Trials on Trial: What Can Be Done to Sustain and Preserve RCTs in the Future:

KISS Principle for Trials- Keep it Large and Simple

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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, CSL, GSK, Merck, Portola, Regado, sanofi-aventis, TMC
- **Consulting/Advisory:**
  - Adverse Events, Amgen, Element Science, Gilead, Merck, MyoKardia, TMC, Vida Health, WebMD
- **Board of Directors**
  - AHA, Scanadu, SignalPath

Outline

- RCT basics
- Current state of RCTs: large and complicated
- Pragmatic trials (examples)
- Digital data collection

Types of Clinical Trial

- **Explanatory or mechanistic trials**
  - aimed at impact of a treatment on biological measures
- **Pragmatic or evaluative trials**
  - aimed at impact of a treatment on what matters to patients and their care providers (living longer, feeling better, avoiding unpleasant experiences, spending less money)

Looking Back at a Disruptive Technology

EFFECTIVENESS OF INTRAVENOUS THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION

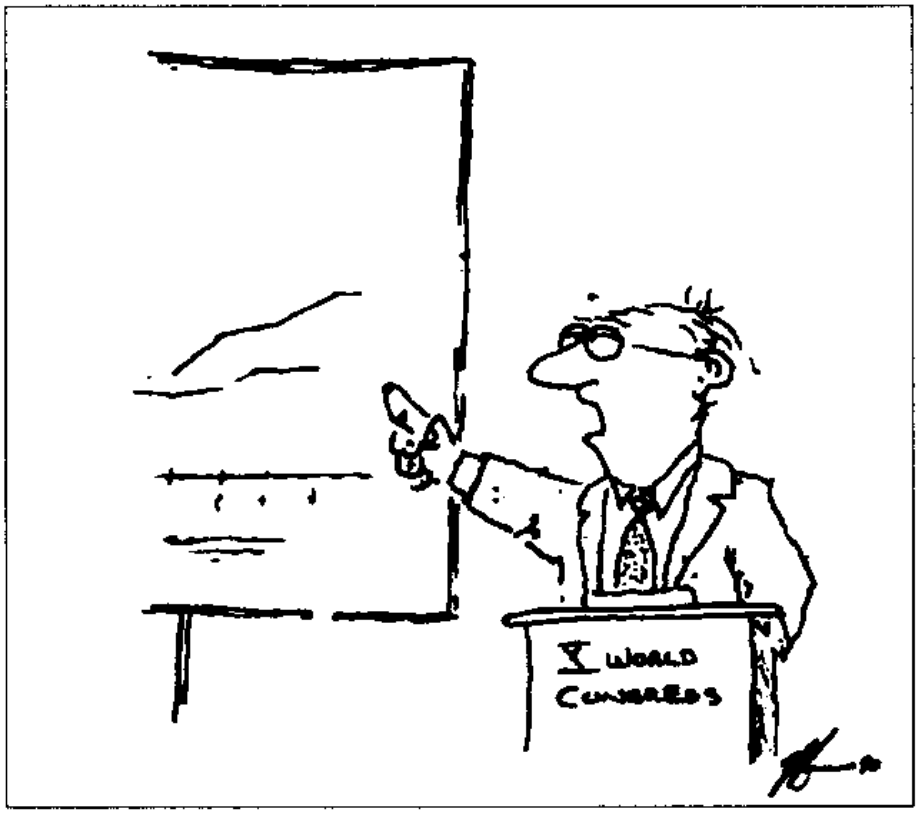
GRUPPO ITALIANO PER LO STUDIO DELLA STREPTOCHINASI NELL'INFARTO MIOCARDICO (GISSI)*

Summary In an unblinded trial of intravenous streptokinase (SK) in early acute myocardial infarction, 11 806 patients in one hundred and seventy-six coronary care units were enrolled over 17 months. Patients admitted within 12 h after the onset of symptoms and with no contraindications to SK were randomised to receive SK in addition to usual treatment and complete data were obtained in 11 712. At 21 days overall hospital mortality was 10·7% in SK recipients versus 13% in controls, an 18% reduction (p=0·0002, relative risk 0·81). The extent of the beneficial effect appears to be a function of time from onset of pain to SK infusion (relative risks 0·74, 0·80, 0·87, and 1·19 for the 0–3, 3–6, 6–9, and 9–12 h subgroups). SK seems to be a safe drug for routine administration in acute myocardial infarction.

The Lancet · Saturday 22 February 1986

"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."

http://eurheartj.oxfordjournals.org/content/31/9/1023.full



"This randomized, double-blind trial involving over 20,000 patients was conducted over a 10 year period. Unfortunately we've forgotten why."

It Took A LOT 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

Selecting Revascularization Strategies in Patients with Coronary Disease

Robert A. Harrington, M.D.

The treatment of patients with coronary artery disease includes risk-factor modification (e.g., treatment of hypertension, hyperlipidemia, and diabetes) and some combination of medical therapies and coronary revascularization.[1] For patients for whom revascularization is deemed to be appropriate, a decision must be made between percutaneous coronary intervention (PCI) and coronary-artery bypass grafting (CABG). In direct comparisons, CABG has been shown to be associated with fewer repeat revascularizations than PCI. However, questions have been raised about incremental improvements in stent technologies that might narrow the outcome gap be-

N ENGL J MED 372;13 NEJM.ORG MARCH 26, 2015

The New England Journal of Medicine

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

National Heart Lung and Blood Institute

ISCHEMIA

Journal of the American College of Cardiology
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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."

What is A Quality Clinical Trial?

