Enrolling Interventional Studies

› **RADIANCE HTN - PI: Yale Wang, MD**
  ‣ Patients with essential hypertension being treated ≤2 antihypertensive medications; treatment resistant hypertension being treated with 3 antihypertensive medications
  ‣ Study product: ReCor Medical Paradise System (Renal Denervation)
  ‣ 1° Endpoint: feasibility, safety, and efficacy of autologous MSCs and CSCs, alone or in combination
  ‣ Contact: Rose Peterson, RN, CCRC  phone 612.863.6051  pager 612.654.1650

› **COBRA REDUCE - PI: Daniel Lips, MD**
  ‣ Patients on coumadin or non-vitamin K oral anticoagulants with ischemic symptoms (stable or unstable) with up to 2 lesions in one or more vessels.
  ‣ Study product: COBRA PzF stents with 14 days of DAPT after stenting provide –vs- DES of choice
  ‣ 1° Endpoint: safety and feasibility of allo-MSCs
  ‣ Contact: Rose Peterson, RN, CCRC  phone 612.863.6051  pager 612.654.1650

› **EVOLVE Short DAPT – PI: Ivan Chavez, MD**
  ‣ Subjects at high risk for bleeding undergoing PCI where 3 mth DAPT
  ‣ Study product: Synergy Stent
  ‣ 1° Endpoint: The rate of recurrent events of HF readmissions during follow-up period.
  ‣ Contacts: Rose Peterson, RN, CCRC  phone 612.863.6051  pager 612.654.1650
2017 HOWARD B. BURCHELL MEMORIAL LECTURE
Rethinking Randomized Clinical Trials

Robert A. Harrington, MD
Arthur L. Bloomfield Professor of Medicine
Chairman, Department of Medicine
Stanford University

LEARNING OBJECTIVES
Upon completion, participant will be able to:

- Recognize the increasing need for evidence generation to support clinical practice and health policies.
- Identify the limitations of randomized clinical trials as a mechanism to provide reliable information on the therapeutic strategies.
- Identify the opportunities to “rethink” the construct of randomized trials using new tools as leveraging the EHR, digital data collection and engaging the research community through social media.

MINNEAPOLIS HEART INSTITUTE FOUNDATION CARDIOVASCULAR GRAND ROUNDS
Date: Monday, April 3, 2017
Time: 7:00 – 8:00 AM
Location: Abbott Northwestern Hospital Education Building, Auditorium A/B
Webinar: If you cannot attend grand rounds in person, attend via webcast (you can join the webinar up to 15 minutes before the presentation starts at 7:00am). New attendees: Register to attend live webinar

ABOUT DR. HOWARD B. BURCHELL
Howard B. Burchell, MD, was born in Athens, Ontario, Canada. He received his medical degree from the University of Toronto in 1932. He continued his training at Toronto General Hospital, the University of Pittsburgh, the Mayo Graduate School, and the London Hospital Medical School and Heart Hospital in England. After World War II, during which Dr. Burchell served in the U.S. Army Medical Corps, he returned to the Mayo Clinic as a consultant, ultimately becoming Professor of Medicine. In 1968, Dr. Burchell was appointed Chief in Cardiology at the University of Minnesota Medical School, a position he held until his official retirement in 1975. After retirement, Dr. Burchell was Professor Emeritus of Medicine and an active participant in the medical academic life of the Minneapolis/St. Paul community. He received several professional honors both during his career and after retirement. Today he is widely recognized as one of the foremost authorities in cardiology during the 1950s and 1960s. He is considered to have set the stage, with his colleagues, for the ablation of accessory AV connections, which ultimately led to the current era of interventional cardiac electrophysiology. The annual Burchell lecture is a tradition that was created over twelve years ago as a way to honor Dr. Burchell and his contributions to the world of medicine.
ACCREDITATION STATEMENT

Physician
Allina Health is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Allina Health designates this live activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Nurse
This activity has been designed to meet the Minnesota Board of Nursing continuing education requirements for 1.2 hours of credit. However, the nurse is responsible for determining whether this activity meets the requirements for acceptable continuing education.

