Current issues in device development and approval – industry perspective

Workshop on Quality Risk Management: Understanding What Matters

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Cartoon deriding chronic disease epidemiology, for randomly generating fears by investigating seemingly unrelated risk factors and diseases
This cartoon contains a grain of truth: observational research is at its methodological best in discovering unexpected adverse effects.

Lancet 2004; 363: 1728–31
What is evidence?

Sharon-Lise T. Normand\textsuperscript{a,b,*\dagger} and Barbara J. McNeil\textsuperscript{a,c}

Table I. MedCAC process of evaluation.

1. Overview: What evidence exists that a new medical item or service is effective and likely to improve health outcomes of Medicare beneficiaries? The quality of the evidence from different sources will vary, and the committee should weigh the evidence according to its quality.

2. Outcomes evaluated: How, compared to alternative or standard management approaches for the condition under review, does the intervention affect: quality of life; morbidity; mortality; diagnostic accuracy; and other health outcomes as appropriate, such as re-hospitalizations.

3. Quality of evidence: Determine whether the scientific evidence is of adequate quality to draw conclusions about the effectiveness of the intervention in routine clinical use in the population of Medicare beneficiaries. This involves the following two questions:

   (a) How close are the effects measured in the study to their true value(s)? The degree to which the study result differs from the underlying truth is composed of two factors: chance and bias.

   (b) How applicable are the results to the Medicare population, in the settings in which they received care? The studies are often conducted in settings that differ from those in which the typical Medicare beneficiary receives care.

4. Size of health effect and net health outcomes: Establish how the effectiveness of the new intervention compares to the effectiveness of established services and medical interventions. Is there a net health benefit; does the magnitude of beneficial health effect outweigh the adverse health effects.
What is evidence?

Sharon-Lise T. Normand and Barbara J. McNeil

1. Overview: What is the condition or intervention of interest? What is the evidence from different sources? What is the evidence according to its quality?

2. Outcomes evaluation: What are the outcomes that matter? What is the diagnostic accuracy?

3. Quality of evidence: What is the evidence of adequate quality to draw clinical conclusions about the effectiveness of Medicare beneficiary receives care?

(a) How close are the study results to the target population? The degree to which the two factors: chance and bias are value(s)?

(b) How close are the results to the Medicare population, in the settings in which they received care? The studies are often conducted in settings that differ from those in which the typical Medicare beneficiary receives care.

4. Size of health effect and net health outcomes: Establish how the effectiveness of the new intervention compares to the effectiveness of established services and medical interventions. Is there a net health benefit? Does the magnitude of beneficial health effect outweigh the adverse health effects?
Current Demands for Clinical Evidence (1)

• Interest in effectiveness over efficacy
  – Healthcare value

• Keeping pace with technology compels more than head-to-head and time-to-time focus
  – Need for timely and dynamic evidence in practice
  – Real-time data analysis
  – Real time learning

• More continuity between fragmented studies
  – Better coordination, efficiency, longitudinal follow-up

Adapted from “Learning What Works,” IOM, 2011
Current Demands for Clinical Evidence (2)

• Comparison of two or more practical alternatives rather than placebo alone
  – Comparative effectiveness research (CER)

• Focus on the unique patient rather than the average population effect
  – Patient-centered outcomes research (PCOR)

• Expanded analysis
  – Systematic reviews
  – Innovative research strategies
  – Clinical registries
  – Coverage with Evidence Development

Adapted from “Learning What Works,” IOM, 2011
Trends Transforming Clinical Research

EVIDENCE
COSTS

PAST
+15%
PRESENT
FUTURE
Trends Transforming Clinical Research

Cost of satisfying Global Evidence Demand is growing at an unsustainable rate; MDT Total ~ $400M/year

EVIDENCE demanded by more stakeholders (hospital administrators, etc.) in more geographies for more products

PAST

PRESENT +15%

FUTURE
EVIDENCE COSTS

- EVIDENCE demanded by more stakeholders (hospital administrators, etc.)
- in more geographies for more products with more focus upon economic value approaching total product lifecycle for even more stakeholders (global payers, patients, public)

Cost of satisfying Global Evidence Demand is growing at an unsustainable rate; MDT Total ~ $400M/year

Increasingly complex Randomized Clinical Trials with more fields and longer follow-up coupled with heightened demand for post-market data could perpetuate rapid cost growth

Trends Transforming Clinical Research
Trends Transforming Clinical Research

**EVIDENCE COSTS**

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**PAST**

Cost of satisfying Global Evidence Demand is growing at an unsustainable rate; MDT Total ~ $400M/year

**PRESENT**

Increasingly complex Randomized Clinical Trials with more fields and longer follow-up coupled with heightened demand for post-market data could perpetuate rapid cost growth

**FUTURE**

Learning Health Systems with:
(a) broad adoption and advancement of Digital Clinical Records (EHR) 
(b) concurrent incorporation of Large Simple Trials & Observational Registries