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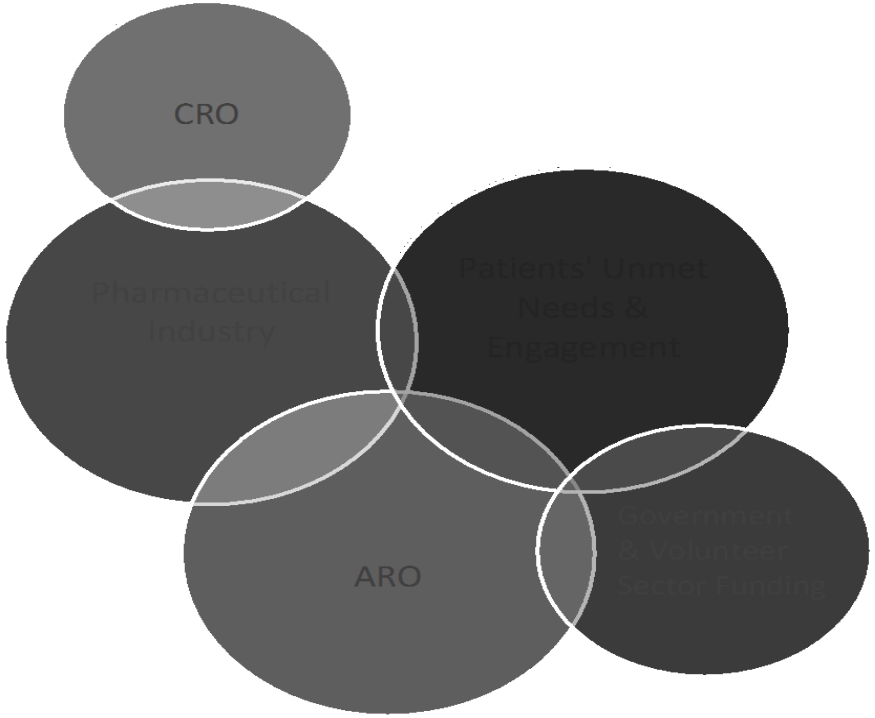
1. Relevant question being addressed
2. A protocol that is clear, practical, focused
3. Adequate number of events to answer question with confidence
4. In a general practice setting to make results generalizable
5. With proper randomization
6. With reasonable assurance that patients receive (and stay 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

-Slide courtesy LG Berdan

Paradigm for Collaboration

- **Independent Executive/Steering Committee**
- **Independent access to data**
- **Publication rights and oversight of analyses**
- **“Reasonable” duration of confidentiality**
- **Intellectual property protection**



-Roe MT et al. Am Heart J; 169;2015

Engaging the Public in A Truly Large Simple Randomized Clinical Trial

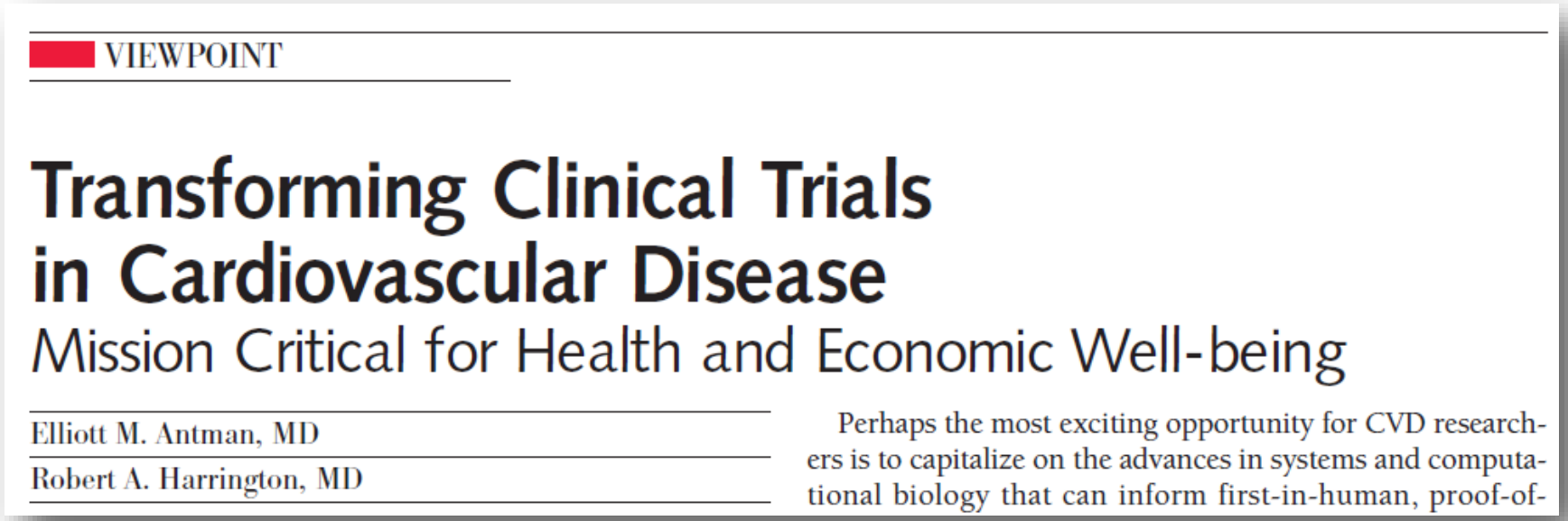
CLINICAL TRIALS *HISTORY* *Clinical Trials* 2004; **1**: 122–130

