Pragmatic Trials and Novel Interventional Cohort Studies

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BD2K Workshop: Enabling Research Use of Clinical Data
September 11, 2013
Matthew Fontaine Maury

- “Depot of Charts and Instruments”
- “Patterns Everywhere”
- Inventories of barometers, compasses, sextants, chronometers, log-books, maps, and charts – “rubbish”
- Standard log forms and “bottles in the sea”
The Result: Data as A Disruptive Technology

- 1.2 million data points
- Transformed shipping
- “Conceived outside traditional academic circles”
- “Unearthing data from material that no one thought had any value”
- Data use many times

http://www.raremaps.com/gallery/detail/18671?view=print
“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
Datafication is Here

Quantitative Analysis of Culture Using Millions of Digitized Books

Useful Data from Twitter?!

Golder and Macy. Science 2011;333:1878-81
Disruptive, Creative Destruction

The Innovator’s Dilemma

The Creative Destruction of Medicine

How the Digital Revolution Will Create Better Health Care

Eric Topol, M.D.
Why We Must Pay Attention

With 10 to 15% paylines at some institutes (or even less), the current situation makes grant evaluation nearly impossible and is putting truly excellent laboratories out of business. In the spirit of “never waste a good crisis,” a serious evaluation of many NIH extramural policies and programs is warranted. They include centers and other large collective funding efforts as well as expensive clinical and epidemiological research.
“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
“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
Disruption: Keep it VERY Simple

PROTOCOL

TRIAL TO EVALUATE THE EFFECT OF DIGITALIS ON MORTALITY IN HEART

FAILURE:

Digitalis Investigation Group (DIG)

DIGITALIS INVESTIGATION GROUP

BASELINE FORM

Randomization Number

Local Center Name

PRINT Patient Name

Date of Randomization Mo __ Day __ Yr __

Items 1 through 9 must be transmitted over the telephone at the time of randomization.

1. SOCIAL SECURITY NUMBER ___________________________ __-__-____

2. DATE OF BIRTH ___________________________ Mo __ Day __ Yr __

3. EJECTION FRACTION (percent) ___________________________ __%
   A. METHOD (1=Radionuclide, 2=Angiography, 3=2-D Echo) ___________________________

4. SEX (1=Male, 2=Female) ___________________________ __
Robust Findings


N = 6800
HR = 0.99, 95% 0.91 – 1.07
Practical Clinical Trials
Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy

Sean R. Tunis, MD, MSc
Daniel B. Stryer, MD
Carolyn M. Clancy, MD

Decision makers in health care are increasingly interested in high-quality scientific evidence to support clinical and health policy decisions. However, the quality of available scientific evidence is often insufficient.

Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial). A multicenter, prospective, randomized, controlled clinical registry trial based on the Swedish angiography and angioplasty registry (SCAAR) platform. Study design and rationale

Ole Fröbert, MD, PhD, Bo Lagerqvist, MD, PhD, Thórarinn Gudnason, MD, PhD, FESC, Leif Thuesen, MD, PhD, Roger Svensson, MSci, Góran K. Olivecrona, MD, PhD, and Stefan K. James, MD, PhD Örebro, Uppsala and Lund, Sweden; Reykjavik, Iceland; and Aarhus, Denmark
Disruptive Research in Action (Scandinavia)

All primary PCI:s

Randomized

Cost (incremental) = US $300,000 ($50 per patient)
It Can Be Done …

Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction

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

N Engl J Med (posted online September 1, 2013)
“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.”
Frequent Ventricular Ectopy after Exercise as a Predictor of Death

Joseph P. Frolkis, M.D., Ph.D., Claire E. Pothier, M.S., Eugene H. Blackstone, M.D., and Michael S. Lauer, M.D.

Disruptive EMR Research in Action (Canada)

Transfusion Outcomes Research Collaborative

BREAKING NEWS:
We are also very pleased to announce that the TORC endorsed INFORM study has been successfully funded by the Canadian Institutes for Health Research for C$1,606,292 over four years.

