TIME TO REBOOT
CLINICAL TRIALS 2.0

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The Cycle of Clinical Therapeutics

Concept → Clinical Trials → Patient Outcomes → Performance Indicators → Guidelines → Performance
Level of Evidence A
Current Guidelines*

- AF: 11.7%
- Heart failure: 26.4%
- PAD: 15.3%
- STEMI: 13.5%
- Perioperative: 12.0%
- Secondary prevention: 22.9%
- Stable angina: 6.4%
- SV arrhythmias: 6.1%
- UA/NSTEMI: 23.6%
- Valvular disease: 0.3%
- VA/SCD: 9.7%
- PCI: 11.0%
- CABG: 19.0%
- Pacemaker: 4.9%
- Radionuclide imaging: 4.8%

*Guidelines expressing Level of Evidence

Tricoci, JAMA, 2009
How Big Was ROCKET AF??

- 45 countries
- 1178 sites
- 14,264 patients
- 10,373 Serious Adverse Events
- 10,895 Clinical Events Triggered for Adjudication
- 332,627 Concomitant Therapies
- 478,001 Repeat Visits
- 2,511,247 eCRF pages
- 27,252,226 Data Points
“This randomized, double-blind trial involving over 20,000 patients was conducted over a 10 year period. Unfortunately we’ve forgotten why.”
Conclusion: Clinical trials registered in ClinicalTrials.gov are dominated by small trials and contain significant heterogeneity in methodological approaches, including reported use of randomization, blinding, and DMCs.
What is A Quality Clinical Trial?
Quality by Design

1. Have we enrolled the right participants according to the protocol with adequate consent?
2. Did participants receive the assigned treatment and did they stay on the treatment?
3. Was there complete ascertainment of primary and secondary efficacy data?
4. Was there complete ascertainment of primary and secondary safety data?
5. Were there any major GCP related issues?
Registry-based randomized clinical trials—a new clinical trial paradigm

Stefan James, Sunil V. Rao and Christopher B. Granger

Abstract | Randomized clinical trials provide the foundation of clinical evidence to guide physicians in their selection of treatment options. Importantly, randomization is the only reliable method to control for confounding factors when comparing treatment groups. However, randomized trials have limitations, including the increasingly prohibitive costs of conducting adequately powered studies. Local and national regulatory requirements, delays in approval, and unnecessary trial processes have led to increased costs and decreased efficiency. Another limitation is that clinical trials involve selected patients who are treated according to protocols that might not represent real-world practice. A possible solution is registry-based randomized clinical trials. By including a randomization module in a large inclusive clinical registry with unselected consecutive enrolment, the advantages of a prospective randomized trial can be combined with the strengths of a large-scale all-comers clinical registry. We believe that prospective registry-based randomized clinical trials are a powerful tool for conducting studies efficiently and cost-effectively.

James, S. et al. Nat. Rev. Cardiol. 12, 312–316 (2015); published online 17 March 2015;
doi:10.1038/nrcardio.2015.33

-Slide courtesy S James
Ongoing Registry-RCTs in Sweden

VALIDATE (n=6000)
- *Bivalirudin versus Heparin in NST and ST- Elevation myocardial infarction in patients on modern antiplatelet therapy* in SWEDHEART

DETOX-AMI (n=7000)
- *DETermination of the role of OXygen in Acute Myocardial Infarction*,

SWEDEPAD (n=2480)
- *SWEdish Drug Elution trial in Peripheral Arterial Disease. DES vs BMS and DEB vs POBA.*

IFR SWEDHEART (n=2000)
- *Instantaneous Wave-Free Ratio versus Fractional Flow Reserve in ACS*

PROSPECT-2 (n=1200, hybrid trial)
- *Providing Regional Observations to Study Predictors of Events in the Coronary Tree.* Evaluate future events from cholesterol plaques detected by near infrared spectroscopy

DISCO (n=2480)
- Evaluate if patients with out of hospital cardiac arrest should undergo routine coronary angiography

U-CARE (n=500)
- Evaluation of internet based cognitive behavioural therapy (iCBT) versus usual care in patients with depression/anxiety post MI.
2500 hospitals
> 2000 cardiologists
20 million clinical records

Registry-Based Trials in the United States?
PCORNET: DEVELOPING PARTNERSHIPS IN CV RESEARCH

Adrian Hernandez, MD, MHS
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**
ADAPTABLE Study Design