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

Liza Dawson

The year 2004 marks the fiftieth anniversary of the celebrated 1954 Salk polio vaccine trial. This enormous clinical trial, involving 1.8 million children, was carried out with the co-operation and assistance of hundreds of thousands of lay volunteers, along with medical professionals and local health departments throughout the USA. While the trial was an impressive public health achievement, firmly establishing the efficacy of the killed virus vaccine and paving the way for eradication of the disease, it was not without controversy. This article recounts the story of this important early clinical trial and how the social and political conditions at the time affected its planning and execution. *Clinical Trials* 2004; **1**: 122–130. www.SCTjournal.com

Current State of Clinical Trials



VIEWPOINT

Transforming Clinical Trials in Cardiovascular Disease

Mission Critical for Health and Economic Well-being

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

Perhaps the most exciting opportunity for CVD research-ers is to capitalize on the advances in systems and computa-tional biology that can inform first-in-human, proof-of-

"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."

-Antman E, Harrington RA. JAMA 2012;338:1743-4.

NIH National Heart, Lung, and Blood Institute

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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., Elmir Omerovic, M.D., Ph.D., Thorarinn Gudnason, M.D., Ph.D., Michael Maeng, M.D., Ph.D., Mikael Aasa, M.D., Ph.D., Oskar Angerås, M.D., Fredrik Calais, M.D., Mikael Danielewicz, 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., Iwar Sjögren, M.D., Ollie Östlund, Ph.D., Jan Harnek, M.D., Ph.D., and Stefan K. James, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Unmet Aspirations — Where To Now for Catheter Thrombectomy?

Robert A. Byrne, M.B., B.Ch., Ph.D., and Adnan Kastrati, M.D.

Perspective

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

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

The randomized trial is one of the most powerful tools clinical researchers possess, a tool that enables them to evaluate the effectiveness of new (or established) therapies while accounting for

United States and abroad have collected vast amounts of data from patients with acute coronary syndromes, stable coronary disease, and heart failure, as well as

An RCT within NCDR

Stanford MEDICINE

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http://dx.doi.org/10.1016/j.jcin.2014.04.007

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. Aberle, BSPH,* Kevin J. Anstrom, PhD,* Tejan B. Patel, MD,† Jesse P. Jorgensen, MD,‡ Ernest L. Mazzaferri Jr., MD,§ Sanjit S. Jolly, MD,‖ Alice Jacobs, MD,¶ L. Kristin Newby, MD,* C. Michael Gibson, MD,# David F. Kong, MD,* Roxana Mehran, MD,** Ron Waksman, MD,†† Ian C. Gilchrist, MD,‡‡ Brian J. McCourt,* John C. Messenger, MD,§§ Eric D. Peterson, MD, MPH,* Robert A. Harrington, MD,‖‖ Mitchell W. Krucoff, MD*

Aspirin Dosing: A Patient-Centric Trial Assessing Benefits and Long-term Effectiveness (ADAPTABLE) Trial

PCORnet's First Pragmatic Clinical Trial

pcornet

The National Patient-Centered Clinical Research Network

PCORnet's goal

PCORnet seeks to improve the nation's capacity to conduct **clinical research** by creating a large, highly representative, national patient-centered network that supports more efficient clinical trials and observational studies.

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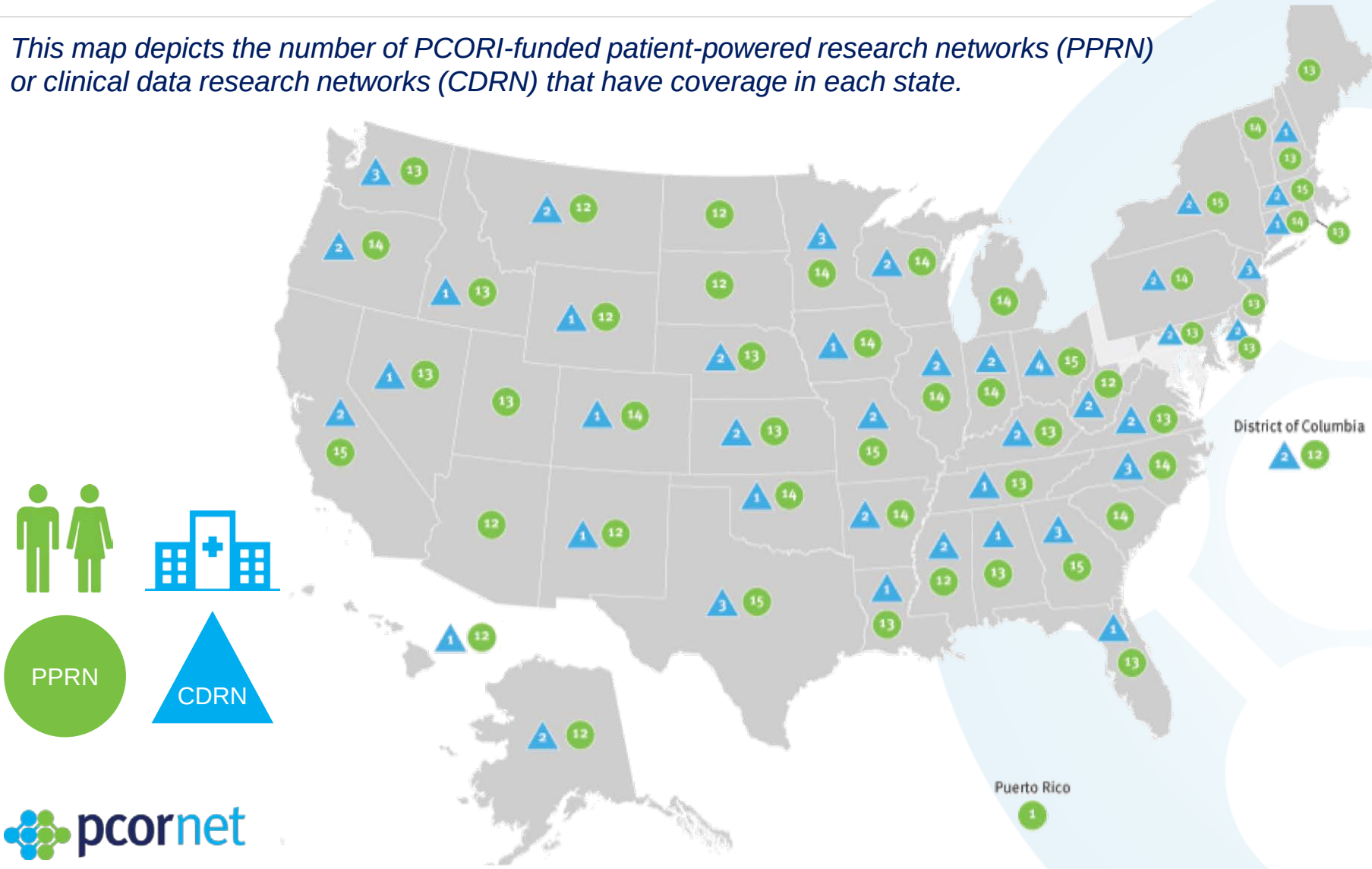
CDRNs and PPRNs Participating in PCORnet

