Finding Research Questions: Look at Both the New and the Old

September 23, 2016
Josie Briggs MD
NIA – Aging Research for the Specialties
Quirky Ideas From Outside the Mainstream

Physical resistance training is good for people recovering from major physical trauma:
Joseph Pilates, 1915

Relaxation and breathing techniques help with pain of childbirth:
Ferand Lamaze 1940

Breast feeding is good for babies:
Edwina Froelich, La Leche League founder 1950’s

Extensive palliative support, and reduced medical interventions should be provided to dying patients:
Saunders, Wald, Kubler-Ross 1960’s
Yoga may help with pain management

Tai-chi may help prevent falls

Yoghurt may reduce antibiotic induced diarrhea

Meditation may help treat PTSD
Ask questions

Of conventional wisdom

Of the evidence
Use of Screening Mammography and Incidence of Stage-specific Breast Cancer in the United States, 1976-2008

Use of Screening Mammography and Incidence of Stage-specific Breast Cancer in the United States, 1976-2008

“Unfortunately, the number of women in the United States who present with distant disease, only 25% of whom survive for 5 years, appears not to have been affected by screening.”

“We estimate that breast cancer was overdiagnosed (i.e. tumors were detected that would never have led to clinical symptoms) in 1.3 million U.S. women in the past 30 years.”

Bleyer A and Welsh HG. NEJM 2012
The price of imprecision
CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea

R. Doug McEvoy, M.D., Nick A. Antic, M.D., Ph.D., Emma Hecley, Ph.D., Yueming Luo, M.D., Qing Ou, M.D., Xilong Zhang, M.D., Dipe Medicino, M.D., Rui Chen, M.D., Luciano F. Dragot, M.D., Ph.D., Zhihong Liu, M.D., Ph.D., Guofeng Chen, M.D., Beidong Du, M.D., Nigel MacArdle, M.D., Subhash Muthukrishna, M.D., Ph.D., Manoj Tripathi, M.D., Laurent Billaud, M.Sc., Xiang Li, M.S., Rafael Salazar-Filho, M.D., Ferran Barbe, M.D., Susan Redline, M.D., M.P.H., Jiguang Wang, M.D., Ph.D., Hisanori Azuma, M.D., Ph.D., Bruce Neal, M.D., Ph.D., David P. White, M.D., Ron R. Grunstein, M.D., Ph.D., Nanrui Zhong, M.D., and Craig S. Anderson, M.D., Ph.D., for the SAVE Investigators and Coordinators

Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sceur, M.D., Ph.D., Henry T. Gehonson, M.P.H., Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippen, Ph.D., Monica Basling, M.A., Mary Fenig, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michele L. Sevier, M.S.P.H., Ph.D., Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Oliver Lack, M.B., B.Ch., for the LEAP Study Team

Reasons for wrong (or incomplete) answers:

• Lack of fundamental biological understanding

• Inadequate research tools – inappropriate outcome measures

• Lack of unbiased efficacy data

• Limitations of efficacy data:
  • lack of external validity,
  • heterogeneity of treatment effect
The Range of Research Questions about Interventions – (new and old)

- How does it work?
- Do we know how to study it in people?
- Is it beneficial?
- How effective is it in real world settings?

Basic Science

Translational Research

Efficacy Studies

Effectiveness Research
Questioning conventional wisdom

• Understand potential intervention(s) and what doing nothing means

• Understand the measures of effectiveness

• Consider risk and benefit
The Range of Research Questions about interventions – (new and old)

- **Basic Science**: How does it work?
- **Translational Research**: Do we know how to study it in people?
- **Efficacy Studies**: Is it beneficial?
- **Effectiveness Research**: How effective is it in real world settings?
What is a Practical or Pragmatic Trial?

• 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, policy makers

Tunis S, Stryer D, Clancy C. JAMA 2003;290:1624-32
<table>
<thead>
<tr>
<th>Pragmatic</th>
<th>Explanatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad eligibility</td>
<td>Narrow eligibility</td>
</tr>
<tr>
<td>Flexible interventions</td>
<td>Strict instructions</td>
</tr>
<tr>
<td>Typical practitioners</td>
<td>Expert practitioners</td>
</tr>
<tr>
<td>No follow-up visits</td>
<td>Frequent follow-up visits</td>
</tr>
<tr>
<td>Objective clinical outcome</td>
<td>Surrogate outcomes</td>
</tr>
<tr>
<td>Usual compliance</td>
<td>Close monitoring</td>
</tr>
<tr>
<td>Intent-to-treat</td>
<td>ITT plus per protocol</td>
</tr>
</tbody>
</table>