Patients with known ASCVD + ≥1 “Enrichment Factor”

Identified through EHR screening and electronic patient contact by CDRNs/PPRNs (PPRN patients would need to connect through a CDRN to participate)

Patients contacted electronically with trial information and e-consent via web portal
Treatment assignment will be provided directly to patient

*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

ASA 81 mg QD
ASA 325 mg QD

Randomized Electronic Follow-Up: 3 vs 6 months
Supplemented with EHR/CDM Data Queries

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
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.
Enabling and Testing Pragmatic Research: 
e-Data Collection and e-Follow-Up

N=20,000

ADAPTABLE
Enrollee

Baseline Data

Patient Web Portal Follow-Up
- Randomized to 3 vs. 6 months contact
- Patient Reported Hospitalizations
- Medication use
- Health outcomes

PCORNet Coordinating Center Follow-Up
- Via Common Data Model
- Validated coding algorithms for endpoints

Death Ascertainment
National Death Index (NDI) & Social Security Database

6 12 18 24 30
## Cost Comparisons

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th># Pts</th>
<th>Cost/Pt</th>
<th>Total Budget</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAPTABLE</td>
<td>20,000</td>
<td>$850</td>
<td>$17 M</td>
</tr>
<tr>
<td>PROMISE</td>
<td>10,003</td>
<td>$3,100</td>
<td>$27 M</td>
</tr>
<tr>
<td>Diabetes Outcome</td>
<td>14,757</td>
<td>$23,175</td>
<td>$342 M</td>
</tr>
</tbody>
</table>

✔️ *Outcomes of Anatomical versus Functional Testing for Coronary Artery Disease*  

✔️ **Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation**  
Crowded Precision Medicine Landscape

Need for differentiation and sense of urgency
# The Precision Health difference

<table>
<thead>
<tr>
<th>Precision Health</th>
<th>Precision Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precise</td>
<td>Precise</td>
</tr>
<tr>
<td>Personalized</td>
<td>Personalized</td>
</tr>
<tr>
<td>Proactive</td>
<td>Reactive</td>
</tr>
<tr>
<td>Includes prediction and prevention</td>
<td>Relies on diagnosis and treatment</td>
</tr>
<tr>
<td>Focuses on keeping you healthy</td>
<td>Focuses on treating you when you’re sick</td>
</tr>
<tr>
<td>Health care</td>
<td>Sick care</td>
</tr>
</tbody>
</table>

Courtesy, Lloyd Minor
Precision Health Strategic Priorities

Wellness and Vitality Discovery

Biobank and Data Hub Infrastructure

Cutting-Edge Translational Diagnostics

Transformative Clinical Applications

Precision Health Education

Social Justice and Value

Connected Personalized Experiences

Thought Leadership and Governance

Courtesy, Harrington RA
A new platform for biomedical science: A collaboration between verily, Stanford, and DUKE to develop An integrated understanding of human health
A comprehensive study of human health and transition to disease
A longitudinal cohort study to extensively characterize participants at baseline and serially using a battery of clinical, imaging, psychosocial, behavioral, socioeconomic, geospatial, physiometric, and molecular tools.
STUDY GOALS

Create a deep biomedical information structure

Develop a comprehensive understanding of health and disease state transitions

Extensively characterize participants at baseline and serially
OVERALL OBJECTIVES

- Identify biomarkers of disease-related transitions, including those related to cardiovascular disease and cancer
- Measure the phenotypic diversity observed in a participant population, defining a range of expected values for multiple types of data
- Characterize participants across clinical, molecular, imaging, sensor, self-reported, behavioral, psychological, environmental, and other health-related measurements
- Evaluate investigational wearable and passive sensors for the collection of continuous, accurate health information
- Create a dataset encompassing a wide spectrum of phenotypic measures for future exploratory analysis
ASSESSMENTS

- Omics
  - Genomics
  - Epigenomics
  - Transcriptomics
  - Metabolomics
  - Microbiome

- Imaging
  - Echo
  - Coronary CT
  - Whole Body MRI

- Immune Status

- EMR
  - History
  - Family Tree

- Physical Exam

- Standard Lab Tests
  - Blood work
STUDY TIMELINE

- Invitation to Participate, Web Consent
- Prescreen
- Screen
- Baseline Visit
- 24-hour Internet Participant Portal
- Year 1, Year 2, Year 3, Year 4
- Yearly Follow Up Visits (in-person)
- Quarterly Interim Follow Up (web-based/phone)
- Confirm Consent in Person
SUMMARY

