Area Patient Centered Outcomes Research Network (CRAPiCORN)
  - The Chicago Community Trust
- Greater Plains Collaborative (GPC)
  - University of Kansas Medical Center
- Kaiser Permanente & Strategic Partners Patient Outcomes Research Institute for Learning (PORTAL) Network
  - Kaiser Foundation Research Institute
- Research Action for Health Network (REACHnet)
  - Louisiana Public Health Institute (LPHI)
- Mid-South CDRN
  - Vanderbilt University
- National PEDSnet: A Pediatric Learning Health System
  - The Children’s Hospital of Philadelphia
- New York City Clinical Data Research Network (NYC-CDREN)
  - Weill Medical College of Cornell University
- OneFlorida Clinical Data Research Network
  - University of Florida
- Patient-Centered Network of Learning Health Systems (LHSNet)
  - Mayo Clinic
- Patient-oriented SCALABLE National Network for Effectiveness Research (pSCANNER)
  - University of California, San Diego (UCSD)
- PATHi: Towards a Learning Health System
  - University of Pittsburgh
- Scalable Collaborative Infrastructure for a Learning Healthcare System (SCILHS)
  - Harvard University

MHIF CV Grand Rounds – Sept. 17, 2018
This map depicts the number of PCORI-funded Patient-Powered or Clinical Data Research Networks that have coverage in each state.
## PCORnet Demographics

<table>
<thead>
<tr>
<th></th>
<th>PCORnet*</th>
<th>2010 US Census</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-20</td>
<td>34%</td>
<td>27%</td>
</tr>
<tr>
<td>21-44</td>
<td>27%</td>
<td>34%</td>
</tr>
<tr>
<td>45-64</td>
<td>24%</td>
<td>26%</td>
</tr>
<tr>
<td>65-74</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>75+</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>55%</td>
<td>51%</td>
</tr>
<tr>
<td>Male</td>
<td>45%</td>
<td>49%</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black/African American</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>White</td>
<td>54%</td>
<td>72%</td>
</tr>
<tr>
<td>Other/Missing</td>
<td>32%</td>
<td>15%</td>
</tr>
<tr>
<td><strong>Hispanic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19%</td>
<td>16%</td>
</tr>
<tr>
<td>No</td>
<td>52%</td>
<td>84%</td>
</tr>
<tr>
<td>Other/Missing</td>
<td>29%</td>
<td></td>
</tr>
</tbody>
</table>

*Number of patients with given characteristic with an encounter in any care setting divided by the total number of patients with an encounter in any care setting (2014).

## Selected Condition Counts:

### 23 Data Marts

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>530,000</td>
</tr>
<tr>
<td>Pulmonary Disease</td>
<td>1,900,000</td>
</tr>
<tr>
<td>Any Malignancy</td>
<td>740,000</td>
</tr>
<tr>
<td>MI</td>
<td>230,000</td>
</tr>
<tr>
<td>Stroke</td>
<td>230,000</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>139,000</td>
</tr>
<tr>
<td>Ulcerative Colitis</td>
<td>46,000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3,420,000</td>
</tr>
<tr>
<td>Renal Disease</td>
<td>671,000</td>
</tr>
<tr>
<td>Influenza/ Pneumonia</td>
<td>578,000</td>
</tr>
</tbody>
</table>
Particularly Relevant for Clinical Trials

<table>
<thead>
<tr>
<th>Randomized Clinical Trials (RCTs) in Cardiovascular Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current challenges</strong></td>
</tr>
<tr>
<td>Scientific and operational complexity</td>
</tr>
<tr>
<td>Waning site and patient participation</td>
</tr>
<tr>
<td>Regulatory issues</td>
</tr>
<tr>
<td>Inefficient and costly</td>
</tr>
</tbody>
</table>

Objectives

- **Why** PCORnet was created
- **What** PCORnet will do for research
- **How** it (is intended to) works
- **Lessons** learned along the way
I am not a clinical trialist.

I did not design the studies we will discuss.

My interest in PCORNet relates to the underlying framework for clinical research.

