The Promise of Comparative Effectiveness Research- 2013 and Beyond

Fifth National Comparative Effectiveness Summit
September 17, 2013
Three Chapters:

Chapter 1: We don’t always know what we think we know

Chapter 2: Big data is great but....

Chapter 3: Putting partnership to the trial
Chapter 1:

We don’t always know what we think we know
NHIS Survey, Top Natural Products and Other NVNMNPs

NVNMNP = non-vitamin/non-mineral natural products

% of adults using NVNMDS

- Echinacea
- Ginseng
- Ginkgo biloba
- Garlic Supplements
- Glucosamine
- St. John's Wort
- Peppermint
- Fish Oil/Omega 3
- Ginger Supplements
- Soy Supplements

2002

2007
How Many Contemporary Medical Practices Are Worse Than Doing Nothing or Doing Less?
Mayo Clinic Proceedings: A Breakdown of NEJM Articles Concerning a Medical Practice

363 (27.0%) Test an established practice

138 (38.0%) Find the practice beneficial (reaffirmation)
146 (40.2%) Find the practice no better or worse (reversal)

756 (77.1%) Find the practice beneficial (replacement)

79 (21.8%) Are inconclusive
Reversals

- Examples:
  - Mortality was higher with recommended glycemic targets as opposed to more permissive standards (ACCORD, NEJM 2008)
  - Routine use of pulmonary artery catheters worsened ICU outcomes (NEJM, 2009)
  - Breast cancer survival was not improved by autologous stem cell transplant and intensified chemo compared with standard chemo (Tallman et al NEJM 2005)
  - Impermeable bedcovers have no benefit for adults with asthma, in spite reduced dust mite exposure (Woodcock, 2003 NEJM)

IOM: The Imperative for Action
Drivers of the Problem

- Scientific uncertainty

Clinical evidence development is not keeping pace with the emergence of new diagnostics, treatments and insights into individual variation.

- Underinvestment in population health
Chapter 2:

Big data is great, but.....
Myriad Data Types

Genomic

Imaging

Other ‘Omic

Phenotypic

Administrative

EHR
A Story in Real-World Comparative Effectiveness

ESRD - End stage Renal Disease

- and

ESA’s - Erythropoiesis-stimulating Agents
We have flipped

2008 - Dialysis Facility Quality Core Indicator – Portion of patients receiving ESA and having Hgb at least 10 g/dl

MORE IS BETTER

Since 2011 – Dialysis Facility Quality Core Indicator and CPM for ESRD Quality Incentive Program: Portion of patients with Hgb > 12

LESS IS BETTER

New consensus: High dose ESA contributes to CVD risk
Data Resources in ESRD

- Single payer in US
- All administrative CMS data available through USRDS Annual Reports
- Anemia management parameters regularly measured and analysed
- Data sets readily available to academic and federal researchers, and reasonably easy to use
- Several large international data registries
- Major dialysis providers also made large investments in data resources

Pretty Big Data!
Pretty Big Data told us:

- Multiple analyses revealed ESA doses are strongly correlated with CVD risk (eg. Zhang et al. AJKD 2004)

- Consensus: This correlation is not causal

- Interpretation: ESA non-responsiveness is associated with multiple risk factors such as infection and inflammation – it is a prognostic factor

- Conclusion: No reasons not to push ESA agents hard to achieve Hgb of 12 or so. Higher Hgb associated with risk.
What changed:

- Growing concern for risks associated with ESA’s in Cancer trials

- RCT’s in ESRD or CKD:
  
  - Besarab NEJM, 98. Worse outcome in ESRD with target normal hematocrit
  
  - Singh NEJM 2006. CHOIR study. Correction of anemia with epoetin alpha in CKD. Worse outcome with target Hgb 13.5
  
  - Pfeffer NEJM 2009 CKD trial. Compared Epo with target 13 to placebo, with rescue at Hgb of 9. Increased stroke with EPO.
CHOIR Data – Hazard Ratio for CVD Events
McCulloch et al AJKD, 2013

[Diagram showing hazard ratios for different tertiles of average Hb in month 4 and tertile of average weekly EPO dose through 1st event/cessation]
Why did we get it wrong?

Expectations

Powerful confounding factors – observational data failed to untangle correlation and causality

Lack of definitive RANDOMIZED TRIALS
Big data sets don’t guarantee the right answer
Chapter 3:

Putting partnership to the trial
The overall goal of the **Commons Fund’s Health Care System (HCS) Collaboratory** is to strengthen the national capacity to implement cost-effective large-scale research studies that engage health care delivery organizations as research partners.
The best model of a cat is another cat (or perhaps the same cat).