This map depicts the number of PCORI-funded patient-powered research networks (PPRN) or clinical data research networks (CDRN) that have coverage in each state.



Goals for each clinical data research network (CDRN)

- Create a research-ready dataset of at least 1 million patients that is secure and comprehensive
- Involve patients, clinicians, and health system leaders in all aspects of creating and running the network
- Develop the ability to embed clinical trials into healthcare operations
- Identify 3 cohorts of patients who have a condition in common and who can be characterized and surveyed

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Goals for each patient-powered research network (PPRN)

- Establish patient population with a condition of interest (>50 patients for rare diseases; >50,000 for common conditions)
- Collect patient-reported data for ≥80% of patients
- Involve patients in network governance
- Create standardized research databases

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Learning health care system and pragmatic trials

- Leverage available medical data from electronic health record (EHR) data to identify eligible patients
- Ascertain endpoints as part of routine healthcare delivery and administrative claims
- Simplify baseline and follow-up data collection through systematic direct patient contact (patient-reported outcomes) and multiple data sources
- Large sample sizes embedded within healthcare systems and randomization provide large scale, limit selection biases, and provide more generalizable results (by comorbidities, concomitant medication use, and subgroups)

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Guidelines for the Management of Patients with Stable Ischemic Heart Disease: Antiplatelet Therapy

Treatment with aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications in patients with SIHD.

Treatment with clopidogrel is reasonable when aspirin is contraindicated in patients with SIHD.

Guidelines for the Management of Patients with NSTE ACS:
Late Hospital and Post-hospital Oral Antiplatelet Therapy

Recommendations	COR	LOE
Aspirin should be continued indefinitely. The maintenance dose should be 81 mg daily in patients treated with ticagrelor and 81 mg to 325 mg daily in all other patients.	I	A
In addition to aspirin, a $P2Y_{12}$ inhibitor (either clopidogrel or ticagrelor) should be continued for up to 12 months in all patients with NSTE-ACS without contraindications who are treated with an ischemia-guided strategy. Options include: a. Clopidogrel: 75 mg daily or	I	B
b. Ticagrelor‖: 90 mg twice daily		B

‖The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

NCDR ACTION Registry-GWTG

- 221,199 patients with MI from 525 US hospitals
- Aspirin dosing on discharge:
  - 325 mg: 61%
  - 81 mg: 36%
  - Other: 4%
- By Treatment
  - Percutaneous coronary intervention: 73% 325 mg
  - Medical Management: 45% 325 mg
  - Concomitantly with ADP and warfarin: 44% 325-mg
- Experienced major in-hospital bleeding: 57% 325-mg dose.

pcornet

Hall et al. Circulation Cardiovascular Quality and Outcomes 2014

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

Exclusion criteria

- Age <18 years
- ASA allergy or contraindication (including pregnancy or nursing)
- Significant GI bleed within past 12 months
- Significant bleeding disorder
- Requires warfarin, direct oral anticoagulant, or ticagrelor

ASA 81 mg QD | ASA 325 mg QD

Electronic follow-up: Every 3–6 months
Supplemented with EHR/CDM/claims data

Duration: Enrollment over 24 months; maximum follow-up of 30 months

***Enrichment factors**

- Age >65 years
- Creatinine >1.5 mg/dL
- Diabetes mellitus (type 1 or 2)
- Known 3-vessel CAD
- Current CVD or PAD
- Known EF <50% by echo, cath, nuclear study
- Current smoker

Primary endpoint:
Composite of all-cause mortality, hospitalization for MI, or hospitalization for stroke

Primary safety endpoint:
Hospitalization for major bleeding

† A subset of participants who do not have internet access may be consented and followed via a parallel system.

