Bridging Research and Policy: The Ontario Drug Policy Research Network (ODPRN)

October 2012
Objectives

• To review the experience of a recent program of research that blends academic research with drug policy

• To outline the benefits and challenges of working with academics and policy-makers to produce valid, useful research to impact public policy
Perceptions

That wasn't chicken.
Mock-up websites presented to consumers with different pictures

Author Photo Results

believable

trustworthy

competent

credible

unbiased

expert

COMPOSITE

Fogg, BJ, et al, What makes Websites Credible?
Stanford Persuasive Technology Lab
Numeric Literacy  
(Horton and Switzer, NEJM, 2005)

- Sophistication of statistical methods or articles published in the NEJM has been increasing over time.

- Some statistical tests
  - T-tests
  - Contingency tables
  - Non-parametric tests
  - Epidemiologic statistics
  - Pearson’s correlation
  - Nonparametric correlation (e.g. spearman’s correlation)
  - Simple linear regression
  - Analysis of variance
  - Transformations

- Only 21% of articles published between January 2004 – June 2005 would be considered accessible by those with basic training in biostatistics.
Numerical Approaches

- Lacy et al, Am J Cardiol, 2001
  - Assessed 400 health professionals for their willingness to prescribe based on different measures for reporting the same likelihoods.

FIGURE 1. First choice drug ranked by likelihood to prescribe based on outcome descriptors. Distribution of respondents’ first choice drug selection based on identical mortality data presented in different outcome terms. Absolute Risk = absolute risk reduction; NNT = number of patients needed to be treated to prevent 1 death; Relative Risk = relative risk reduction.
The Trouble with Research
Example: H. pylori eradication and non-ulcer dyspepsia

• McColl et al (NEJM, 1998)
  – Treatment (n=154): Omeprazole 20 mg bid + amoxicillin 500 mg tid + 400 mg metronidazole tid x 2 weeks
  – Comparison (n=154): omeprazole 20 mg bid x 2 weeks
  – Symptom resolution at 1 year: Tx = 21% vs. Comparison = 7% (p<0.001)

• Blum et al (NEJM, 1998)
  – Treatment (n=164): Omeprazole 20 mg bid + amoxicillin 1000 mg bid + 500 mg clarithromycin bid x 1 week
  – Comparison (n=164): omeprazole 20 mg bid x 1 week
  – Symptom resolution at 1 year: Tx = 27% vs. Comparison = 21% (p=0.17)
Belief vs. Truth

Count the black dots! :o)
Scientists: How Do We Perceive Ourselves?

"I'm sorry. We're looking for a computer geek and judging from your résumé, you're just a geek."
Perceptions of Scientists

- National Science Foundation (NSF) 2001 Survey
  - 96%: scientists are helping to solve challenging problems
  - 86%: scientific researchers are dedicated people who work for the good of humanity
  - 80%: would be happy if their son/daughter became a scientist
  - 29%: scientists have few interests outside their work
  - 25%: scientists are odd/peculiar people
ESF World Conferences

ESF-ORI First World Conference on RESEARCH INTEGRITY: FOSTERING RESPONSIBLE RESEARCH
A Portuguese European Union Presidency and European Commission Event Initiated and Organized by the European Science Foundation & the US Office of Research Integrity

The European Science Foundation (ESF) and the US Department of Health and Human Services Office of Research Integrity (ORI) have organized the first World Conference on Research Integrity in Lisbon, Portugal.


RESEARCH INTEGRITY
World Conference
Outcome & Follow-Up

Stem-cell fraudster ‘is working in Thailand’

Disgraced South Korean cloning scientist Woo Suk Hwang has set up a research base in Thailand, according to reports from South Korea last week. Science-policy officials in South Korea say they are worried about the reports, as they know nothing about this.

Se PI Park, a fertility expert at Cheju National University in South Korea, says Hwang and ten colleagues have gone to Thailand to carry out cloning research.

Woo Suk Hwang is said to have moved to Thailand to continue cloning. He is accused of fabricating data in his experiments.

Science editor Pradon Chatikavanij, who is in charge of drafting the regulations, is in charge of the Thai government's science editor. He says that the Thai government has not yet made any decisions on this matter.
Research: Why Do We Do It?

The ‘End Game’ of Research

- To advance ‘science’ / improve patient care
- Publication
- Promotion
- Impact clinical practice
- Impact public policy
- Satisfy personal curiosity
How Good Are We At It?