Thorpe KE et al.  CMAJ 2009;180:E47
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 MacIntyre, 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-
Tools for EHR-Based Phenotyping

Created by the Collaboratory Phenotypes, Data Standards, and Data Quality Core

On this page, you will find a series of recommendations for collecting and querying data from electronic health records for patient characteristics and clinical features. These phenotype definition recommendations are intended to support the conduct of pragmatic clinical trials, as well as encourage standardized reporting of baseline characteristics of research populations in interventional and observational studies. Also included are resources for identifying additional phenotype definitions through literature search or other groups engaged in electronic phenotyping. Background information on the identification, evaluation, and implementation of phenotype definitions is available in the Living Textbook chapter.

Recommended Phenotype Definitions

Demographics
- Race/ethnicity
- Sex

Common Conditions
- Type 2 diabetes mellitus

Resources for Additional Phenotype Definitions
- Suggestions for Identifying Phenotype Definitions Used in Published Research
- Phenotypes Environmental Scan (survey of phenotype-related efforts)

Patient characteristics:

Multiple phenotype definitions:

Table 1 Project

Standardizing Phenotypes for the Table 1 Project

What is the Table 1 Project?

In a research publication, the baseline characteristics for a study population are conventionally reported in Table 1. The goal of the Table 1 Project is to identify important person characteristics and clinical features, along with explicit definitions and representations, for the reporting of baseline characteristics of research populations in interventional and observational studies. Interpreting a research result without an understanding of the population enrolled in the study is treacherous at best. Validated, reproducible, reliable, and generalizable fundamental patient characteristics could support:

- The submission of datasets from NIH-funded studies for archival and secondary use
- The submission of results from NIH-funded studies for archival, retrieval, and comparison purposes
- The standardized reporting of results from NIH-funded studies to ClinicalTrials.gov
- Better practices for describing research populations in publications submitted to medical journals
- The conduct of both multisite pragmatic clinical trials and observational studies
Risk and benefit
Limitations of Applying Summary Results of Clinical Trials to Individual Patients
The Need for Risk Stratification

David M. Kent, MD, MS; Rodney A. Hayward, MD
A. Population Distribution of Baseline Outcome Risk

Patients enrolled in clinical trials often have greatly different baseline risks for the outcome of interest. The risk distribution is often skewed; a relatively small group of high-risk patients with multiple risk factors account for a large number of the outcomes and the mean risk might be considerably higher than the risk in the typical (median) patient.

B. Outcome Risk With Treatment

A constant relative risk reduction (25% in this case) leads to increasing benefits as baseline risk increases; treatment and control outcome rates progressively diverge at higher baseline risks. When a therapy is associated with even a small amount of treatment-related harm, low-risk patients are unlikely to benefit at all. When the treatment-related risk of harm is 1%, patients with baseline risks lower than 4% have net harm from the therapy. The average baseline risk of the enrolled patients will determine whether the trial’s summary results are positive overall. But the overall results may not reflect the trade-offs between the risks and benefits of many individual patients in the trial.

C. Relative Risk Reduction

There is considerable variation in relative risk reduction given the assumptions of risks and benefits shown in B. The overall trial results (average baseline risk) indicate a 12.5% relative risk reduction but the typical patient (median baseline risk) does not benefit at all. One-variable-at-a-time subgroup analyses typically compare groups of patients that do not differ dramatically from the average risk (a 2-fold difference in risk), because the treatment effect differences may not be statistically significant, which can misleadingly imply a consistent treatment effect. Using multivariate risk indices compares patients across a broader range of baseline risks, exposing larger differences in the relative treatment effect, which are often clinically and statistically significant.
Heterogeneity of treatment effect (HTE)

The TACT Trial
TACT: Primary Endpoint

Kaplan-Meier Estimates of the Primary Composite Endpoint
EDTA Chelation Therapy vs. Placebo

Subset of Patients with Diabetes: Hx, Med Use or Baseline Glucose ≥ 126

**EDTA Chelation**
**Placebo**

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Months since randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDTA Chelation</td>
<td>Placebo</td>
</tr>
<tr>
<td>322</td>
<td>286</td>
</tr>
<tr>
<td>262</td>
<td>243</td>
</tr>
<tr>
<td>217</td>
<td>198</td>
</tr>
<tr>
<td>187</td>
<td>177</td>
</tr>
<tr>
<td>157</td>
<td>126</td>
</tr>
<tr>
<td>101</td>
<td>74</td>
</tr>
</tbody>
</table>