My Invitation to Participate in LHSNet

• Allina had successfully participated in CDM

• PI leaving Allina

• Asked to serve as PI “couple hours a week”
Demonstration Projects

- **INVESTED**
  - Influenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure

- **ADAPTABLE**

INVESTED Trial

- More than 35,000 influenza-associated deaths each flu season

- Over 200,000 influenza-related excess hospitalizations

- Association between acute respiratory infections and cardiovascular events

Thompson et al JAMA. 2003;289:179-186
Thompson et al JAMA. 2004;292:1653-1660
Majid et al. EOH 2007(28):1205-1210
Association Between Respiratory Infections and MI or Stroke

Flu Vaccine Reduces CV Risk

Flu Vaccine

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Total</th>
<th>Placebo/Control</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Govaert</td>
<td>7</td>
<td>927</td>
<td>5</td>
<td>911</td>
</tr>
<tr>
<td>FLUVACS</td>
<td>32</td>
<td>145</td>
<td>54</td>
<td>147</td>
</tr>
<tr>
<td>FUCAD</td>
<td>16</td>
<td>325</td>
<td>30</td>
<td>333</td>
</tr>
<tr>
<td>DeVilliers</td>
<td>20</td>
<td>1620</td>
<td>20</td>
<td>1622</td>
</tr>
<tr>
<td>Phrommikitik</td>
<td>20</td>
<td>221</td>
<td>42</td>
<td>218</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>3238</td>
<td>151</td>
<td>3231</td>
</tr>
</tbody>
</table>

Absolute Risk Difference: 1.74%
Number Needed to Treat: 58

JAMA 2013;310;1711-1720.
Reduced Immune Response Among Patients with Heart Failure

**INfluenza Vaccine to Effectively Stop CardioThoracic Events and Decompensated Heart Failure (INVESTED)**

*Post-MI or HF Hospitalization*

- **Randomized 1:1 Double Blind Annual Vaccine Strategy**
  - High Dose Trivalent Influenza Vaccine
  - Standard Dose Quadrivalent Influenza Vaccine
  - All other CV Rx per treating MD

- **Duration**
  - 3 Influenza Seasons + Vanguard Season
  - Followed up to 4 times a year with annual re-vaccination to assigned strategy

**Primary EP**
- Death or Cardiopulmonary Hospitalization
What makes INVESTED “pragmatic”

- Strategy of high- vs low-dose vaccine (formulations could change)
- Straightforward inclusion criteria (large number of potential subjects)
- Recruitment leverages EHR
- Intervention a “one-shot” deal
- Endpoint ascertainment more simple and requires minimal adjudication

Leveraging the Common Data Model for Patient Enrollment

- Query on:
  - Enrollment criteria
  - Follow-up in Allina Health
  - Upcoming visits

- Targeted recruitment
  - Allina leading enroller for all of PCORnet!!
Allina’s Success

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Principal Investigator</th>
<th>Number Randomized</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Abbott Northwestern Hospital</td>
<td>Frank Blume</td>
<td>57</td>
</tr>
<tr>
<td>2. OneFlorida CHI</td>
<td>Carl Papiore</td>
<td>42</td>
</tr>
<tr>
<td>3. University of Iowa</td>
<td>Patricia Winkenski</td>
<td>40</td>
</tr>
<tr>
<td>4. Northwestern University</td>
<td>Naja Muthumase</td>
<td>36</td>
</tr>
<tr>
<td>5. Healthpartners-Riverside Research</td>
<td>Karen Maggio</td>
<td>32</td>
</tr>
<tr>
<td>6. Loyola University Medical Center</td>
<td>Alan Hoerner</td>
<td>30</td>
</tr>
<tr>
<td>7. Medical University of South Carolina</td>
<td>Mohammad Hossain</td>
<td>27</td>
</tr>
<tr>
<td>8. University of North Carolina Chapel Hill</td>
<td>Jo Ellen Rodgers</td>
<td>21</td>
</tr>
<tr>
<td>9. Mayo Clinic</td>
<td>Paul McKee</td>
<td>17</td>
</tr>
<tr>
<td>10. Vanderbilt University</td>
<td>H. Kepp Talbot</td>
<td>13</td>
</tr>
</tbody>
</table>

Signs of Trouble

![Wong-Baker FACES® Pain Rating Scale](image)
Demonstration Projects

• INVESTED
  – Influenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure

• ADAPTABLE

What if an over-the-counter choice...
What if an over-the-counter choice...

19,000 Deaths/Heart Attacks
Or
Thousands of Bleeds
Annually in the United States

The Role of Platelets in Acute Cardiovascular Events

Quiescent plaque

Vulnerable plaque

Heart Attack

Minneapolis Heart Institute
Center for Healthcare Delivery Innovation

Allina Health
Abbott Northwestern Hospital
Aspirin: A wonder drug

- Proven clinical benefit in reducing ischemic vascular events
- Cost effective
- Benefit with combination antiplatelet therapies
- But there are issues:
  - Emerging evidence for dose modifiers (ASA resistance, genetics, P2Y12 inhibitors)
  - Equal efficacy across patients?
  - Intolerance

Most effective dose uncertain

Clinical Equipoise

Distribution of aspirin dosing at discharge

High (25-fold) Variation Across Hospitals on Use of High Dose (325mg) Aspirin

- 325 mg: 57%
- 81 mg: 50%
- Other: 0.01%
The ADAPTABLE Aspirin Study

- 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

E-data Collection and Follow-up

N=20,000

- ADAPTABLE enrollee
- Baseline data
- 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