Adaptable

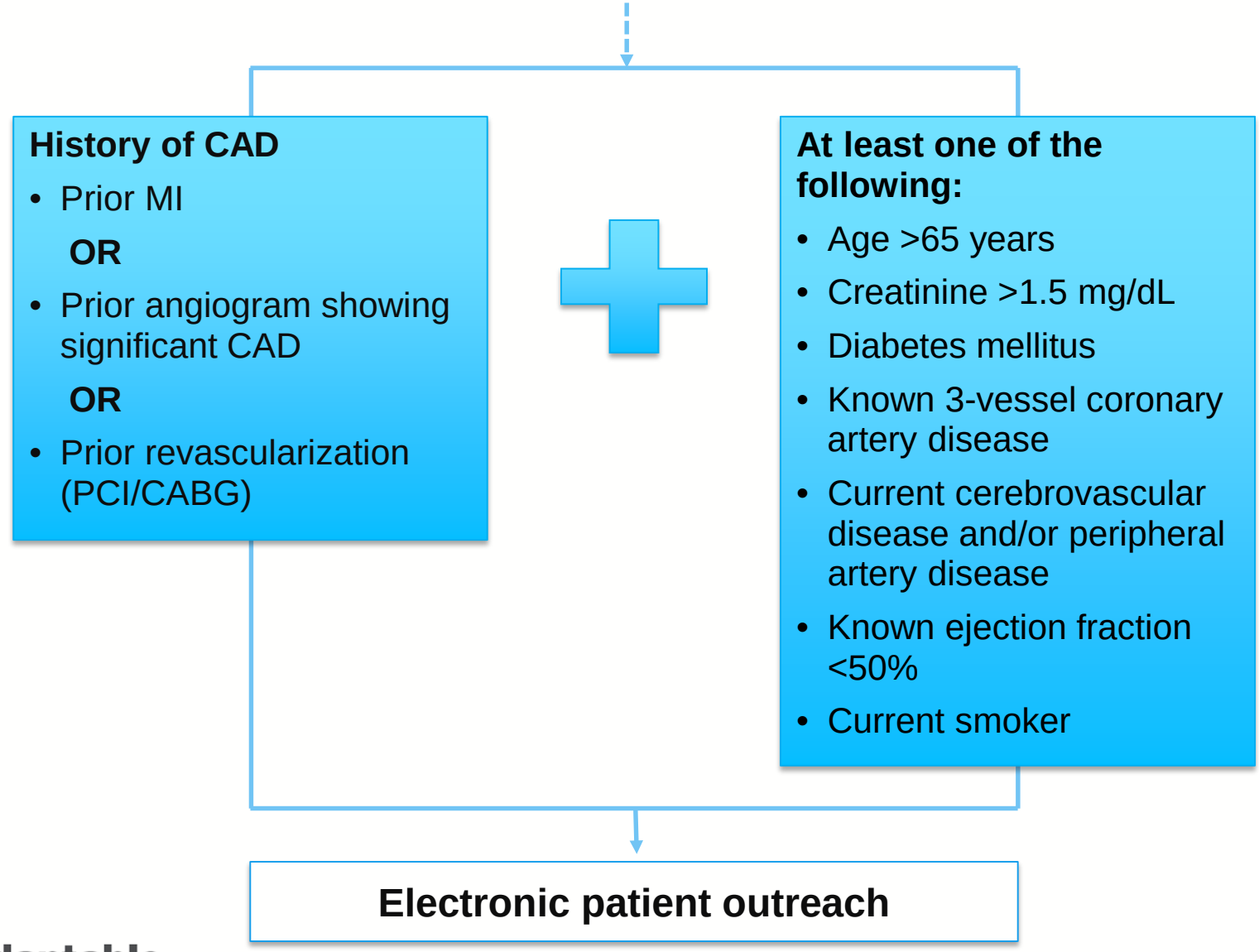
Open science

- Protocol and survey questions posted for public review and comment in July 2015
- Public and CDRN feedback contributed to key protocol changes
  - Exclusion of ticagrelor-treated patients
  - Exclusion of patients with potential indications for an oral anticoagulant, even if not treated with one
  - Inclusion of patients regardless of prior use of aspirin before randomization
- All ADAPTABLE materials and information are posted publicly (www.pcornet.org/aspirin)
- Open dissemination plan for trial results

