Stanford Drug Discovery Conference:

Rethinking Randomized Clinical Trials

Robert A. Harrington MD
Arthur L. Bloomfield Professor of Medicine
Chair, Department of Medicine
Stanford University
Twitter: @HeartBobH
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
## Strength of Study Designs for Treatment Comparisons/Inferences

<table>
<thead>
<tr>
<th>Method</th>
<th>Reliability</th>
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<tbody>
<tr>
<td>Clinical experience</td>
<td>poor</td>
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<tr>
<td>Targeting disease process with surrogate endpoints</td>
<td>poor</td>
</tr>
<tr>
<td>Case-control study</td>
<td>fair</td>
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<tr>
<td>Observational database analysis</td>
<td>good</td>
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<tr>
<td>Large randomized clinical trial</td>
<td>best</td>
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“Classic” Clinical Trial Business Model

Size
- Mostly small N
- Huge budgets

Endpoints
- Mostly surrogate
- Clinical trials employ adjudication

Setting
- Research enterprise – “parallel universe”
- “High-grade” data – audited, monitored

Califf RM et al. JAMA 2012;307:1838-47
Risk in Cardiovascular Drug Development: Some Issues to Consider

• Challenges with traditional Phase 1 testing
• Lack of reliable biomarkers and surrogates in Phase 2
• Challenges with planning and implementing phase 3 trials (sample size, comparators)
• Understanding unusual or infrequent AEs
• Complexity of placing research into clinical practice
• Complexity of dealing with regulators
• Challenges with academic-industry relationships
• Lack of systematic results reporting is problematic for field
Re-thinking RCTs: Outline

• Current state of RCTs: large, complicated, inefficient, out of sync with clinical practice and very expensive; tensions between precision medicine and population health

• Rethinking clinical trials
  – Increase information yield of translational science and early phase investigation
  – Adaptive trial strategies; enrichment strategies; intermediate outcomes and links to outcomes studies
  – Digital data collection and public engagement
  – Pragmatic trials for certain situations
  – Open data and RCT data transparency
  – Learning health care, clinical research and ethical framework
Deming, data and observational studies
A process out of control and needing fixing

“Any claim coming from an observational study is most likely to be wrong.”
“This randomized, double-blind trial involving over 20,000 patients was conducted over a 10 year period. Unfortunately we’ve forgotten why.”
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
Trialists!
No more need to wait for symptoms or survival to improve!

Biomarkers and surrogate endpoints get the job done in half the time*

Accept ONLY OUR substitutes!

Contact your friendly Biomarkers Unlimited Inc representative today!

*According to 583 professors surveyed by Biomarkers Unlimited Inc
Time

Intervention

Disease → Surrogate end point → True Clinical Outcome

-- Fleming and DeMets, Annals Int Med, 1996
A Disease -> Surrogate end point -> True Clinical Outcome

B Disease -> Surrogate end point -> True Clinical Outcome

--- Fleming and DeMets, Annals Int Med, 1996 ---
A New Approach to Drug Development

Using these complex systems approaches, one can learn about many drugs’ off-target actions. One example of this point is a study by Campillos and colleagues, who showed that 20% of all drugs in the US Pharmacopoeia have common side effects that are indicative of their affecting common, previously unrecognized pathways. This kind of analysis, then, offers a better understanding of the universe of actions of any drug, can be used to predict potentially undesirable side effects of a drug, and can be used to identify previously unrecognized potential therapeutic actions of a drug.

Similarly, one can use a comprehensive systems pharmacology approach to understand differences among drugs of a specific class, as Xie and colleagues recently did for the cholesteryl ester transfer protein inhibitors. As you remember, the first of these, torcetrapib, increased high-density lipoprotein cholesterol as predicted from drug target analysis and development, but was associated with an unanticipated increase in clinical events compared with the control arm of the trial. Using a systems approach coupled with structural similarity network analysis, Xie and colleagues showed that in contrast to two other members of this class of agents, torcetrapib activated the renin-angiotensin-aldosterone system, likely accounting, at least in part, for these differences in outcome and supporting the development of other members of the class, such as anacetrapib.