DISCLOSURE STATEMENTS

Moderator(s)/Speaker(s)

Planning Committee
Dr. Alex Campbell, Dr. Kevin Harris, Rebecca Lindberg, Dr. Michael Miedema, Dr. JoEllyn Carol Moore, Dr. Scott Sharkey, and Jolene Bell Makowesky have declared that they do not have any conflicts of interest associated with the planning of this activity. Dr. David Hurrell declares the following relationship –Boston Scientific: Chair, Clinical Events Committee.

PLEASE SAVE A COPY OF THIS FLIER AS YOUR CERTIFICATE OF ATTENDANCE:

Signature: ______________________

My signature verifies that I have attended the above stated number of hours of the CME activity.

Allina Health - Learning & Development - 2925 Chicago Ave - MR 10701 - Minneapolis MN 55407

We gratefully acknowledge the following organizations for their financial contributions for this activity:

Bristol-Myers Squibb  Novartis

Together, we can create a world without heart and vascular disease.

Facebook.com/MinneapolisHeart
Twitter.com/MHIF_Heart
Howard B. Burchell MD Memorial Lecture

Rethinking Randomized Clinical Trials

Robert A. Harrington MD, MACC, FAHA, FESC
Arthur L. Bloomfield Professor of Medicine
Chair, Department of Medicine
Stanford University
Twitter: @HeartBobH

Disclosure Statement of Financial Interest

Within the past 12 months, I have had a financial interest/arrangement or affiliation with the organization(s) listed below.

• Research grants/contracts:
  – NHLBI, PCORI, Duke, Harvard, Astra, BMS, CSL, GSK, Janssen, Merck, Novartis, Portola, sanofi-aventis, TMC

• Consulting/Advisory:
  – Advera, Amgen, Element Science, Gilead, MyoKardia, TMC, Vida Health, WebMD

• Board of Directors
  – AHA, Stanford Health Care, Scanadu (mobile health), SignalPath (software)
Greetings from Vista Verde Vineyards  
Santa Cruz Mountains Appellation

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Thank you for the invitation
“Chronic, multifactorial disease problems can be studied, but not by the methods of the present or past. If one wishes to create useful information… computer technology must be exploited.”

—Eugene Stead, MD
(1908-2005)
2017 HOWARD B. BURCHELL MEMORIAL LECTURE
Rethinking Randomized Control Trials

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Rethinking Randomized Clinical Trials

- Demands for evidence
- Limitations/challenges traditional RCTs
- New sources of data (amounts, types)
- New methods (collection, analyses)
- New partners (patients, tech)
- The evolution in RCTs: bigger, faster, cheaper, better!
  - Examples: registry RCTs, EHR, PCORnet
- Critical issues to address
  - Ethical constructs of trials; open data and data sharing
Healthcare and Evidence:
Big Societal Issues and Themes

- Demands for evidence to practice medicine
  - Professional society practice guidelines
  - Increasing emphasis on quality in care delivery
  - Including ties to MD compensation incentives
  - Studies support notion that guidelines-based care is associated with improvements in quality/outcomes

- Demands for evidence to guide policy
  - Regulatory approvals
  - Reimbursement policy (MACRA, MIPS, APM, etc)
  - Comparative effectiveness research (CER)

Strength of Study Designs for Treatment Comparisons/Inferences

<table>
<thead>
<tr>
<th>Method</th>
<th>Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical experience</td>
<td>poor</td>
</tr>
<tr>
<td>Targeting disease process with surrogate endpoints</td>
<td>poor</td>
</tr>
<tr>
<td>Case-control study</td>
<td>fair</td>
</tr>
<tr>
<td>Observational database analysis</td>
<td>good</td>
</tr>
<tr>
<td>Large randomized clinical trial</td>
<td>best</td>
</tr>
</tbody>
</table>
Large-Scale Randomized Evidence

“There is simply no serious scientific alternative to the generation of large-scale randomized evidence. If trials can be vastly simplified, as has already been achieved in a few major diseases, and thereby made vastly larger, then they have a central role to play in the development of rational criteria for the planning of health care throughout the world.”