- David Hamilton (Science 1990)
  - Institute for Scientific Information (ISI) report
    - ISI covered the top 4,500 science and social science journals out of 74,000 scientific titles (i.e. < 10%)
    - 55% of articles published between 1981 and 1985 in journals indexed by the ISI received no citations within 5 years following publication
  - MIT biology professor Robert Young
    - If the bottom 80% of the literature "just vanished," he says, "I doubt the scientific enterprise would suffer."
How Do Policy-Makers Perceive Researchers?

**OFF THE MARK** by Mark Parisi

NEVERMIND, YOU CAN GO... WE DON'T WANT ANY OF YOUR DNA... SEE YA... BYE, NOW...

RODNEY COULDN'T DECIDE IF HE SHOULD FEEL RELIEVED OR INSULTED.
# Conflicting Perspectives of Researchers and Policy-makers

<table>
<thead>
<tr>
<th></th>
<th>Researchers</th>
<th>Policy Makers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End-Goal(s)</strong></td>
<td>Publication Promotion</td>
<td>Policy Decisions Avoid media Enhance Public Image</td>
</tr>
<tr>
<td><strong>Research Question</strong></td>
<td>Well-Defined</td>
<td>Obscure</td>
</tr>
<tr>
<td><strong>Timeliness</strong></td>
<td>Research takes time – months to years</td>
<td>‘NOW’: days / weeks</td>
</tr>
<tr>
<td><strong>Level of precision</strong></td>
<td>As precise as possible</td>
<td>‘Ballpark’</td>
</tr>
<tr>
<td><strong>Metrics of Value</strong></td>
<td>‘Academic’: relative risks</td>
<td>‘Pragmatic’: absolute risks, temporal trends</td>
</tr>
<tr>
<td><strong>Level of Complexity</strong></td>
<td>Maximal</td>
<td>Minimal</td>
</tr>
</tbody>
</table>
Where Does Evidence Fit Into the Decision-Making Process?

Evidence → BELIEFS → BEHAVIOUR

BELIEFS:
- Personal Values / Experience
- Societal Values
- ‘Other’ Factors

BELIEFS is influenced by evidence, personal values/experience, societal values, and other factors, leading to BEHAVIOUR.
Integrating Health Services Research into Health Policy

Have a seat Kermit. What I'm about to tell you might come as big shock...
Drug Policy Research

- Any research that affects beliefs and behaviours of policy-makers

  ➢ Key Characteristics:
    - Timely
    - Accessible, easily interpretable
Ontario Health Policy Research

• Ontario’s Healthcare Data
  – Ontario has universal healthcare coverage
  – Databases record healthcare transactions for administrative purposes
  – Data related to healthcare stored in separate but linkable datasets: physician claims, hospitalizations, drug utilization, emergency department visits

• Institute for Clinical Evaluative Sciences
  – ICES is a non-profit research organization established in 1992
  – Funded by the Ontario Ministry of Health and granting agencies
  – Over 150 faculty and staff
  – Stores many of Ontario’s healthcare administrative databases for research purposes: databases are linked
  – Over 100 research studies being undertaken at any point in time
# Hierarchy of Evidence

<table>
<thead>
<tr>
<th>Level of Evidence</th>
<th>Study Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>RCTs</td>
</tr>
<tr>
<td>Level 2</td>
<td>Cohort Studies</td>
</tr>
<tr>
<td>Level 3</td>
<td>Case-Control Studies</td>
</tr>
<tr>
<td>Level 4</td>
<td>Case Series</td>
</tr>
<tr>
<td>Level 5</td>
<td>Expert Opinion</td>
</tr>
</tbody>
</table>

Oxford Centre for Evidence-Based Medicine, 2002
The Dilemma

• Clinical Trials
  – Good internal validity but poor external validity given the typically strict inclusion/exclusion criteria

• Observational Studies
  – Reflects ‘real world’ but subject to selection bias

Validity Generalizability
Challenges with Using Administrative Databases to Answer Clinical Questions

- Non-randomized nature of the data

- Breadth and depth of the database
  - Population covered (rare events)
  - Number of clinical and demographic variables available

- Quality of the database
  - Coding validity
Traditional Methods in Observational Epidemiology

• Who is being treated?
  – Cross-sectional design

• What are the ‘real world’ risks and benefits of the therapy?
  – Cohort study
  – Case-control study
Approaches to Maximizing Internal Validity in Observational Research

• Group Selection
  – ‘Smart’ Comparator Group Selection
  – Matching Strategies
    • Selected variables: hard matching, propensity score matching
    • Data-driven variable selection: High-dimensional propensity-score matching
  – Restriction