... present an opportunity to bend the evidence cost curve!
Clinical Practice & Research Infrastructure Evolution

**PLATFORM**

**PAST**
- Practice
  - Paper Records
- Clinical Research
  - Paper Case Report Form Studies

**PRESENT**
- EMR
- Electronic Data Entry Studies

**OWNERSHIP**

**Practice**
- Practitioners
- Practitioners, Health Plans, Academia

**Clinical Research**
- Academia/Industry

- **Practice databases** are optimized for internal validity and patient-centric care
- **Research databases** are optimized for external validity and general inference

Control and Dissemination of data is limited by owners, restricting development of a learning health care system
## Transformation of Clinical Evidence Generation

<table>
<thead>
<tr>
<th>Secular Changes</th>
<th>Past</th>
<th>Present</th>
<th>Future</th>
<th>Desired Future</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes</strong></td>
<td>Placebo Control</td>
<td>Comparative Effectiveness</td>
<td>Cost-Effectiveness &amp; Surveillance</td>
<td>Economic Value</td>
</tr>
<tr>
<td><strong>Structure &amp; Methods</strong></td>
<td>Isolated &amp; Confounded Observational Clinical Trials</td>
<td>Complex, Consolidated &amp; Randomized Clinical Trials</td>
<td>Digital Hospital Clinical Records; Systematic Reviews &amp; Controlled Observational Registries</td>
<td></td>
</tr>
<tr>
<td><strong>Scope</strong></td>
<td>Product Performance</td>
<td>Patient Outcomes: Case Studies/Series</td>
<td>Population Outcomes: Evidence-Based Medicine &amp; Large Simple Trials</td>
<td></td>
</tr>
<tr>
<td><strong>Hypothesis</strong></td>
<td>Single Hypothesis / Static Answer</td>
<td>Continuous Update / Bayesian Learning Health System</td>
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</tbody>
</table>
The Sentinel Initiative

- FDA effort to create a national integrated (linked) electronic surveillance system that to monitor product safety continuously, pro-actively, and in real-time as a complement to existing systems.

- Will gather clinical and administrative data held by existing health-information holders
  - EHR Systems
  - Administrative and Insurance Claims Databases
  - Registries

- Data will be managed by its owners
  - Health data kept behind existing privacy firewalls
  - Queries would be sent to the participating data holders
  - Data holders would send summary results to FDA

- Clinical outcomes oriented
  - Focused on following exposure cohorts for outcomes of interest
  - Not focused on events such as out of box, design issues or mechanical failures

- Currently largely drug-focused.
  - Incorporation of UDIs into health-related data sources will expand Sentinel capabilities to conduct active device surveillance
FDA Medical Device Epidemiology Network (MDEpiNet) Initiative

✓ To develop infrastructure and innovative methodological approaches for conducting robust studies to improve medical device safety and effectiveness understanding throughout the device life cycle.
RECENT GUIDANCE FOR PIVOTAL STUDIES

Design Considerations for Pivotal Clinical Investigations for Medical Devices

Guidance for Industry, Clinical Investigators, Institutional Review Boards and Food and Drug Administration Staff

Document issued on: November 7, 2013
The draft of this document was issued on August 15, 2011.

For questions regarding this document that relate to devices regulated by CDRH, contact Gregory Campbell, PhD at (301) 796-5750 or by email at greg.campbell@fda.hhs.gov, if desired.

For questions regarding this document that relate to devices regulated by CBER, contact Stephen Ripley at 301-827-6210.

3 Regulatory Framework for Level of Evidence and Study Design

3.1 The Statutory Standard for Approval of a PMA: Reasonable Assurance of Safety and Effectiveness

3.2 Valid Scientific Evidence

3.3 Benefit-Risk Assessment

3.4 Clinical Study Level of Evidence and Regulation

3.5 The Least Burdensome Concept and Principles of Study Design

3.6 Approval of an Investigational Device Exemption
Why did observational studies get it “wrong”? (HRT and CHD for postmenopausal women)

- Popular theory: residual confounding
  - insufficient adjustment for lifestyle and socioeconomic indicators
  - Corollary: causal inference from observational data is a hopeless undertaking

- An alternative: Observational and randomized studies asked different questions
Exception: adjustment for baseline confounders

- Observational studies need adjustment for baseline confounders
- Randomized trials do not
  - At least when they are large
- But, other than that, analysis should be identical
  - Both observational and randomized studies need adjustment for time-varying confounders
TABLE 2. TOTAL NUMBER OF SUBJECTS AND SUMMARY ESTIMATES FOR THE EFFECT OF FIVE INTERVENTIONS ACCORDING TO THE TYPE OF RESEARCH DESIGN.