“Realistically moderate expectations of what treatment might achieve (or, if one treatment is to be compared with another, realistically moderate expectations of how large any difference between those treatments is likely to be) should, in contrast, tend to foster the design of studies that aim to discriminate reliably between differences in outcome that are moderate but worthwhile, and differences in outcome that are too small to bother with.”

The rationale and the question

- Lowering LDL using statins among patients with known coronary artery disease improves clinical outcomes

- Lowering LDL to ~70 (with high intensity statin) is associated with better clinical outcomes than achieving an LDL of ~100 (with moderate intensity statin)

- Ezetimibe added to a statin provides additional LDL lowering; does this strategy confer incremental clinical benefit to patients with a recent ACS event?

10+ years of work

- 9 Data Safety Monitoring Board Reviews
- 33 Investigator Meetings
- 14,709 CEC events sent for adjudication
- 15,000+ SAEs processed
- 30,000+ Monitoring visits
- 300,000 Patient visits completed
- 2.7 Million CRF data forms completed
**ISCHEMIA Overview**

*International Study of Comparative Health Effectiveness with Medical and Invasive Approaches*

Chair - Judith Hochman, Co-Chair/PI - David Maron  
Co-PIs William Boden, Bruce Ferguson, Robert Harrington, Gregg Stone, David Williams

- **Patients**: stable, at least moderate ischemia (core lab)
- **Primary Aim**: to determine whether an initial invasive strategy of cath and revascularization (PCI or CABG) + OMT is superior to a conservative strategy of OMT alone, with cath reserved for OMT failure
- **Composite Primary Endpoint**: CV death or MI
- **Major Secondary Endpoint**: angina-related QOL
- **Sample Size**: 8,000
- **Follow-up**: average ~4 years

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**EDITORIAL COMMENT**

**American Industry and the U.S. Cardiovascular Clinical Research Enterprise**

*An Appropriate Analogy?*

Robert M. Califf, MD,†‡  
Robert A. Harrington, MD‡$  
*Durham, North Carolina*

“This report is one of a number of recent reports that raise the question of whether American clinical research, like so many other US industries, has become so expensive and inefficient that it is no longer a viable competitive enterprise within our borders.”
“Datafication”

- Render virtually anything into data
- “Like other infrastructural advances it will bring fundamental changes … different mindset”
- OK to re-use data
- $N = \text{All}$

Mayer-Schonberger V, Cukier K, Houghton Miflin, 2013
More than 40,000 people downloaded a smartphone app and joined an ongoing global research study to measure how activity affects heart health.

"Just to be clear, 2 months ago this didn’t exist; there was nobody in this study," said Euan Ashley, MD, from Stanford University in California, who is one of the creators of the app. "Over the course of 2 weeks in March, 30,000 people signed up," he reported.

The response demonstrates that big data can be harnessed at minimal cost, which could help revolutionize the way research is done, Dr. Ashley explained.

"We’re really in a new era, and one we don’t really understand," he said at the Big Data in Biomedicine Conference in Stanford.

Stanford researchers, in collaboration with the American Heart Association, designed the free smartphone app called MyHeart Counts. Anyone 18 or older with an iPhone 5s, 5c, or 6 Plus can download the app, give consent to be included in the study, answer survey questions about risk factors, and then let sensors record their movements for 7 days. The app will ask users to
Feasibility of Obtaining Measures of Lifestyle From a Smartphone App
The MyHeart Counts Cardiovascular Health Study

Michael V. McConnell, MD, MSEE; Anna Shcherbina, MEng; Aleksandra Pavlovic, BS; Julian R. Humberger, BS; Rachel L. Goldfeder, MS; Daryl Waggot, MSc; Mildred K. Cho, PhD; Mary E. Rosenberger, PhD; William L. Haskell, PhD; Jonathan Myers, PhD; Mary Ann Champagne, RN, MS; Emmanuel Mignet, MD, PhD; Martin Landray, MB, ChB, PhD; Lionel Tarassenko, MA, DPhil; Robert A. Harrington, MD; Alan C. Yeung, MD; Evan A. Ashley, MB, ChB, DPhil