To many in the burgeoning field of personalized medicine, identification of unique drug targets in individuals, rather than in populations, followed by development of specific inhibitors of those targets will lead to more effective, safer medicines that can be used in well-characterized disease phenotypes. A very good example of this concept is crizotinib (Xalkori), which targets a unique abnormal fusion product of the ALK receptor in a select group of patients with non–small-cell lung cancer (ie, 4% of all non–small-cell lung cancers), and has been viewed as a clear proof-of-concept of the potential benefits of personalized medicine. Another example is the use of the RAF inhibitor, PLX4032 (vemurafenib), in patients with BRAF mutant melanoma. One such patient recently reported by Wagle and colleagues with widely metastatic melanoma had a fantastic response, with the melanoma initially melting away with this treatment; however, resistance developed as a consequence of an acquired mutation in the downstream MEK1 kinase, MEK1<sup>C121S</sup>, a mutation that was not present before treatment with PLX4032 (Figure 7). As a result, the melanoma recurred with wide and rapid dissemination leading to the patient's demise.
Phenomapping for Novel Classification of Heart Failure With Preserved Ejection Fraction

Sanjiv J. Shah, MD; Daniel H. Katz, MD; Senthil Selvaraj, MD, MA; Michael A. Burke, MD; Clyde W. Yancy, MD, MSc; Mihai Gheorghiade, MD; Robert O. Bonow, MD; Chiang-Ching Huang, PhD; Rahul C. Deo, MD, PhD

Background—Heart failure with preserved ejection fraction (HFpEF) is a heterogeneous clinical syndrome in need of improved phenotypic classification. We sought to evaluate whether unbiased clustering analysis using dense phenotypic data (phenomapping) could identify phenotypically distinct HFpEF categories.

Methods and Results—We prospectively studied 397 patients with HFpEF and performed detailed clinical, laboratory, ECG, and echocardiographic phenotyping of the study participants. We used several statistical learning algorithms, including unbiased hierarchical cluster analysis of phenotypic data (67 continuous variables) and penalized model-based clustering, to define and characterize mutually exclusive groups making up a novel classification of HFpEF. All phenomapping analyses were performed by investigators blinded to clinical outcomes, and Cox regression was used to demonstrate the clinical validity of phenomapping. The mean age was 65±12 years; 62% were female; 39% were black; and comorbidities were common. Although all patients met published criteria for the diagnosis of HFpEF, phenomapping analysis classified study participants into 3 distinct groups that differed markedly in clinical characteristics, cardiac structure/function, invasive hemodynamics, and outcomes (eg, phenogroup 3 had an increased risk of HF hospitalization [hazard ratio, 4.2; 95% confidence interval, 2.0–9.1] even after adjustment for traditional risk factors [P<0.001]). The HFpEF phenogroup classification, including its ability to stratify risk, was successfully replicated in a prospective validation cohort (n=107).

Conclusions—Phenomapping results in a novel classification of HFpEF. Statistical learning algorithms applied to dense phenotypic data may allow improved classification of heterogeneous clinical syndromes, with the ultimate goal of defining therapeutically homogeneous patient subclasses. (Circulation. 2015;131:269-279. DOI: 10.1161/CIRCULATIONAHA.114.010637.)