- We expect specific findings from the *Baseline Study* will change the science of systems biology
- The creation of an ongoing, high-quality interactive data and analytical approach should lead to a new ability to continually accrue knowledge in a publicly-available structure
- The study will free the limitations of availability of high-quality data and adequate capacity to analyze it in multiple dimensions necessary to understand and predictably modify health outcomes
- This multi-dimensional analysis will enable an unprecedented comprehension of the relationships between individual assessments and related biological, physiological, and behavioral systems
- The common effort will create a comprehensive platform for the modern community of biomedical scholars and medical practitioners
National Research Trends:

- 60% of sites fail to meet enrollment goals
- 80% fail to finish on time
- 50% of sites enroll one or no patients in their studies
- Less than 5% of cancer patients get into clinical trials
Level of Trust in Clinical Research Study Information Sources

<table>
<thead>
<tr>
<th>Information Source</th>
<th>Mean Ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>The online clinical trial registry/database maintained by your government</td>
<td>2.01</td>
</tr>
<tr>
<td>Posters/pamphlets in a doctor's office or clinic</td>
<td>2.86</td>
</tr>
<tr>
<td>Online patient communities or social media sites</td>
<td>3.17</td>
</tr>
<tr>
<td>Pharmaceutical company websites</td>
<td>3.36</td>
</tr>
<tr>
<td>Advertisements about clinical trials (TV, newspapers)</td>
<td>3.60</td>
</tr>
</tbody>
</table>

Source: 2015 CISCRP Perceptions & Insights Study – All Respondents (n=12,009)
Top Reasons Not Willing to Participate

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percent Mentioning 2013</th>
<th>Percent Mentioning 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>I do not want to take a chance with my health</td>
<td>20%</td>
<td>43%</td>
</tr>
<tr>
<td>I have concerns about the risks associated with clinical research studies</td>
<td>12%</td>
<td>26%</td>
</tr>
<tr>
<td>I don't want to be treated like an experimental test subject as opposed to a patient/person</td>
<td>14%</td>
<td>25%</td>
</tr>
<tr>
<td>I do not know enough about clinical research</td>
<td>14%</td>
<td>21%</td>
</tr>
<tr>
<td>I do not want to risk getting an inactive drug</td>
<td>15%</td>
<td>19%</td>
</tr>
<tr>
<td>Too much time is required to participate</td>
<td>14%</td>
<td>20%</td>
</tr>
<tr>
<td>I do not have any reason to participate</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>I am not interested in clinical research</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>I could not afford the time away from my job</td>
<td>12%</td>
<td>18%</td>
</tr>
<tr>
<td>I am concerned about protecting my privacy</td>
<td>9%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Source: CISCRP Perceptions & Insights Studies – Respondents Not Willing to Participate
### What Did You LEAST Like about Your Clinical Research Study Experience?

<table>
<thead>
<tr>
<th>Issue</th>
<th>Percent Mentioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>There was nothing I didn’t like about my clinical study experience</td>
<td>30%</td>
</tr>
<tr>
<td>The possibility of getting a placebo (e.g., inactive substance/sugar pill)</td>
<td>24%</td>
</tr>
<tr>
<td>The location of the medical center (i.e., too far away from my home, not convenient)</td>
<td>20%</td>
</tr>
<tr>
<td>The side effects of the study drug</td>
<td>12%</td>
</tr>
<tr>
<td>The study visits were too time-consuming</td>
<td>11%</td>
</tr>
<tr>
<td>The compensation (money) I received was not enough</td>
<td>10%</td>
</tr>
<tr>
<td>The procedures I had to follow at home were too cumbersome</td>
<td>9%</td>
</tr>
<tr>
<td>The overall time commitment was too much</td>
<td>9%</td>
</tr>
<tr>
<td>Missing too much work</td>
<td>8%</td>
</tr>
<tr>
<td>The procedures during my study visits were too cumbersome</td>
<td>7%</td>
</tr>
<tr>
<td>Childcare cost too much</td>
<td>4%</td>
</tr>
<tr>
<td>The study doctor was not friendly</td>
<td>4%</td>
</tr>
<tr>
<td>The study staff was not friendly</td>
<td>3%</td>
</tr>
<tr>
<td>Not sure</td>
<td>6%</td>
</tr>
<tr>
<td>Other</td>
<td>8%</td>
</tr>
</tbody>
</table>

Source: 2015 CISCRP Perceptions & Insights Study – Clinical Trial Participants (n=3,152)
What Did You MOST Like about Your Clinical Research Study Experience?