Patient engagement

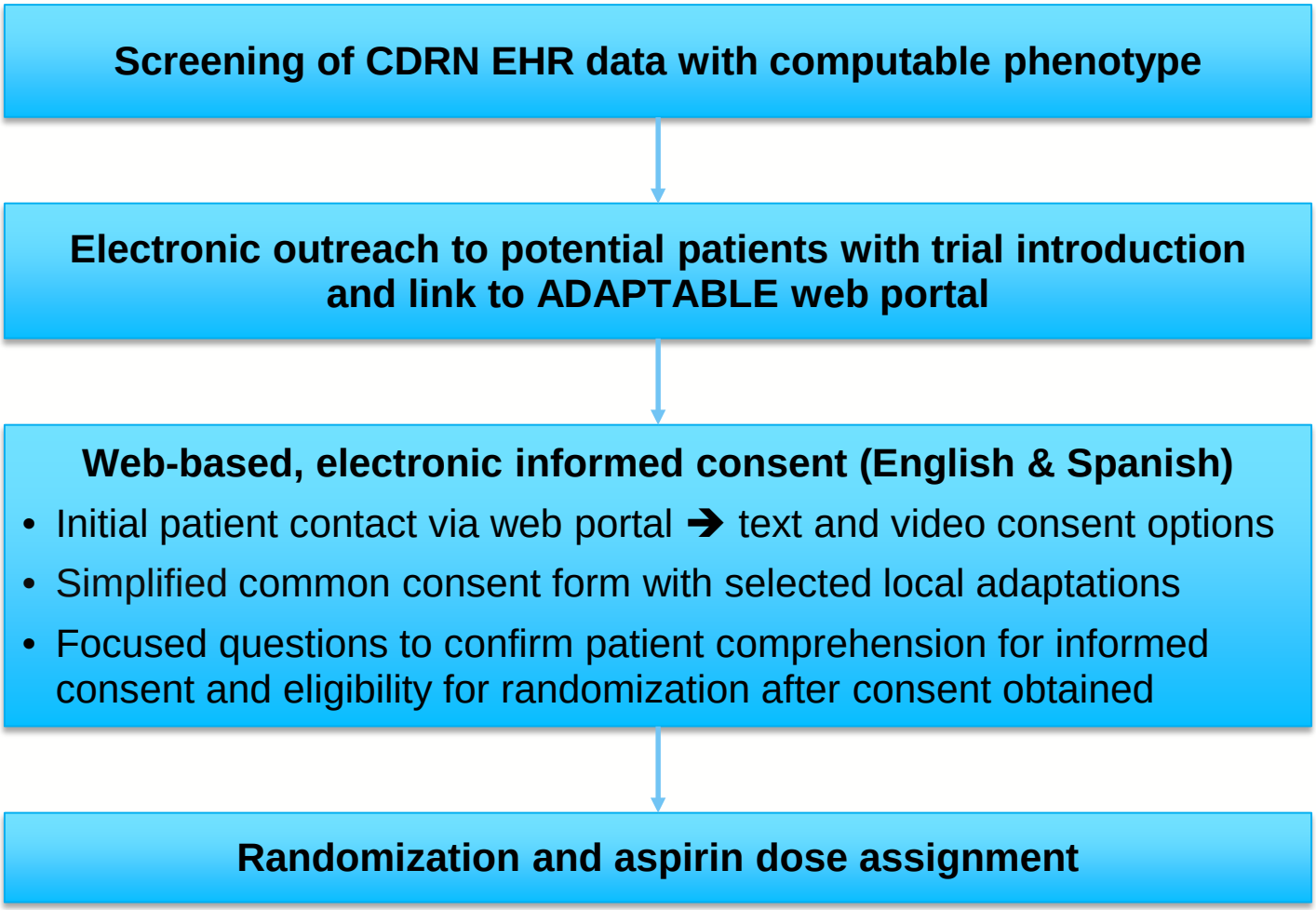
- Patients involved in prioritization of the research topic, protocol design, trial conduct, and plans for trial results dissemination
- Patients involved in:
  - Executive Committee (2 patients)
  - Steering Committee (1 patient from each CDRN)
  - ADAPTORS Patient Group
  - Data Safety Monitoring Board (2 patients)
- Patients integral to empirical development of participant-centric consent form and comprehension assessment
- ADAPTABLE Co-learning Community (ACLC) for study team members
- Health eHeart PPRN with a critical role

Computable phenotype for CDRNs



Adaptable

Informed consent and randomization



Enabling and testing pragmatic research: e-data collection and e-follow-up

N=20,000

ADAPTABLE enrollee

Baseline data

mytrus.

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*

6 | 12 | 18 | 24 | 30

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*

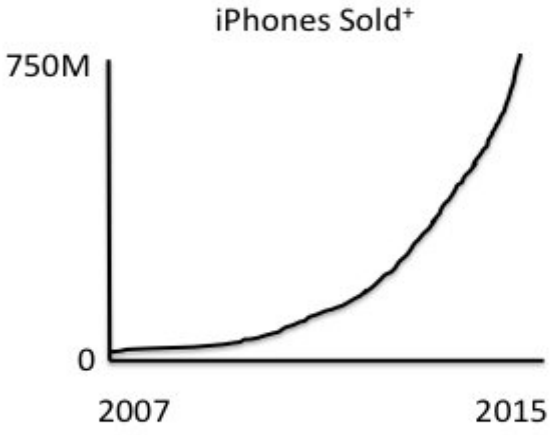
Death ascertainment

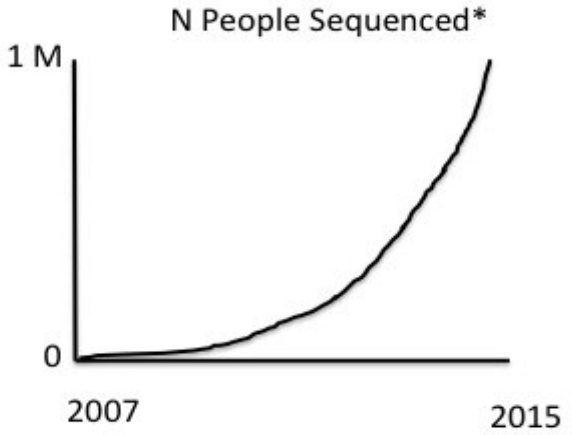
National Death Index (NDI) & Social Security Database

