Lessons Learned from Cardiovascular Trials: Getting to the Heart of the Matter in Uniting Patients, Clinicians and Systems for Evidence Generation
Evolving Themes

Integration with the Real World

Informed patients grow as partners
- Participant-Partnered Research

“System-ness” of care
- Networked partnerships for research

Built in Quality (by Design)
Real World?
“It started with no funding and skepticism in some quarters but today GISSI is recognized as an Italian achievement that has changed cardiology treatment worldwide.”
### Duke Databank

**1969**

1st and largest CV clinical registry

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### GUSTO

Global Utilization of Streptokinase and t-PA

**GUSTO**

For Occluded Coronary Arteries

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### Evolving Technology!

- **1989**
  - GUSTO
  - 40,000+ pts
  - 3-page faxed CRF
  - 100’s of papers!

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### 2016

**ADAPTABLE**

Patient Centric RCT

- 20,000 pts; EHR driven
- Mobile based pt follow-up
NATRECOR®

- FDA approved on Aug 10, 2001
  - Intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity
Real World Challenges - Equipoise?

Short-term Risk of Death After Treatment With Nesiritide for Decompensated Heart Failure
A Pooled Analysis of Randomized Controlled Trials

Risk of Worsening in Patients With Acute Heart Failure

Nesiritide — Not Verified

Expert Panel Gives Advice That Surprises A Drug Maker
Design of ASCEND-HF: Guiding Principles

- Investigator independence in context of joint Executive Committee/large Steering Committee
- Large, pragmatic trial model
  - Focused
  - Efficient study design
  - Streamlined procedures
  - Simple follow-up
- Enroll clinical heart failure
- Meaningful outcomes
- ‘Real world’ treatment (standard of care)
- Feasible sub-studies to advance knowledge in acute heart failure
ASCEND-HF North American Enrollment

- Projection
- Actual
## Benchmarking

<table>
<thead>
<tr>
<th></th>
<th><strong>XXX XXXX (&gt;10,000)</strong></th>
<th><strong>ASCEND-HF (n=7142)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Trial</strong></td>
<td>Chronic CV</td>
<td>Acute Heart Failure</td>
</tr>
<tr>
<td><strong>Traditionally Reported SAEs</strong></td>
<td>10,373</td>
<td>964</td>
</tr>
<tr>
<td><strong>Triggered Events</strong></td>
<td>10,895</td>
<td>1480</td>
</tr>
<tr>
<td><strong>Coded AEs</strong></td>
<td>65,296</td>
<td>386</td>
</tr>
<tr>
<td><strong>Concomitant Therapies</strong></td>
<td>332,677</td>
<td>&lt;50,000</td>
</tr>
<tr>
<td><strong>Visits</strong></td>
<td>478,001</td>
<td>14,200</td>
</tr>
<tr>
<td><strong>eCRF pages</strong></td>
<td>&gt;2.5 million</td>
<td>&lt;200,000</td>
</tr>
<tr>
<td><strong>Data Points</strong></td>
<td>&gt;30 million</td>
<td>&lt;3 million</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>++++++++++</td>
<td>++</td>
</tr>
</tbody>
</table>
Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction

Ole Fröbert, M.D., Ph.D., Bo Lagerqvist, M.D., Ph.D., Göran K. Olivecrona, M.D., Ph.D., Elnur Omerovic, M.D., Thorarinud Guðnason, M.D., Ph.D., Michael Maeng, M.D., Ph.D., Mikael Aasa, M.D., Ph.D., Oskar Angerå, Fredrik Calais, M.D., Mikael Daniewicz, M.D., David Erlinge, M.D., Ph.D., Lars Hellsten, M.D., Ulf Jensen, M.D., Ph.D., Agneta C. Johansson, M.D., Amra Kåregren, M.D., Johan Nilsson, M.D., Ph.D., Lotta Robertson, M.D., Lennart Sandhall, M.D., Ivar Sjögren, M.D., Ollie Östlund, Ph.D., Jan Harne, M.D., Ph.D., and Stefan K. James, M.D., Ph.D.