Hazard Ratio: 0.59, 95% CI: 0.44, 0.79, P-value (log-rank): .0002

Subset of Patients without Diabetes (Hx, Med Use or Baseline Glucose ≥ 126)

**EDTA Chelation**
**Placebo**

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Months since randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDTA Chelation</td>
<td>Placebo</td>
</tr>
<tr>
<td>517</td>
<td>474</td>
</tr>
<tr>
<td>441</td>
<td>407</td>
</tr>
<tr>
<td>371</td>
<td>339</td>
</tr>
<tr>
<td>320</td>
<td>299</td>
</tr>
<tr>
<td>268</td>
<td>232</td>
</tr>
<tr>
<td>155</td>
<td>115</td>
</tr>
</tbody>
</table>

Hazard Ratio: 1.02, 95% CI: 0.81, 1.28, P-value (log-rank): .8768

**Kaplan-Meier** Estimates of the Primary Composite Endpoint

**EDTA Chelation**
**Placebo**

**Diabetes Patients (633)**

**No Diabetes (1075)**

THE VISION OF PRESIDENT OBAMA

“My hope is that this becomes the foundation, the architecture, whereby in 10 years from now we can look back and say that we have revolutionized medicine.”

- PRESIDENT BARACK OBAMA
Building a Cohort of 1,000,000 Volunteers
## Estimated disease incidence and prevalence in one million people

<table>
<thead>
<tr>
<th>Disease</th>
<th>Expected prevalent cases</th>
<th>Incident cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>5 years</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>135,658</td>
<td>40,411</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>73,723</td>
<td>21,315</td>
</tr>
<tr>
<td>Asthma</td>
<td>62,149</td>
<td>17,292</td>
</tr>
<tr>
<td>COPD</td>
<td>48,728</td>
<td>15,396</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>39,273</td>
<td>14,981</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>33,426</td>
<td>4,161</td>
</tr>
<tr>
<td>Breast cancer (female)</td>
<td>20,470</td>
<td>12,068</td>
</tr>
<tr>
<td>Stroke</td>
<td>16,016</td>
<td>8,969</td>
</tr>
<tr>
<td>Lupus</td>
<td>14,659</td>
<td>3,283</td>
</tr>
<tr>
<td>Dementia</td>
<td>13,373</td>
<td>7,028</td>
</tr>
<tr>
<td>ADHD</td>
<td>13,039</td>
<td>7,213</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>9,407</td>
<td>3,745</td>
</tr>
</tbody>
</table>
PMI RESEARCH PROGRAMS AT NIH

• **PMI for Oncology:** Apply precision medicine to cancer
  • Use NCI clinical trials as models
  • Identify new cancer subtypes, targets
  • Test precision therapies, with private sector partners

• **PMI Cohort Program:**
  • Generate knowledge base to move precision medicine into the full range of health and disease
  • Large longitudinal cohort donating data from self-report, physicals, biospecimens, medical records, technological and geographic sources
THE PRECISION MEDICINE INITIATIVE® COHORT

• One million or more volunteers, reflecting the broad diversity of the U.S.

• Opportunities for volunteers to provide data on an ongoing basis

• Data shared freely and fast to inform a broad variety of research studies
A TRANSFORMATIONAL APPROACH TO DIVERSITY

Reflecting the country’s rich diversity to produce meaningful health outcomes for historically underrepresented communities.
PMI Core Values

1. Participation is open to interested individuals
2. Participants are partners in all phases of the cohort program
3. Participants have access to study information and data about themselves
4. Data can be accessed broadly for research purposes
5. Adherence to the PMI privacy principles and forthcoming security framework
6. PMI is a catalyst for progressive research programs and policies
Initial Core Data Set

- Centrally collected and stored in a Coordinating Center
- Align with other data sets when possible
- Leverage existing data standards and common data models when possible

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Data Provided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self report measures</td>
<td>Diet, substance use, self-report of disease and symptoms (e.g., cognitive or mood assessment)</td>
</tr>
<tr>
<td>Baseline health exam</td>
<td>Vitals (e.g., pulse, blood pressure, height, weight), medical history, physical exam</td>
</tr>
<tr>
<td>Structured clinical data (EHR)</td>
<td>ICD and CPT codes, medication history, select laboratory results, vitals, encounter records</td>
</tr>
<tr>
<td>Biospecimens</td>
<td>Blood sample</td>
</tr>
<tr>
<td>mHealth data</td>
<td>Passively-collected data (e.g., location, movement, social connections) from smartphones, wearable sensor data (activity, hours and quality of sleep, time sedentary).</td>
</tr>
</tbody>
</table>
Building evidence is serious business

Take on the hard questions