<table>
<thead>
<tr>
<th>Percent mentioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helping advance science and the treatment of my disease/condition</td>
</tr>
<tr>
<td>Helping others who may suffer from my disease/condition</td>
</tr>
<tr>
<td>The compensation (money) I received</td>
</tr>
<tr>
<td>The amount of care and attention that I received from the study doctors and staff</td>
</tr>
<tr>
<td>The information that I learned about my disease/condition</td>
</tr>
<tr>
<td>My relationship with the study staff</td>
</tr>
<tr>
<td>The positive response that I had to the study drug/intervention</td>
</tr>
<tr>
<td>The free medical procedures and care that I received</td>
</tr>
<tr>
<td>The free study drug that I received</td>
</tr>
</tbody>
</table>

Source: 2015 CISCRP Perceptions & Insights Study – Clinical Trial Participants (n=3,152)
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 health systems on the development of recruitment plans and materials

ClinicalTrials.gov: NCT02697916
Lessons Learned for Recruitment

- Eligible patients want to know their clinician endorses the study
  - Local patient engagement should be customized to the environment
- Remote recruitment rarely successful without multiple follow-up contacts
  - Staffing resources are needed to support this model are uncertain
- Deep collaborations between informatics experts and clinicians are necessary to optimize implementation of the computable phenotype
  - Local common data models have unique features
- Sustained clinician engagement and buy in is critical for success
  - Recruitment doesn’t happen without champions!
Recruitment and Retention Enhancement Core (R₂EC)

- Community Advisory Board
- Recruitment Strategies
- EPIC & STRIDE
- Hospital Partnership
  - Honest Broker
  - Registry
  - Participant Engagement Platforms

Engage ➔ Educate ➔ Empower
- Science
- Operations
- Regulations

OUR MISSION

Advancing digital health through meaningful collaboration

Building better products, better experiences, and better outcomes
Participant Engagement Platforms

- Provide tools to investigators to enhance recruitment and retention
- Evaluating several vendors:
  - Clinithink
  - TrialSpark
  - Evidation
  - TriNetx
- Academic partnerships
- Signed contract with Hawthorne Effect
A recruitment management system can help reduce enrollment times.

**TrialSpark Improve Enrollment Times**

![Graph showing improvement in enrollment times with and without TrialSpark](image)

**Details**
- Multi-site Study
- ⅔ of sites randomized to use Trialspark
- Measured time between date of first patient contact to date of enrollment
- Sites that used Trialspark enrolled significantly faster compared to sites that did not use Trialspark

Cox Proportional Hazards Model showing our system pushes people faster to enrollment

Questions? Contact Ben@trialsparck.com
Take follow-up to the patient
How we do it

HERO = Hawthrone Effect Research Outcome professional

- Slide courtesy J Akin
MyHeart Counts Research App: 
Global mHealth Assessment of Daily Activity 
and Cardiovascular Health

Make your heart count!

What keeps your heart its healthiest? Help us find out.

Download and join today!
Stanford's ResearchKit app gained more users in 24 hours than most medical studies find in a year.

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.
Feasibility of Obtaining Measures of Lifestyle From a Smartphone App
The MyHeart Counts Cardiovascular Health Study

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

A Mean proportion of time spent active per state

C Difference in the mean life satisfaction

B

Activity Cluster

Inactive Drivers Weekend Warriors Active

Life Satisfaction
Large, Real-World 6MWT Database

6-Minute Walk Test Comparison
You vs Others
820 yards

Prior reference study
MyHeart Counts v 2.0

- Launched January 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

Courtesy, Ashley E
Primary Study Objective:

- Evaluate the efficacy of a mobile adherence platform compared to usual physician or nurse-guided care, to improve adherence to rivaroxaban in subjects who have recently initiated rivaroxaban for stroke prevention in Atrial Fibrillation

- Two-arm, open-label, randomized controlled study

- 378 subjects, 189 in each arm

- 25 Sites in US

- 6 months follow-up
“You can’t list your iPhone as your primary-care physician.”
Summary

• Current approach to clinical trials not sustainable.
• Need a return to large and simple trials
• Patient engagement will be critical
• Mobile technologies need rigorous and efficient evaluation