24,000 patients

< $ 2 million
Full Coverage for Preventive Medications after Myocardial Infarction

Niteesh K. Choudry, M.D., Ph.D., Jerry Avorn, M.D., Robert J. Glynn, Sc.D., Ph.D., Elliott M. Antman, M.D., Sebastian Schneeweiss, M.D., Sc.D., Michele Toscano, M.S., Lonn Reisman, M.D., Joaquim Fernandes, M.S., Claire Spettell, Ph.D., Joy L. Lee, M.S., Raisa Levin, M.S., Troyen Brennan, M.D., J.D., M.P.H., and William H. Shrank, M.D., M.S.H.S., for the Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial

First Fatal or Nonfatal Vascular Event

Cumulative Incidence (%)

Usual insurance coverage
Full prescription coverage

No. at Risk
Usual insurance coverage 3010 2361 1652 1099 662 379 131
Full prescription coverage 2845 2295 1572 1013 625 340 135

P = 0.03

National Cohort

Biolimus-eluting biodegradable polymer-coated stent versus durable polymer-coated sirolimus-eluting stent in unselected patients receiving percutaneous coronary intervention (SORT OUT IV): a randomised non-inferiority trial

Christiansen EH et al. Lancet 2013;381:661-9
no prior experience in clinical research. Finally, the efficient design meant that the total cost of the trial, including the decolonizing product and contributed personnel effort, was less than $3 million, or approximately $40 per patient.
Another Disruptive Technology: Patients

“The LAM Foundation urgently seeks safe and effective treatments, and ultimately a cure, for LAM through **advocacy and the funding of promising research**. We are dedicated to serving the scientific, medical and patient communities by offering information, resources and a worldwide network of hope and support.”

Lessons from a Rare Disease Trial

Efficacy and Safety of Sirolimus in Lymphangioleiomyomatosis

NIH Office of Rare Diseases
FDA
CIHR
Pfizer
Japanese MOH
LAM Foundation
Tuberous Sclerosis Alliance
Cincinnati Children’s Hospital
Adler Foundation
NHLBI (DIR)

Improved QOL and functional performance (P=0.03 both)

“This research study shows that when patients and researchers work together toward a common goal, advances can be made. The research community contributes ideas and investigative know-how, and patients who have the illness contribute their personal insights, biologic samples, and their time to prove principles. Most important, patients with such a rare disease are willing to put themselves at risk in order to find a treatment or a cure.”

“Biomedical knowledge is a public good, available to any individual even if that individual does not contribute to it. Participation in research is a critical way to support an important public good. Consequently, all have a duty to participate. The public goods argument implies that individuals should participate unless they have a good reason not to. Such a shift would be of great aid to the progress of biomedical research, eventually making society significantly healthier.”
Network News: Powering Clinical Research

Joseph V. Selby,¹ Harlan M. Krumholz,²,3 Richard E. Kuntz,³,4 Francis S. Collins³,5,*

The Patient-Centered Outcomes Research Institute announces bold plans to build a National Patient-Centered Clinical Research Network that will unite millions of patients through a coordinated collaboration with researchers and health care delivery organizations.

Selby JV et al. Sci Transl Med 2013;5:182fs13
"Attempting to establish the efficacy of a treatment in a prospective manner inevitably draws comparisons with methodologies that have the highest standards of rigor, and by comparison this discipline is in its infancy."
Possible “New” Disruptive Models

Size – both bigger and smaller
  - Huge N – robust estimates, heterogeneity
  - Streamlined budgets – grows a bigger pie

Endpoints – what really matters
  - Patient-oriented with minimal adjudication

Setting – increasingly integrated world
  - Within patient-care units and communities
  - Leverage digital data sources
  - Patients as partners, not subjects
How to Win with Disruptive Technologies

Embed into existing projects
Create “small sub-organizations”
- Generate excitement
- Thrilled with “small wins”

Fail early, often, and inexpensively
Utilize resources, but not processes/values
Look for new markets, compete elsewhere
  - Existing markets can mislead us

Notice of Intent to Publish a Funding Opportunity Announcement for Low-Cost Pragmatic Patient-Centered Randomized Controlled Intervention Trials (UH2/UH3)

Notice Number: NOT-HL-13-187

Key Dates
- Release Date: August 1, 2013
- Estimated Publication Date of Announcement: October 2013
- First Estimated Application Due Date: January 2014
- Earliest Estimated Award Date: September 2014
- Earliest Estimated Start Date: September 2014

Issued by
- National Heart, Lung, and Blood Institute (NHLBI)
- National Institute on Aging (NIA)
- National Institute on Deafness and Other Communication Disorders (NIDCD)
- National Institute on Drug Abuse (NIDA)
- National Institute of Nursing Research (NINR)
- National Center for Complementary and Alternative Medicine (NCCAM)
Models for Clinical, “Big-Data” Research

- L
  - Large
  - LEveraged
- E
  - Embedded
  - External
- V
  - Valuable
- I’
  - Inexpensive
  - Innovative
- S
  - Sound Science