Norbert Weiner
Defined Practical (pragmatic) Trials as those in which “the hypothesis and study design are developed specifically to answer the questions faced by decision makers”

- Decision makers include patients, clinicians, payers,
- & health care system policy makers
<table>
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<th>Pragmatic</th>
<th>vs.</th>
<th>Explanatory</th>
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<td>Broad eligibility</td>
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<td>Narrow eligibility</td>
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<tr>
<td>Flexible interventions</td>
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<td>Strict instructions</td>
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<tr>
<td>Typical practitioners</td>
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<td>Expert practitioners</td>
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<tr>
<td>No follow-up visits</td>
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<td>Frequent follow-up visits</td>
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<td>Objective clinical outcome</td>
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<td>Usual compliance</td>
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<td>Close monitoring</td>
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<td>Intent-to-treat</td>
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<td>ITT plus per protocol</td>
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A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers

Kevin E. Thorpe MMath, Merrick Zwarenstein MD MSc, Andrew D. Oxman MD, Shaun Treweek BSc PhD, Curt D. Furberg MD PhD, Douglas G. Altman DSc, Sean Tunis MD MSc, Eduardo Bergel PhD, Ian Harvey MB PhD, David J. Magid MD MPH, Kalipso Chalkidou MD PhD

Published at www.cmaj.ca on Apr. 16, 2009. An abridged version of this article appeared in the May 12 issue of CMAJ. This article was published simultaneously in the May 2009 issue of the Journal of Clinical Epidemiology (www.jclinepi.com).

See related commentaries by Zwarenstein and Treweek, page 998, and by Maclure, page 1001.

Randomized trials have traditionally been broadly categorized as either an effectiveness trial or an efficiency trial, by research funders, ethics committees, trial registers and journal editors to make the same assessment, provided trial-
Pragmatic Study Elements

- Broad eligibility criteria
- Flexible interventions
- Typical practitioners
- No follow-up visits
- Clinical outcomes
- Usual compliance
- Intent-to-treat

Thorpe KE et al. CMAJ 2009;180:E47
Pragmatic Trial Demonstration Projects

1. Preventing hospital acquired infections: (PI Huang) Do intensified antibacterial bathing measures reduce hospital-acquired infections? Cluster randomized trial - HCA randomizing 50 hospitals – 375,000 patients
The implications of this study are highly important. The lack of effectiveness of active detection and isolation should prompt hospitals to discontinue the practice for control of endemic MRSA in ICUs….
Pragmatic Trial Demonstration Projects


4. **Lumbar Spine imaging:** *(PI Jarvik)* Does insertion of epidemiological information into imaging reports reduce subsequent diagnostic and therapeutic interventions? *Kaiser, N Ca; Group Health, Mayo, Henry Ford.* Cluster randomized 128 clinics, 135,000 imaging reports.

5. **Nocturnal blood pressure control:** *(PI Rosenthal)* Does taking anti-hypertensive medications at night reduce CV events? *U of Iowa and Duke primary care clinics,* 6,000 patients.

6. **Collaborative care pain management model:** *(PI Debar)* Study impact of integration of psycho-social supports for patients with chronic pain on pain measures and opioid use. *3 Kaiser regions, Georgia, Hawaii, Northwest.* Cluster randomized by practice. Several hundred practices, 6,000 patients.

7. **Longer dialysis duration:** *(PI Dember)* Does increasing dialysis duration reduce mortality? *Partners Fresenius, da Vita,* Cluster randomized trial of 402 dialysis units. 7000 patients.
Test and Strengthen Models for Clinical Research in Partnership with Health Care Delivery Systems

- Develop capacity to leverage resources of major integrated health care systems for large scale clinical research studies
- Test and improve methods to extract research quality data from electronic health information systems
- Strengthen relevance and translatability of research results to ‘real world’ health practice
- Develop and test more cost-effective models for large scale randomized clinical trials
Thorny issues

- Defining the right questions
- Ethical issues surrounding research on standards of care: eg. when is waiver of consent appropriate
- Optimum trial design for group or cluster randomized trials
- Preserving effective public-private partnerships

https://www.nihcollaboratory.org/
### Part 1. Overview Information

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<th>Participating Organization(s)</th>
<th>National Institutes of Health (NIH)</th>
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<tr>
<td><strong>Components of Participating Organizations</strong></td>
<td>This Funding Opportunity Announcement (FOA) is developed as a Common Fund initiative (<a href="http://commonfund.nih.gov">http://commonfund.nih.gov</a>) through the NIH Office of the NIH Director, Office of Strategic Coordination (<a href="http://oscd.nih.gov/oscd">http://oscd.nih.gov/oscd</a>). The FOA will be administered by the National Center for Complementary and Alternative Medicine (NCCAM), (<a href="http://nccam.nih.gov">http://nccam.nih.gov</a>) on behalf of the NIH. Office of Strategic Coordination (<a href="http://commonfund.nih.gov">Common Fund</a>)</td>
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<td>NIH Health Care Systems Research Collaboratory - Demonstration Projects for Pragmatic Clinical Trials Focusing on Multiple Chronic Conditions (UH2/UH3)</td>
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| **Related Notices** | • **August 23, 2013**  - See Notice NOT-RM-13-024. The purpose of this notice is to inform the research community that a technical assistance videocast will be conducted.  
• **August 21, 2013**. Removed reference to ASSIST in section IV.3, since ASSIST is currently only available for multi-project applications. |
| **Funding Opportunity Announcement (FOA) Number** | RFA-RM-13-012 |
September 17, 2:30 - 4:30

Technical assistance videocast:
National Center for Complementary and Alternative Medicine

Clearinghouse: 1-888-644-6226

Web site: nccam.nih.gov

Twitter: @NCCAM