- 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

Death ascertainment
  - National Death Index (NDI) & Social Security Database

Timeline:
- 6 months
- 12 months
- 18 months
- 24 months
- 30 months
Cost Comparisons for Trial Design

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

Signs of Trouble

Wong-Baker FACES® Pain Rating Scale

0: No Hurt
2: Hurts Little Bit
4: Hurts Little More
6: Hurts Even More
8: Hurts Whole Lot
10: Hurts Worst

Used with permission. Originally published in Wong & Wong's Nursing Care of Infants and Children, 6th Edition Inc.
Vetting the Computable Phenotype

• Eligible Patients
  – Any ASCVD (prior MI, prior PCI or CABG, coronary angio with $\geq 75\%$ stenosis, or h/o chronic ischemic heart dx, CAD, or ASCVD)
  – No ASA safety concerns (allergy, bleeding)
  – No anticoagulant or ticagrelor
  – Enrichment factor (>65 yo, creat >1.5, diabetes, CVD, PAD, 3V CAD, CHF, SBP>140, LDL>130)

• Any problems here?

Allina’s Recruitment Approach

<table>
<thead>
<tr>
<th>Week</th>
<th>Email/Letter and Phone Recruitment</th>
<th>Number of patients</th>
<th>Estimated Conversions</th>
<th>In-person Conversions</th>
<th>Weekly Conversions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>Initial email and letter – Group 1</td>
<td>100</td>
<td>2</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Week 2</td>
<td>Initial email and letter – Group 2</td>
<td>96</td>
<td>4</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Follow-up email – Group 1</td>
<td>100</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>Final email – Group 1</td>
<td>90</td>
<td>4</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Follow-up email – Group 2</td>
<td>96</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial email and letter – Group 3</td>
<td>100</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>Final phone call – Group 1</td>
<td>85</td>
<td>8</td>
<td>7</td>
<td>25 (anticipated steady state)</td>
</tr>
<tr>
<td></td>
<td>Final email – Group 2</td>
<td>90</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up email – Group 3</td>
<td>96</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial email and letter – Group 4</td>
<td>100</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Why Letters Won’t Work

- Familial Hyperlipidemia Project
  - QI project to identify and improve care of patients with FH
  - Patients identified using labs in EDW

- Letters to ~120 patients → 1 preventive clinic appointment

Future of PCORI Funding
More Trouble Brewing

Wong-Baker FACES Pain Rating Scale

- 0: No Hurt
- 2: Hurts Little Bit
- 4: Hurts Little More
- 6: Hurts Even More
- 8: Hurts Whole Lot
- 10: Hurts Worst

The Power of MHI and MHIF

A Fresh Start
Just Ahead
Rethinking Our Approach

- Leverage new ways of patient identification (CDM)
- Leverage tried and true for patient enrollment

My View of Clinical Research
Additional PCORNet Studies in Early Stages

• Comparison of Oral Anticoagulants for extended VEnous Thromboembolism (COVET)

• Patient Reported Outcomes inVestigation following Initiation of Drug therapy with Entresto (Sacubitril/Valsltaran) in Heart Failure (PROVIDE-HF)

Observational Studies

• Trends and prevalence of PCSK9 inhibitor use

• Epidemiology of pre-diabetes

• Obesity and Heart Failure Survey Studies

• TVTR Linkage
PCORnet® for many kinds of research

Pre-research
- Feasibility queries
- Engagement
- Match-making

Interventional studies
- Clinical trials
- Pragmatic randomized clinical trials
  - e-Identification
  - e-Consent
  - e-Randomization
  - e-Follow-up
- Cluster randomization

Observational studies
- Cross-sectional
- Epidemiology
- Health services
- Comparative effectiveness or safety

Reengaged in a New Day
Conclusion

• PCORnet is a national network of networks to support pragmatic research

• Traditional approach to clinical trials can bridge to a refined pragmatic approach

• Important to participate in a changing research environment

Thank You

• MHIF Team
  – Christine Majeski
  – Ross Garberich
  – Scott Sharkey
  – Kris Fortman

• Allina LHSNet Team
  – Cass Rodgers
  – Narayana Mazumder
  – Kai Hanson
  – Vani Nilakantan

• Study Clinical PIs
  – Frank Rhame, MD
  – Peter Eckman, MD
  – Michael Miedema, MD
  – Neda Skeik, MD
  – Paul Sorajja, MD
  – Richard Bae, MD
  – Thomas Knickelbine, MD
  – ...and you?!?!