<table>
<thead>
<tr>
<th>CLINICAL TOPIC</th>
<th>TYPE OF STUDY</th>
<th>META-ANALYSIS*</th>
<th>TOTAL NO. OF SUBJECTS</th>
<th>SUMMARY ESTIMATE (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacille Calmette–Guérin vaccine and tuberculosis</td>
<td>13 Randomized, controlled</td>
<td>Colditz et al.¹⁴</td>
<td>359,922</td>
<td>0.49 (0.34–0.70)</td>
</tr>
<tr>
<td></td>
<td>10 Case–control</td>
<td>Colditz et al.¹⁴</td>
<td>6,511</td>
<td>0.50 (0.39–0.65)</td>
</tr>
<tr>
<td>Mammography and mortality from breast cancer</td>
<td>8 Randomized, controlled</td>
<td>Kerlikowske et al.¹⁵</td>
<td>429,043</td>
<td>0.79 (0.71–0.88)</td>
</tr>
<tr>
<td></td>
<td>4 Case–control</td>
<td>Kerlikowske et al.¹⁵</td>
<td>132,456</td>
<td>0.61 (0.49–0.77)</td>
</tr>
<tr>
<td>Cholesterol levels and death due to trauma</td>
<td>6 Randomized, controlled</td>
<td>Cummings and Psaty¹⁶</td>
<td>36,910</td>
<td>1.42 (0.94–2.15)</td>
</tr>
<tr>
<td></td>
<td>14 Cohort</td>
<td>Jacobs et al.¹⁷</td>
<td>9,377</td>
<td>1.40 (1.14–1.66)</td>
</tr>
<tr>
<td>Treatment of hypertension and stroke</td>
<td>14 Randomized, controlled</td>
<td>Collins et al.¹⁸</td>
<td>36,894</td>
<td>0.58 (0.50–0.67)</td>
</tr>
<tr>
<td></td>
<td>7 Cohort</td>
<td>MacMahon et al.¹³</td>
<td>405,511</td>
<td>0.62 (0.60–0.65)</td>
</tr>
<tr>
<td>Treatment of hypertension and coronary heart disease</td>
<td>14 Randomized, controlled</td>
<td>Collins et al.¹⁸</td>
<td>36,894</td>
<td>0.86 (0.78–0.96)</td>
</tr>
<tr>
<td></td>
<td>9 Cohort</td>
<td>MacMahon et al.¹³</td>
<td>418,343</td>
<td>0.77 (0.75–0.80)</td>
</tr>
</tbody>
</table>

*Meta-analyses that included either randomized, controlled trials or observational studies are cited.
†CI denotes confidence interval.

Conclusions  The results of well-designed observational studies (with either a cohort or a case–control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic. (N Engl J Med 2000;342:1887-92.)
Drug-Eluting or Bare-Metal Stents for Acute Myocardial Infarction


From Brigham and Women’s Hospital (L.M., P.G., M.R.V., Z.Z.), the Harvard Clinical Research Institute (L.M.), Harvard Medical School (L.M., T.S.S., R.E.W., K.Z., A.L., S.L.T.N.), and the Harvard School of Public Health (S.L.T.N.—all in Boston. Address reprint requests to Dr. Mauri at Brigham and Women’s Hospital, 75 Francis St., Boston, MA 02115, or at lmauril@partners.org.


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Figure 1 (facing page). Clinical Outcomes after Stenting for Myocardial Infarction.

The graphs show the cumulative 2-year incidence of death (Panel A), myocardial infarction (Panel B), and repeat target-vessel revascularization (Panel C) in the matched sample of patients receiving bare-metal or drug-eluting stents. Error bars are 95% confidence intervals. P values were calculated by the paired t test.

• Mass DPH PCI Database
• 7217 patients: AMI, 4/03 – 9/04
• DES-4016, BMS-3201
• Propensity score matching
• 2-year mortality, repeat revascularization, recurrent MI
Clinical Practice & Research Infrastructure Evolution

**PLATFORM**

**PAST**
- Practice: Paper Records
- Clinical Research: Paper Case Report Form Studies

**PRESENT**
- EMR
  - Electronic Data Entry Studies

**FUTURE**
- Single Electronic Health Record & Research Platform (5-15 years, variable roll-out)

**OWNERSHIP**

**PRACTICE**
- Practitioners

**CLINICAL RESEARCH**
- Industry

**FUTURE**
- Shared data through open transparency

Practitioners, Health Plans, Academia
“In a world of rigorous observational studies, expending effort to argue that one methodology is superior to another (e.g., RCTs versus observational studies) is counter-productive. The importance lies not in arguing about which method is better than the other, but what can be learned about disease activity and therapy from each type of study.”

*Nat Clin Pract Rheumatol* 2006;2:286
CONCLUSIONS

1. Well-conducted observational studies can provide valid results, similar to randomized trials

2. Novel methods of observational studies (e.g., propensity scores) are useful but do not “work miracles”

3. Scientific rigor is based on pertinent research questions, suitable study designs, high-quality data, and appropriate statistical analyses
Thank you!

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