Published online December 14, 2016.
MyHeart Counts v 2.0 (launched Jan 2017)

- Randomized study of coaching strategies
  - Transition prompts
  - Step count prompt
  - Personalized educational materials
  - Generic educational materials
- More personalized/aggregated data return
- Old and new media campaign to offset population skew towards young/male
  - ACC, WHS
  - Ad word campaign
- 23andme integration
- Coming
  - EHR integration
  - Further international launches
  - Android version

Precision Medicine

http://www.research.va.gov/mvp/
http://www.nih.gov/precisionmedicine/
BASELINE Study

Observational, longitudinal, prospective cohort design – 4 years of follow-up
Extensively characterize participants at baseline and serially
Characterize cancer and cardiovascular disease in participants
Annual in-person visits, online quarterly assessments, track events

STUDY OVERVIEW
ASSESSMENTS

“Omics”
- Genomics
- Epigenomics
- Transcriptomics
- Metabolomics

Cognitive and Physical Performance Tests

Family history Surveys

Continuous Monitoring – Wearable device, Sleep sensor

Imaging
- Chest X-ray
- Echocardiography

H&P, Eye exam

Audiometry

PFT

Blood, urine, stool
Saliva

Microbiome

ORIGINAL ARTICLE

Spontaneous Coronary Artery Dissection: A Disease-Specific, Social Networking Community-Initiated Study

Marya A. Tweed, MD; Rajiv Ollati, MD, PhD; Lee A. Aase, BS; and Sharonne N. Hayes, MD

OBJECTIVE: To develop and assess the feasibility of a novel method for identification, recruitment, and prospective and retrospective evaluation of patients with rare conditions.

PATIENTS AND METHODS: This pilot study is a novel example of “patient-initiated research.” After being approached by several members of an international disease-specific support group on a social networking site, we used it to identify patients who had been diagnosed as having at least 1 episode of spontaneous coronary artery dissection and recruited them to participate in a clinical investigation of their condition. Medical records were collected and reviewed, the original diagnosis was independently confirmed to review of imaging studies, and health status (both current and current) was assessed via specially designed questionnaires and validated assessment tools.

RESULTS: Recruitment of all 31 participants was complete within 1 week of institutional review board approval (March 16, 2010). Data collection was completed November 19, 2010. All participants completed the study questionnaires and provided the required medical records and coronary angiography and ancillary imaging data.

CONCLUSIONS: This study involving patients with spontaneous coronary artery dissection demonstrates the feasibility of and is a successful model for developing a “virtual” multicenter disease registry through disease-specific social media networks to better characterize an uncommon condition. This study is a prime example of patient-initiated research that could be used by other health care professionals and institutions.


For editorial comment, see page 836

patients undergoing angiography in more registries and series. 

Among reported case series ranging from 3 to 47 cases, there is an approximate 2:1 female predominance. About one third of the cases in women occur in the peripartum period. SCAD may present as sudden death, angina, or myocardial infarction and may be responsible for as many as 1 of 10 episodes of acute coronary syndrome in women younger than 50 years. Despite hundreds of published case reports and small case series, to our knowledge only 1 SCAD patient registry has been developed, and no data from multicenter clinical trials are available to guide treatment. Because of the paucity of clinical data and inconsistent follow-up and reporting, the prevalence, recurrence rate, and long-term prognosis after SCAD remain uncertain, and the underlying etiology and optimal short- and long-term management are ambiguous. As with other poorly understood conditions, many survivors are highly active in seeking information from any available source and seek to learn from experiences of others similarly affected.

PATIENTS AND METHODS
Twitter as a Potential Data Source for Cardiovascular Disease Research

Lauren Sienkiewicz, BA; Christine L. Sillers, BA; tháng 3, Christine Macchino, BA; et al.

JAMA Cardiol. Published online September 28, 2016. doi:10.1001/jamacardio.2016.3209

Twitter and Cardiovascular Disease: Useful Chirps or Noisy Chatter?