• Statistical Adjustment

• Supplemental Analyses
  – Tracer Analyses: exposure and outcome
  – Sensitivity Analyses
Consequence of Maximizing Internal Validity of a Study

• Generalizability often gets compromised as one tries to maximize internal validity
• Communicating findings often becomes more complex
"Are you sure this is the only way the nicotine patch will work for you?!"
ODPRN: Objectives and Overview

- **Primary Objective**
  - Provide **high quality**, relevant drug research to OPDP in a **timely manner** on an as-needed basis

- **Secondary Objective**
  - To engage leading clinical researchers across Ontario interested in drug policy research

- **Types of Research Supported**
  - Observational epidemiology using databases at ICES
  - Basic pharmacoeconomic / drug policy research

- **Outputs**
  - OPDP Reports
  - Scientific Publications
  - And much more....
ODPRN Core Principles

• Scientific Rigor / Quality
  ➢ Leading clinical researchers from five medical schools across Ontario

• Timeliness
  ➢ Standardized data extraction and analysis algorithms
  ➢ Ready access to administrative data at ICES, with expedited project and ethics review
  ➢ Typical turn-around times of days / weeks

• Policy Relevance
  – Policy-makers generate questions and involved in research process

• Effective Communications
  ➢ Regular communication and feedback with policy-makers
  ➢ Simple, understandable research briefings
Current ODPRN Structure

- Rapid Response Unit (RRU)
  - Pharmaco-epi Program
  - Pharmaco-economics Program
- Core Academic Unit (CAU)
  - Student Training Program
- Knowledge Translation Unit (KTU)
- Ontario Public Drug Program (OPDP)
Example: Macrolides and Digoxin Drug Interactions

Figure 1: Decision Tree for Selection of Initial Study Design

Determine Study Design

Do you want to study changes in drug use or adherence over time?

Yes

Are you interested in whether an event changes drug use patterns over time?

Time Series Analysis

No

Adherence Study (See Figure 4)

No

Are there more than 2 exposure groups?

Yes

Cohort Study

No

Is matching required to obtain an unexposed cohort comparable to the exposed cohort?

Yes

Propensity-Matched Cohort Study (See Figure 3)

No

Cohort Study

No

Do you need a measure of absolute risk?

Yes

Is your study population well-defined, and are there potentially many controls which would be cumbersome to analyze OR Are you interested in a drug-drug interaction study?

No

Nested Case Control Study
ODPRN Project Prioritization and Examples

CAROL, SCHEDULE A STAFF MEETING.

WHAT’S THE TOPIC?

I PLAN TO FUSE SIX SIGMA WITH LEAN METHODS TO ELIMINATE THE GAP BETWEEN OUR STRATEGY AND OUR OBJECTIVES.

I’LL JUST SAY “WASTE OF TIME.”

© Scott Adams, Inc./Dist. by UFS, Inc.
Prioritization: “The Queue”

- Projects are added to the queue according to the following prioritization:

  - OPDP Projects (up to 70%)
  - Non-OPDP Projects (at least 30%)

  - Student Projects
    - Policy-Relevant Projects
    - Non-policy-Relevant Projects

  - Faculty Projects
    - Policy-Relevant Projects
    - Non-policy-Relevant Projects

Priority Level
Three Examples of ODPRN Projects

- Selected Examples
  - Potentially Inappropriate Opioid Analgesic Utilization
  - Thiazolidinediones and Adverse Cardiovascular Events
How are Opioids being Prescribed in Ontario?

• How has opioid prescribing changed in Ontario over the past 20 years?
• Has opioid-related mortality increased over this time?
• How has dosing of opioids changed over time?
• Are higher doses associated with risk of mortality?
• Where should educational interventions be targeted?
• Should certain prescribers be targeted?
4-fold increase in prescribing of oxycodone

2-fold increase in opioid-related deaths

Dhalla I et al, CMAJ, 2009
9-fold increase in oxycodone-related deaths

Before addition of OxyContin onto public drug formulary

After addition of OxyContin onto public drug formulary

Number of deaths per 1 000 000 per year

Dhalla I et al, CMAJ, 2009
One-third of people prescribed OxyContin receive doses that exceed clinical practice guidelines

Gomes T et al. Open Medicine 2011

![Bar chart showing the percentage of population receiving doses exceeding clinical practice guidelines over the years 2003 to 2008. The chart indicates a decrease from 33% in 2008 to 22% in 2004, with 33% in 2008 again.]