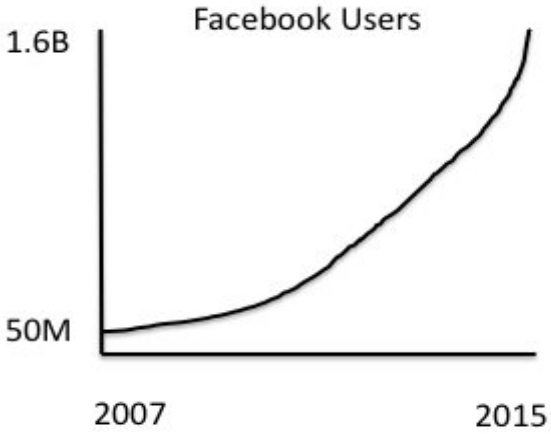
Adaptable

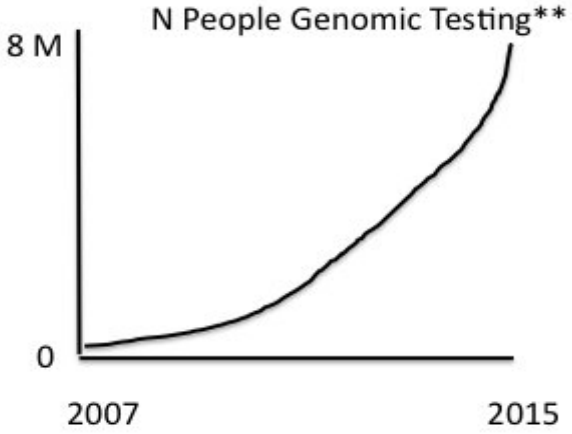
Traditional trials vs. ADAPTABLE

	Traditional	ADAPTABLE
I/E criteria reviewed	Sample via CRA visit	CDM
Representative cohort	Narrow	Broad
Consent	Facilitated	Patient-directed
Comprehension tested	No	Yes
Format	Paper	e-consent
Data collection	Patient-reported	Patient-reported
	Site-recorded	CDM
Source documents	Only seen by site	Received via CDM
Endpoint adjudication	Yes	CDM, EHR data
Patient involvement	Participants only	Protocol design, committee, analyses, dissemination









+1st iPhone 6/07; Numbers/plots are approximate bases on web searches

*exome + WES; **23andMe, all NIPT, all cancer testing

Eric Topol @EricTopol · 14h

A lot happened in just 8 years

Stanford MEDICINE

Smartphone fitness apps enable researchers to gather health data from large numbers of people.

MOBILE DATA

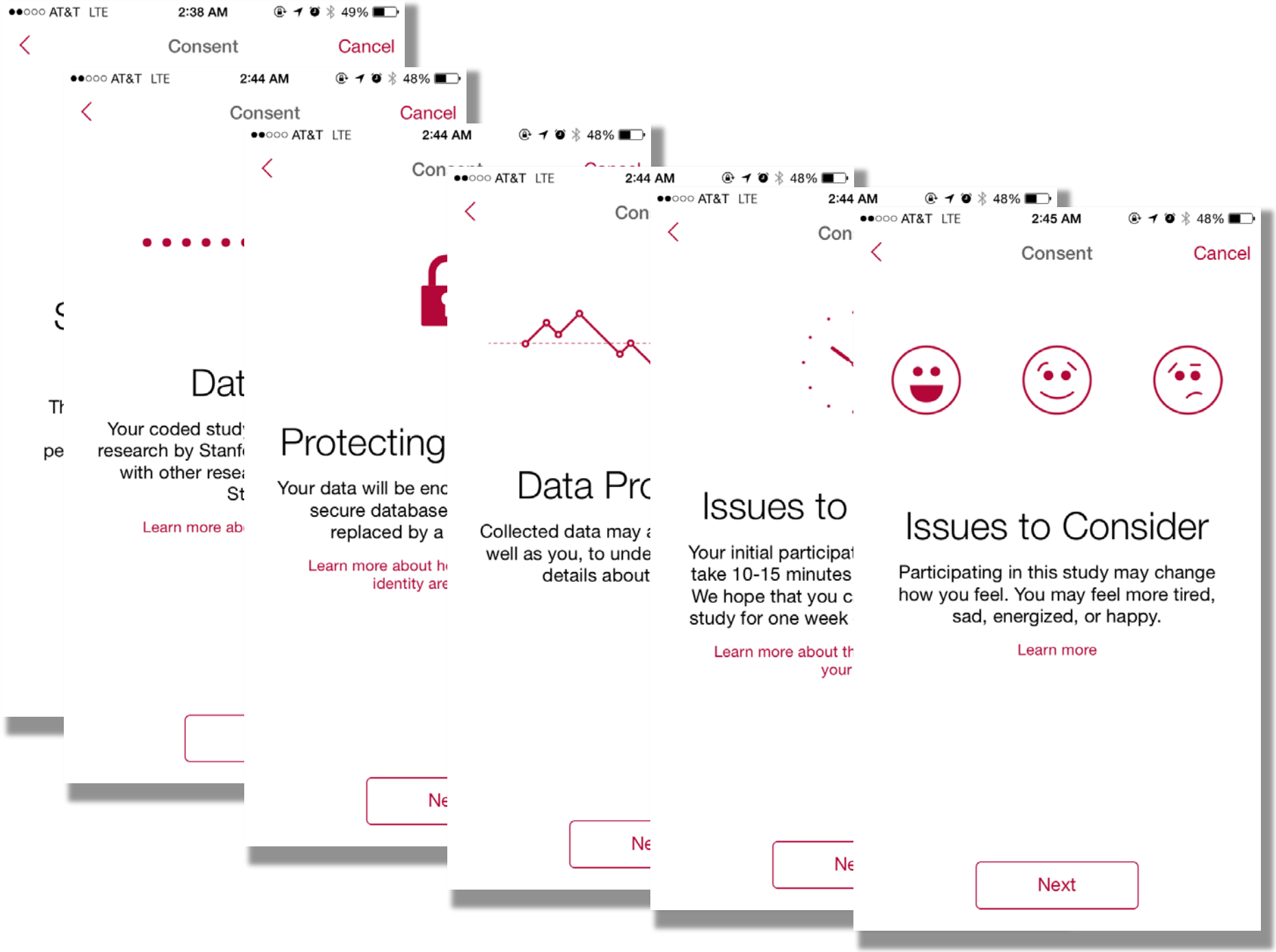
Made to measure

Wearable sensors and smartphones are providing a flood of information and empowering population-wide studies.