Mintu R. Tanka, MD, MAS; Robert A. Harrington, MD

JAMA Cardiol. Published online September 28, 2016. doi:10.1001/jamacardio.2016.3150

Health disparities and clinical trial recruitment: Is there a duty to tweet?

Arthur Caplan*, Phoebe Friesen

Division of Medical Ethics, New York University School of Medicine, New York, New York, United States of America

*Arthur.Caplan@nyumc.org

Abstract

While it is well known that the homogeneity of clinical trial participants often threatens the goal of attaining generalizable knowledge, researchers often cite issues with recruitment, including a lack of interest from participants, shortages of resources, or difficulty accessing particular populations, to explain the lack of diversity within sampling. It is proposed that social media might provide an opportunity to overcome these obstacles through affordable, targeted recruitment advertisements or messages. Recruiters are warned, however, to be cautious using these means, since risks related to privacy and transparency can take on a
Registry Data Linked to Medicare Data for Clinical and Comparative Effectiveness

<table>
<thead>
<tr>
<th><strong>Clinical Registry Data</strong></th>
<th><strong>Medicare Claims Data</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Wealth of data on clinical characteristics, symptoms, comorbid conditions, vital signs, laboratories, treatments, short term outcomes</td>
<td>Minimal clinical data</td>
</tr>
<tr>
<td>Limited or absent longitudinal outcome data</td>
<td>Detailed data on hospitalizations, procedures outpatient visits, health care utilization, costs, and deaths (and some data on medications from Part D)</td>
</tr>
<tr>
<td>Often no unique identifiers</td>
<td>Identified</td>
</tr>
</tbody>
</table>

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**Background**
Inpatient clinical registries generally have limited ability to provide a longitudinal perspective on care beyond the acute episode. We present a method to link hospitalization records from registries with Medicare Inpatient claims data, without using direct identifiers, to create a unique data source that pairs rich clinical data with long-term outcome data.

---

**Linking inpatient clinical registry data to Medicare claims data using indirect identifiers**
Bradley G. Hammill, MS, Adrian F. Hernandez, MD, MHS, Eric D. Peterson, MD, MPhil, Gregg C. Fonarow, MD, Kevin A. Schilman, MD, and Lesley H. Curtis, PhD
Duke, NC; Los Angeles, CA

---

**Wearable Fitness Trackers and Heart Disease**

**What Are Fitness Trackers?**
Fitness or activity trackers are devices with special sensors that can monitor your movement. Often referred to as "wearables," these devices are typically worn around the wrist as a bracelet or embedded in a mobile phone or watch. They can measure footsteps taken, distance traveled, type of movement (walk, run, or jog), and quality and duration of sleep. Some wearables have additional sensors to monitor heart rate, blood pressure, blood oxygen levels, and perspiration. Data from wearables can be transferred to a smartphone, computer, database, or website. Connected smartphones or wearables can alarm or vibrate to encourage behaviors, such as exercise or sleep. As wearable technology matures, these devices will likely cost less, and it may become easier to share data from them with your health care professional, clinic, or hospital.

**Can Fitness Trackers Prevent or Treat Heart Disease?**
Professional cardiology society guidelines recommend that most patients participate in regular exercise. However, these societies have not yet given recommendations on how fitness trackers should be used because no long-term studies have been completed that have tested whether the use of fitness trackers can help prevent heart disease. Also, the accuracy of most wearables has not been verified in clinical studies. In fact, some devices may provide inaccurate measurements, particularly when using intensive exercise.

**What Are the Benefits of Using a Fitness Tracker?**
Despite these limitations, fitness trackers still may have benefits for you. Physical inactivity is an important risk factor for heart disease. A wearable device can help you set realistic goals at any level of activity or fitness.

---

*Kaiser DW, Harrington RA, Turakhia MP. JAMA Cardiol online April 13, 2016*
Predicting the Future — Big Data, Machine Learning, and Clinical Medicine
Ziad Obermeyer, M.D., and Ezekiel Emanuel, M.D., Ph.D.