Using “Big Data” to Dissect Clinical Heterogeneity

Russ B. Altman, MD, PhD; Euan A. Ashley, MRCP, DPhil
Use of induced pluripotent stem cell (iPSC) technology for drug discovery.
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 during trial conduct
9. With safeguards against bias in determining clinically relevant outcomes
10. With protection of rights of research patients

Accelerated Approval: Subpart H

Guidance for Industry
Expedited Programs for Serious Conditions—Drugs and Biologics

“A drug that treats a serious condition AND generally provides meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)”
PREVENT IV
Study Design

3000 patients
1st CABG

Edifoligide
Placebo

30-day
Adverse Events

1st 2400: 1-year Angiography

1, 2, 3, 4, 5-year follow-up
Death, MI, Revascularization with VG failure
Guidance for Industry

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

“For the purposes of this guidance, the term enrichment is defined as the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population.”
Despite substantial progress in the prevention of cardiovascular disease and its ischemic complications, it remains the single largest killer in the United States. New treatment options are needed, particularly to respond to the challenges of an aging population and rising rates of obesity and diabetes. Development of novel therapeutic strategies for the management of acute cardiovascular disease is especially challenging. Specific problems include relatively low event rates, diverse patient populations, lack of reliable surrogate end points, and small treatment effects subject to substantial uncertainty. Because the clinical development process is enormously expensive and time consuming, there is considerable interest in statistical methods that use accumulating data from a clinical trial to inform and modify its design. Such redesign might include changes in target sample size and even changes in the target population. This article discusses developments in adaptive design of interest to cardiovascular research.

To illustrate the methods we discuss, we focus on the development of novel therapies for the management of acute coronary syndromes. However, the ideas we discuss have much wider application. We begin by discussing the traditional approach to determination of a fixed sample size for a clinical trial. We then describe group sequential designs and the benefit they provide in the conduct of trials. In the section on Adaptive Sample Size Reestimation, we discuss designs that are adaptive in the sense that they allow an adjustment of the target sample size based on the accumulating data from the trial. In the section on Adaptive Sample Size Reestimation With Enrichment, we discuss enrichment designs that shift the focus to a patient subgroup when the accumulating data suggest greatest benefit for that subgroup. Additional details about population enrichment are provided in the online-only Data Supplement.

The Setting
We consider therapies intended to reduce the risk of acute ischemic complications in patients undergoing percutaneous coronary intervention. For specificity, we consider a placebo-controlled randomized trial with a composite primary end point including death, myocardial infarction, or ischemia-driven revascularization during the first 48 hours after randomization. We assume, based on prior knowledge, that the placebo event rate is in the range of 7% to 10%. The investigational drug is assumed, if effective, to reduce the event rate by 20%, but the evidence to support this assumption is limited. The actual risk reduction could be larger but could also easily be as low as 15%, a treatment effect that would still be of clinical interest given the severity and importance of the outcomes, but that would require a substantial increase in sample size. As is often true when clinical trials are planned, there is substantial uncertainty about both the placebo-group event rate and the treatment effect. In the following sections, we describe how 4 design strategies perform in such situations. We assume throughout that patients are randomized in equal proportions to the experimental and placebo arms. Because the primary objective is to determine whether the new treatment is superior to placebo, our focus will be on 1-sided hypothesis testing.

Fixed Sample Size Designs
The simplest and most common method for determining sample size in the presence of uncertainty is to take best estimates, sometimes based on limited information, of both the placebo group event rate and the treatment effect, apply one of the standard sample size formulas, and perform a fixed sample size trial with that target enrollment. Suppose that $\pi_r$ represents the event rate for the placebo arm, $\pi_t$ the event rate for the experimental arm, and $\rho=(\pi_t/\pi_r)$ the relative risk in the treatment and control groups. We are interested in testing the null hypothesis, $H_0$, that the event rates do not differ in the treatment and placebo arms ($\rho=1$). If we employ a 1-sided level-$\alpha$ test, the combined sample size $N$ (both arms) needed to achieve power $1-\beta$ to reject the null hypothesis when $\rho$ is $<1$ is

$$N = \left\{ \frac{1}{2} \left( \frac{1 - \rho \pi_r}{\rho \pi_c} \right) + \frac{1}{2} \left( \frac{1 - \pi_t}{\pi_c} \right) \right\} \left( \frac{z_{1-\beta} + z_{\alpha}}{\ln(\rho)} \right)^2,$$

where $z_{1-\beta}$ and $z_{\alpha}$ are the appropriate percentiles of the standard normal distribution. For example, when $\pi_r=8\%$, the com-
Health care

Things are looking app

Mobile health apps are becoming more capable and potentially rather useful

Mar 12th 2016 | From the print edition
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.
Using MyHeartCounts to Collect Genetic Data

23andMe to Share DNA Data with Researchers Using Apple iPhone

The consumer genetics company 23andMe plans to let its customers use their iPhones to share their genetic data with researchers carrying out medical studies.