Legend:
- Long-acting oxycodone
- Transdermal fentanyl (no long-acting oxycodone)
- Other long-acting opioids (no long-acting oxycodone or fentanyl)
- Immediate-release single-agent therapy

Gomes T et al Open Medicine 2011
High-dose prescribing is associated with a 3-fold increase risk of opioid-related death

<table>
<thead>
<tr>
<th>Primary Analysis: Overlapping Opioid Prescriptions (Reference: 1 to 19 mg morphine equivalents)</th>
<th>Cases n/N</th>
<th>Controls n/N</th>
<th>Adjusted Odds Ratio* (95% CI†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥200mg</td>
<td>116/498</td>
<td>223/1714</td>
<td>2.88 (1.79 to 4.63)</td>
</tr>
<tr>
<td>100 to 199 mg</td>
<td>82/498</td>
<td>181/1714</td>
<td>2.04 (1.28 to 3.24)</td>
</tr>
<tr>
<td>50 to 99 mg</td>
<td>97/498</td>
<td>273/1714</td>
<td>1.92 (1.30 to 2.85)</td>
</tr>
<tr>
<td>20 to 49 mg</td>
<td>118/498</td>
<td>514/1714</td>
<td>1.32 (0.94 to 1.84)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Analysis: 120 Day Exposure Window (Reference: 1 to 19 mg morphine equivalents)</th>
<th>Cases n/N</th>
<th>Controls n/N</th>
<th>Adjusted Odds Ratio* (95% CI†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥200mg</td>
<td>557/781</td>
<td>1319/2804</td>
<td>2.24 (1.62 to 3.10)</td>
</tr>
<tr>
<td>100 to 199 mg</td>
<td>64/781</td>
<td>303/2804</td>
<td>1.47 (0.98 to 2.19)</td>
</tr>
<tr>
<td>50 to 99 mg</td>
<td>52/781</td>
<td>300/2804</td>
<td>1.31 (0.86 to 1.99)</td>
</tr>
<tr>
<td>20 to 49 mg</td>
<td>41/781</td>
<td>366/2804</td>
<td>0.93 (0.60 to 1.42)</td>
</tr>
</tbody>
</table>

FYIs vs. Actionables

I called the incontinence hotline...

They asked, "Can you hold please?"
Would targeted interventions work?

Should we Target Physicians?

Physicians prescribing high numbers of prescriptions tend to be male, older and have been practicing longer than those prescribing lower amounts of opioids.

Conclusions and Policy Implications

• Opioid prescriptions, the amount of opioid dispensed, and the proportion of people receiving high average daily doses of opioid analgesics has increased substantially in the past few years in Ontario

• 1 of every 114 of people receiving average daily doses that exceed current clinical guidelines died from opioid-related causes within 2 years

• The ‘Narcotics Strategy’ and related legislation has recently been passed, much of which has been informed by this research.
Adverse cardiovascular events during treatment with pioglitazone and rosiglitazone

• The TZDs rosiglitazone and pioglitazone are insulin-sensitizing agents that improve glycemic control and a variety of surrogate outcomes in patients with type 2 diabetes

• The primary mechanism by which these drugs improve glycemic control is through the stimulation of peroxisome proliferator-activated receptors (PPARs)

• PPARγ activation in the nephron increases the absorption of salt and water which can lead to fluid retention, weight gain and heart failure

• Recent evidence suggests that pioglitazone may carry lower risk of heart failure than rosiglitazone

• **Objective:**
  - To compare the risk of acute myocardial infarction, heart failure, and death in patients with type 2 diabetes treated with rosiglitazone and pioglitazone.

• **Retrospective cohort study (2002-2008):**
  - **Cohort:** Ontario residents aged 66 and older who started a TZD during the study period

• **Outcomes of interest:**
  - **Primary Outcome:** Composite of:
    - Hospitalization or ED visit for AMI
    - Hospitalization or ED Visit for Heart Failure
    - All-Cause mortality
  - **Secondary Outcomes:** Each of the above separately
Analysis

• Data were analyzed using time-to-event analyses using rosiglitazone as the reference

• Models were adjusted extensively for important demographic and clinical variables

• Sensitivity Analyses:
  o Dose-response analysis (high-dose vs. low-dose)
  o Excluding patients with heart failure or AMI in the ED who were not admitted to hospital
  o Removing censoring at 3 years of treatment
  o Terminating follow-up one year earlier (March 31, 2007)
## Results