By now, it’s almost old news: big data will transform medicine. It’s essential to remember, however, that data by themselves are useless. To be useful, data must be analyzed, interpreted, and acted on. That’s what algorithms — not data sets — that will prove transformative. We believe, therefore, that attention has to shift to new statistical tools from the field of machine learning that will be critical for anyone practicing medicine in the 21st century.

First, it’s important to understand what machine learning is not. Most computer-based algorithms in medicine are “expert systems” — rule sets encoding knowledge on a given topic, which are applied to draw conclusions.

Machine learning has become ubiquitous and indispensable for solving complex problems in most sciences. The same methods will open up vast new possibilities in medicine.

Translating Artificial Intelligence Into Clinical Care
Andrew L. Beams, Ph.D; Isaac S. Kohane, M.D., Ph.D.

INNOVATIONS IN HEALTH CARE DELIVERY
Adapting to Artificial Intelligence Radiologists and Pathologists as Information Specialists

Development and Validation of a Deep Learning Algorithm for Detection of Diabetic Retinopathy in Retinal Fundus Photographs

Artificial Intelligence With Deep Learning Technology Looks Into Diabetic Retinopathy Screening
FIND FH™
A multiyear screening and engagement initiative to identify and encourage the diagnosis and treatment of FH

Lab & Claims Data Mining
- Healthcare Encounter Data on 89 Million Americans with Cardiovascular Disease
- Data from a significant majority of clinical practices

EHR Data Mining
- Comprehensive EHR data from two academic centers
- Expanding to key integrated health systems

HCP & Individual Engagement
- Multichannel tools to engage health systems and individual HCPs
- Tools for clinicians and individuals with FH
Deming, data and observational studies
A process out of control and needing fixing

“Any claim coming from an observational study (about treatment comparisons) is most likely to be wrong.”

Randomization—There Is No Substitute

Randomized clinical trials are the gold standard for evaluating the efficacy of therapies or comparing one therapy with another. When applied to adequately powered trials, randomization eliminates selection and other forms of bias, generates groups-under-study that are always in all important aspects (except for the intervention received) and provides confounding by measured and unmeasured confounding variables. By design, randomized clinical trials have high internal validity, with the ability to determine cause-effect relationships. Anomalies in controlled clinical trials are considered the highest level of evidence for guiding practice and the fundamental basis of most regulatory agency approvals for drug therapies. However, by virtue of their inclusion and exclusion criteria and participation by volunteers providing unconfounded evidence, randomized clinical trials generally include patients who are adherent to therapy, monitoring, and follow-up and may not be entirely representative of the general patient population. It is also well recognized that high-risk patients, older patients, women, and patients in mental/other minority groups are underrepresented in randomized clinical trials. These differences may influence whether the efficacy and safety demonstrated in randomized clinical trials will completely translate into clinical effectiveness and safety when the same therapy is applied in clinical practice (generalizability and external validity).

There has been substantial and growing interest in using observational data for comparing the outcomes and safety of different therapies in actual clinical practice and in broader cohorts of patients. Because treatment is not assigned at random, these comparisons are subject to various biases and confounding. Unobserved treatment selection bias may lead to incorrectly identifying important treatment differences among patients. Unmeasured variables may affect treatment selection decisions, as well as outcomes. There have been a variety of different statistical approaches developed to account for differences in patient baseline characteristics that are of prognostic importance and to address treatment selection bias in observational studies. These approaches include multivariable risk models, propensity score risk adjustment (e.g., inverse probability of treatment weighting), propensity matching, and instrumental variable analysis. Propensity score adjustment and propensity matching may help control for overt bias in treatment selection. While initially suggested that these propensity methods could replicate clinical trial randomization, it has increasingly been recognized that this form of analysis is still subject to hidden bias and may be more likely to remove bias due to unmeasured confounding when treatment selection bias exists. Instrumental variable analysis has been more recently proposed as an alternative design to control for not only overt bias but also for hidden bias.