A Registry-Based Randomized Trial Comparing Radial and Femoral Approaches in Women Undergoing Percutaneous Coronary Intervention

The SAFE-PCI for Women (Study of Access Site for Enhancement of PCI for Women) Trial

Sunil V. Rao, MD,¹ Connie N. Hess, MD, MHS,¹ Britt Barham, BA,² Laura H. Aberle, BSPH,² Kevin J. Anstrom, PhD,² Tejan B. Patel, MD,³ Jesse P. Jorgensen, MD,³ Ernest I. Mazzaferrì Jr, MD,³ Sanjit B. Jolly, MD,³ Alice Jacobs, MD,³ L. Kristin Newby, MD,³ C. Michael Gibson, MD,³ David F. Kog, MD,³ Roxana Mehran, MD,³ Ron Waksman, MD,³ Ian C. Gilchrist, MD,³ Brian J. McCourt, MD,³ John C. Messenger, MD,³ Eric D. Peterson, MD, MPH,³ Robert A. Harrington, MD,³ Mitchell W. Krueger, MD,³

The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.
Swedish Registry-Trial Hybrids
TASTE Trial: Thrombus-Aspiration in MI

All primary PCI:s
Randomized

Cost (incremental) = US $300,000 ($50 per patient)

Frobert O et al NEJM 2013
HOW CAN WE ENGAGE PATIENTS (PARTICIPANTS)?
Engaging participants Across the continuum?

- Develop the study concept
  - Provide information on unmet need and therapeutic burden
  - Provide input on study design such as barriers to participation, study endpoints, and risk/benefit perception

- Secure Funding
  - Provide feedback on how the patient community will view results

- Prepare the Study Protocol
  - Recruit study participants
  - Serve as a peer advocate during the informed consent procedure

- Create the Study procedure
  - Provide feedback on how the patient community will view results

- Implement the Study
  - Serve on FDA advisory committees or post-market surveillance initiatives

- Monitor the study
  - Write newsletter articles or blog about results

- Analyze data and interpret results
  - Co-present results with researcher at a conference or support group

- Disseminate study information

- Post Approval Studies
  - Serve on FDA advisory committees or post-market surveillance initiatives

- • Work with researcher to secure NIH, PCORI, AHRQ funding
  - DART & Halo Therapeutics, e.g. raise seed funding
  - Fundraise for own research

- • Help finalize eligibility criteria within the study protocol
  - Assist in creating the informed consent form
  - Advise study recruitment

- • Serve on a Data Safety Monitoring Board
  - Provide recommendations for revising study protocol if changes need to be made

- Courtesy: Bray Patrick-Lake, MFS
Common problems with protocols from patient perspective

- Exclusion/inclusion criteria so stringent that no “real” patients meet criteria
- Study not feasible
  - Procedural burden too high
  - Unmanageable dosing regimen
  - Too many study appointments
  - Location not convenient
  - Pediatric patients needing to be seen during school hours

Courtesy: Bray Patrick-Lake, MFS
Participant Engagement is Finally Recognized as Crucial to Research and Regulatory Success

- NIH
- PCORI
- FDA
- Patient-focused drug development
- Patient-preference risk-benefit
- 21st Century Cures
- Precision Medicine Initiative
- Common rule reform

“...there is the whole trend of patient-driven outcomes like the PCORI initiative. Now every NIH-sponsored study wants to see advocates on the steering committee at the time of the conceptual design... And for any of us who want Federal funding, when NIH says ‘jump!’ we jump!”