The plan will allow university researchers to access DNA profiles collected by the Google-backed company and pair them with health-related data currently being collected on participants’ phones.

The tie-up, expected to be announced today in connection with an Apple product event in Cupertino, California, involves Stanford University, the Icahn School of Medicine at Mount Sinai in New York, and an app developer named LifeMap Solutions, according to people familiar with the plans. It is part of a widening effort by tech companies and scientists to reinvent how medical studies are carried out by encouraging wider sharing of health information.

Eventually, consumers may simply “swipe” to share their genetic data as easily they do their location or contact list. For now, it’s a little more complicated. All the DNA data is located on 23andMe’s servers, not on people’s phones. It would be shared, on a case-by-case basis, directly with research groups, but only if volunteers click through a consent
“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 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...
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
ADAPTABLE Study Design

Patients with known ASCVD + \( \geq 1 \) “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

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

Primary safety endpoint:
Hospitalization for major bleeding

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

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

History of CAD
- Prior MI
  OR
- Prior angiogram showing significant CAD
  OR
- Prior revascularization (PCI/CABG)

At least one of the following:
- Age >65 years
- Creatinine >1.5 mg/dL
- Diabetes mellitus
- Known 3-vessel coronary artery disease
- Current cerebrovascular disease and/or peripheral artery disease
- Known ejection fraction <50%
- Current smoker

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

N=20,000

**ADAPTABLE enrollee**

**Baseline data**

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

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**PCORnet Coordinating Center follow-up**
- Via Common Data Model
- Validated coding algorithms for endpoints

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**CMS and private health plans follow-up**
- Longitudinal health outcomes
- Validated coding algorithms for endpoints

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**DCRI call center**
- Patients who miss 2 contacts
- Patient-reported hospitalizations
- Medication use
- Health outcomes

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**Death ascertainment**
- National Death Index (NDI) & Social Security Database
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.
The Proposed Rule for U.S. Clinical Trial Registration and Results Submission
Deborah A. Zarin, M.D., Tony Tse, Ph.D., and Jerry Sheehan, M.S.

Compliance with Results Reporting at ClinicalTrials.gov
Monique L. Anderson, M.D., Karen Chiswell, Ph.D., Eric D. Peterson, M.D., M.P.H., Asba Tasneem, Ph.D., James Topping, M.S., and Robert M. Califf, M.D.

Reporting Discrepancies Between the ClinicalTrials.gov Results Database and Peer-Reviewed Publications
Daniel M. Hartung, PharmD, MPH; Deborah A. Zarin, MD; Jeanne-Marie Guise, MD, MPH; Marian McDonagh, PharmD; Robin Paynter, MLS; and Mark Helfand, MD, MS, MPH
Re-thinking RCTs for Therapeutic Development: Final thoughts

• Need new and more sophisticated approach to early phase investigation that incorporates concepts and principles of systems biology and pharmacology
• No easy answers in Phase 2: biomarkers plentiful but true surrogates missing
• Large trials still provide unparalleled source of information about a therapy’s risks and benefits
• Current mode of doing large trials is unsustainable. Investors and pharma are fleeing CV drug development
• Big data has role to play here but still need randomization
• Original “large simple trials” were disruptive methods and have provided backbone of CV therapeutic evidence base for almost 30 years
• Need a return to large AND simple trials to address important health issues while providing detailed data for more personalized approaches