An ideal instrumental variable needs to be highly correlated with treatment and does not independently affect the outcome of interest (except through a treatment effect), such that it is not otherwise associated with measured or unmeasured patient health status. Analyses of studies using instrumental variable analysis have claimed to have generated findings that have been consistent with the results in randomized clinical trials and thus had greater external validity compared with other observational statistical methodological approaches.
Ten characteristics of a high 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
9. With safeguards against bias in determining clinically relevant outcomes
10. With protection of rights of research patients

Current State of Clinical Trials

Transforming Clinical Trials in Cardiovascular Disease
Mission Critical for Health and Economic Well-being

Elliott M. Antman, MD
Robert A. Harrington, MD

"As large trials became popular...the original simplicity was lost...leading to increasingly complex trials. The unintended consequence has been to threaten the very existence of RCTs, given the operational complexities and ensuring costs. An ideal opportunity would be to embed randomization in the EMR...introducing randomization into registries sponsored by societies."

The Future of Clinical Research and the ACC
Empowerment Through Registries, Data, and Our Members

Patrick O’Gara, MD, FACC, ACC President,
Robert A. Harrington, MD, FACC, ACC Board of Trustees

An RCT within NCDR

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,† Connie N. Hess, MD, MHS,§ Britt Barham, BA,☆ Laura H. Abele, BSc,☆ Kevin J. Anstrom, PhD,☆
Tejan B. Patel, MD,¶ Jesse P. Jorgensen, MD,‖ Ernest L. Mazzafferi Jr., MD,‖ Sanjit S. Jolly, MD,‖ Alice Jacobs, MD,∥
L. Kristin Newby, MD,¶ C. Michael Gibson, MD,¶ David F. Kost, MD,¶ Rezana Mehran, MD,∥ Ren Waksman, MD,∥
Ian C. Gilchrist, MD,¶ Brian J. McCourt,* John C. Messenger, MD,¶ Eric D. Peterson, MD, MPhE,¶
Robert A. Harrington, MD,∥ Mitchell W. Krueger, MD
• 30-50 VA centers
• 13,500 patients
• Point-of-Care Randomization
• Leveraging VA EMR
  – Patient identification
  – Patient randomization
  – All patient follow-up
• $700/patient vs $15,000 in SPRINT ($4.5M VA POC Initiative)

Imagine........

• Having 300,000 patients prequalified at ~30 sites
• Approaching 700 patients in a week at one site
• Having a 5 page consent form
• 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 followup data from the EHR

Randomizing 20,000 patients at 30 sites over 24 months
Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE) Trial

PCORnet's First Pragmatic Clinical Trial
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

ClinicalTrials.gov: NCT02697916

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
E-nabling Pragmatic Research: e-data collection and e-follow-up

N=20,000

ADAPTABLE enrollee

Baseline data

Web portal follow-up
- Randomized to 3 vs 6 mos contact
- Patient-reported hospitalizations
- Medication use
- Health outcomes

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

DCRI call center
- Patients who miss 2 contacts
- Patients without internet access

Death ascertainment
- National Death Index (NDI) & Social Security Database
## Traditional Trials vs. ADAPTABLE

<table>
<thead>
<tr>
<th>Feature</th>
<th>Traditional</th>
<th>ADAPTABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion/Exclusion criteria review</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>
</tbody>
</table>

ClinicalTrials.gov: NCT02697916
Engaging the Public in A Truly Large Simple (Really Important) Randomized Clinical Trial

The Salk Polio Vaccine Trial of 1954: risks, randomization and public involvement in research

Liza Dawson

Ethics and Learning Health Care

Requiring that all activities that are designed to produce generalizable knowledge and that collect data systematically must undergo prior review by an ethics committee, even when patients’ clinical care is in no respect changed, is a misplaced moral criterion of what needs review and is a deep weakness in our current system.

-Hastings Ctr Report Jan-Feb 2013
RCT Transparency

Demands for evidence

Limitations/challenges traditional RCTs

New sources of data (amounts, types)

New methods (collection, analyses)

New partners (patients, tech)

The evolution in RCTs: bigger, faster, cheaper, better!

Examples: registry RCTs, EHR, PCORnet

Critical issues to address

Ethical constructs of trials; open data and data sharing
Thanks for the Opportunity to Visit