CTTI PGCT Academic 2014
Interview Respondent
CAN WE UNITE SYSTEMS FOR THE GOOD OF THE WORLD?
Partners in a National Infrastructure

- Each network developing infrastructure, governance, data curation, analytics, security and software
- Potential partners: disease or treatment-specific networks
PCORnet: uniting people, clinicians, systems

20 Patient-Powered Research Networks (PPRNs) + 13 Clinical Data Research Networks (CDRNs) = PCORnet A national infrastructure for people-centered clinical research
PCORnet as a National Evidence System

Number of people for participation in clinical trials in PCORnet to date:

~ Millions

*Based on data from 57 DataMars as of July 15, 2016

<table>
<thead>
<tr>
<th>Race</th>
<th>Sex</th>
<th>Age</th>
<th>Pool of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>Male</td>
<td>0–14</td>
<td>42,545,341</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0–14</td>
<td></td>
</tr>
<tr>
<td>Non-White</td>
<td>Male</td>
<td>0–14</td>
<td>83,131,450</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0–14</td>
<td></td>
</tr>
</tbody>
</table>
Enabling Pragmatic Research: eScreening, eEnrollment and eFollowup

**DCRI FOLLOW-UP**
- Patient Reported Outcomes
- Medication use
- Health outcomes

**Portal FOLLOW-UP**
- Patient Reported Outcomes
- Medication use
- Health outcomes

**ADAPTABLE**
- Enrollee
- Baseline Data

**PCORNet Coordinating Center FOLLOW-UP**
- Via Common Data Model
- Longitudinal health outcomes

**CMS & Payer Virtual Data Warehouse FOLLOW-UP**
- Longitudinal health outcomes
There are 5 steps to join the study!

The time on each card is an estimate of how long it will take you to complete each section. There are no time limits, so please go at your own pace.

Watch the ADAPTABLE short video
Read more details about participating in ADAPTABLE
Answer a few questions about the study
Join the ADAPTABLE study
Inform us about your current health

Let's Get Started

Adaptable.patient.com
Mission: Strengthen the national capacity to implement cost-effective large-scale research studies that engage healthcare delivery organizations as research partners

- 10 Demonstration Projects spanning 12 NIH institutes and centers
Large, high impact, cost effective studies are possible.

Collaboratory: Health Care Systems Research

<table>
<thead>
<tr>
<th>Pragmatic Trial</th>
<th>Target N</th>
<th>Health Care Systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manage PTSD &amp; Other Conditions</td>
<td>1,000</td>
<td>24 Level I Trauma Centers</td>
</tr>
<tr>
<td>Manage Chronic Pain</td>
<td>1,000</td>
<td>200 Pract in 3 HCS</td>
</tr>
<tr>
<td>ESRD Care</td>
<td>6,400</td>
<td>400 HD Units</td>
</tr>
<tr>
<td>DM, HTN &amp; CKD Care</td>
<td>12,000</td>
<td>80 Clinics in 4 HCS</td>
</tr>
<tr>
<td>Suicide Prevention</td>
<td>16,000</td>
<td>Primary Care in 3 HCS</td>
</tr>
<tr>
<td>Colon Ca Screening</td>
<td>20,000</td>
<td>26 Clinics in OCHIN</td>
</tr>
<tr>
<td>Nursing Home Care</td>
<td>152,160</td>
<td>230 NH in 2 NH Corp.</td>
</tr>
<tr>
<td>Back Pain Imaging</td>
<td>250,000</td>
<td>100 Sites in 4 HCS</td>
</tr>
<tr>
<td>Hospital Infections</td>
<td>285,000</td>
<td>50 Hospitals in HCA</td>
</tr>
</tbody>
</table>

~ Cost/Patient

Average = $1,500

Range = $25 - $7,300
Final Thoughts
QUALITY FIRST: What is A Quality Clinical Trial?

1. Relevant question being addressed
2. A protocol that is clear, practical, focused
3. Adequate number of events to answer question with confidence
4. In a general practice setting to make results generalizable
5. With proper randomization
6. With reasonable assurance that patients receive (and stay on) assigned treatment
7. With reasonably complete follow-up and ascertainment of primary outcome (and other key outcomes like death)
8. With a plan for ongoing measurement, feedback, improvement of quality measures during trial conduct
9. With safeguards against bias in determining clinically relevant outcomes
10. With protection of rights of research patients
Conclusions

- Real world matters & is relevant
  - Right participant
  - Right intervention
  - Right outcome

- Build partnerships with patients, clinicians and systems

- Take advantage of growing interest in population health and “systemness” of care to do research

- Finally….Quality will always matter
  - By design
  - Less ≠ More
Thank You!