-Nature November 2015


9:41 AM
100%
Messages
Calendar
Photos
Camera
Weather
Clock
Maps
Videos
Notes
Reminders
Stocks
Game Center
Newsstand
iTunes Store
App Store
iBooks
Health
Passbook
Settings
MyHeart
Phone
Mail
Safari
Music
9:41 AM
100%
Step 9 of 9
Done
Heart Age Results
Comparison of your actual age and your heart age.
62
Your Age
60
Your Heart Age
10-Year Risk Estimate
According to your answers, your calculated risk of developing Heart Disease or Stroke within 10 years is:
6%
Calculated Risk
7%
Optimal Risk Factors
Heart Age Summary
10-Year Risk Score: In general a 10-year risk > 7.5% is considered high and warrants discussion with your doctor. There may be other medical or family history that can increase your risk and these should be discussed with your doctor.


Cardiovascular Disease
MyHeart Counts
Stanford Medicine
University of Oxford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2:38 AM
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Protecting
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Issues to
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Issues to Consider
Participating in this study may change how you feel. You may feel more tired, sad, energized, or happy.
Learn more
Next

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HEALTH & FITNESS SOFTWARE apple, ios, researchkit, healthkit, iphone

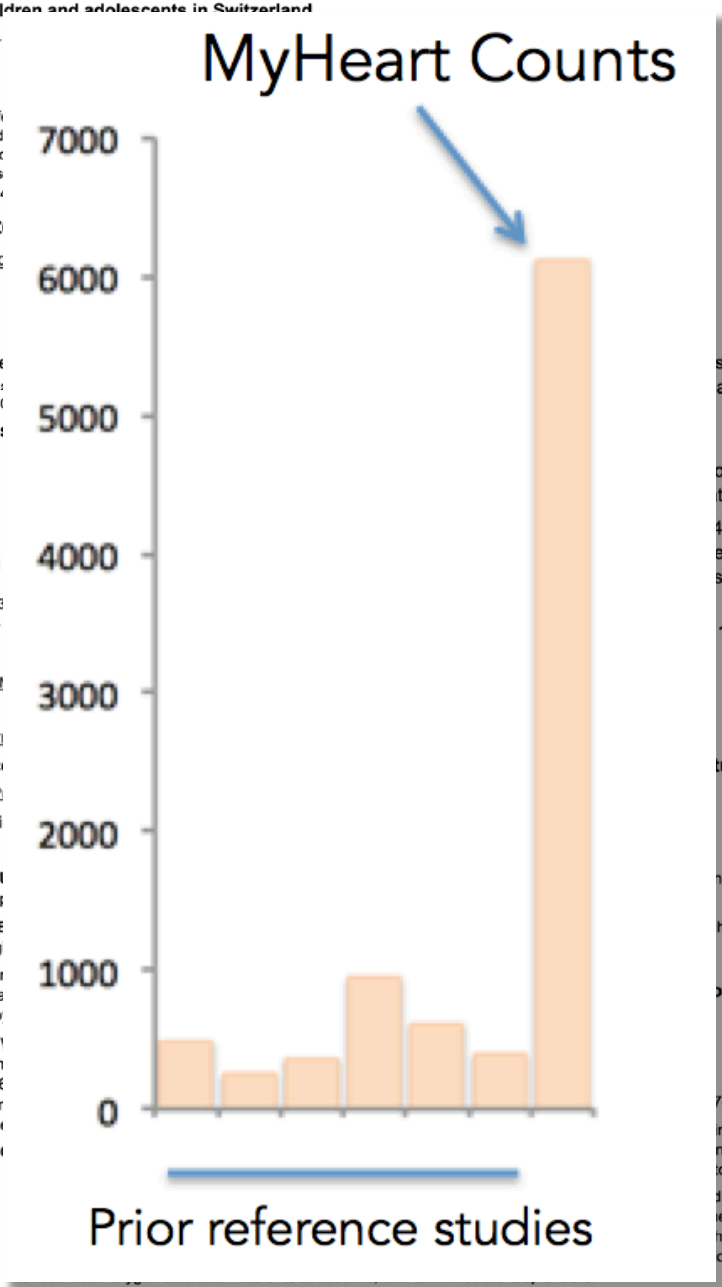
Stanford's ResearchKit app gained more users in 24 hours than most medical studies find in a year

Ian Paul | @ianpaul
ian@ianpaul.net, Macworld

Mar 12, 2015 7:51 AM

Apple's attempt to revolutionize medical studies appears off to a strong start. Just one day after the company released the first five apps using the new ResearchKit framework, 11,000 iPhone users signed up for one of the studies.

Stanford Researchers were amazed at the response for the MyHeart Counts app that studies heart health by measuring a user's daily activity, fitness level, and other factors. "To get 10,000 people enrolled in a medical study normally, it would take a year," Alan Yeung, medical director of Stanford Cardiovascular Health, told Bloomberg Business.



496 participants

259 participants

370 participants

949 participants

617 participants

400 participants

Outline

- RCT basics
- Current state of RCTs: large and complicated
- Pragmatic trials (examples)
- Digital data collection

Learn more about ADAPTABLE

www.pcornet.org/aspirin