<table>
<thead>
<tr>
<th></th>
<th>Events among pioglitazone patients (N=16,951)</th>
<th>Events among rosiglitazone patients (N=22,785)</th>
<th>Unadjusted hazard ratio (95% confidence interval)</th>
<th>Adjusted hazard ratio (95% confidence interval)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>895</td>
<td>1563</td>
<td>0.81 (0.74 to 0.87)</td>
<td>0.82 (0.76 to 0.90)</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Failure</td>
<td>461</td>
<td>869</td>
<td>0.75 (0.67 to 0.84)</td>
<td>0.77 (0.69 to 0.87)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>273</td>
<td>425</td>
<td>0.91 (0.78 to 1.06)</td>
<td>0.94 (0.81 to 1.10)</td>
</tr>
<tr>
<td>Death</td>
<td>377</td>
<td>645</td>
<td>0.82 (0.73 to 0.94)</td>
<td>0.86 (0.75 to 0.98)</td>
</tr>
</tbody>
</table>

*Juurlink et al. 2009. BMJ; 339:b2942*
Results

• Dose-response analysis (reference high-dose rosiglitazone):
  
  o Low-dose rosiglitazone: HR 0.94 (0.83-1.07)
  o Low-dose pioglitazone: HR 0.83 (0.71-0.98)
  o High-dose pioglitazone: HR 0.76 (0.66-0.88)

• Number Needed to Treat to Harm (NNTH) over a 1-year period:
  
  o Composite outcome: 93
  o Heart Failure: 120
  o Death: 267
Policy Implications

- Given the results of this study, and the fact that rosiglitazone doesn’t have a distinct clinical advantage over pioglitazone, continued use of rosiglitazone may not be justified.

- A paper published in JAMA in 2007 *(Lipscombe LL, Gomes T, Levesque LE et al.)* found an increased hazard of adverse cardiovascular events in TZD treated older Ontarians.

- ODB listings for pioglitazone and rosiglitazone were changed from General Benefit to the Exceptional Access Program as of June, 2009.
ODPRN Metrics

OUR CONSULTANT HAS BEEN MINING DATA ALL DAY.

THE RESULTS ARE QUITE SHOCKING.

ACCORDING TO THE DATA, SALES ARE ALWAYS HIGHEST WHEN I DO THIS...
ODPRN Metrics (KT)

• Policy
  – Number of policy reports to the OPDP
  – Number of OPDP-requested presentations
  – OPDP feedback on relevance to decision-making

• Academic
  – Number of publications
  – Impact factor of journals ODPRN publishes in
  – Number of presentations at academic conferences

• Media / Public
  – Number of citations
  – Number of media hits
ODPRN Productivity: 2008-2011

- 30 Publications since 2008 (19 released in 2011)
- 4 Publications currently In Press
- 7 Manuscripts submitted for peer review
- 9 manuscripts under development

Manuscripts under development
Academic Deliverables 2009-10

![Bar chart showing publications and IF (mean) for each quarter from Q1 2009 to Q1 2010.]
OPDP Deliverables 2009-10

![Graph showing the number of presentations and reports for each quarter from Q1 2009 to Q1 2010. The graph indicates a spike in presentations in Q3 2009 and a significant increase in reports from Q4 2009 to Q1 2010.](image-url)
Media Hits 2009-10

Q1 2009
Q2
Q3
Q4
Q1 2010

Q1 2009: 30
Q2: 5
Q3: 60
Q4: 25
Q1 2010: 30
OPDP Feedback on Selected ODPRN Studies

• PPIs & Plavix (CMAJ, 2009)
  – No, but high probability of use in the future, “has potential for future policy change, depending on whether additional studies confirm this interaction in broad range of patient populations”

• Drug Interactions between macrolides and digoxin causing digoxin toxicity (Clin Pharmacol Ther, 2009)
  – No, study not relevant to OPDP, “this would be most relevant at point of care”

• Pioglitazone vs rosiglitazone (BMJ, 2009)
  – Yes, “was key to de-listing the TZDs”
ODPRN Success and Challenges
Rapid Response Policy-related Research: Successes and Challenges

• **Successes:**
  - Deliverables 2008-2011:
    - > 40 publications
    - > 30 policy reports
    - > 20 presentations of findings
  - Efficient processes: SAS code algorithms and templates for analytical plans developed for various study methodologies

• **Challenges:**
  - Loosely-defined questions from policy-makers
  - Analytic resources: staffing models
  - Project prioritization
ODPRN Learnings: Bridging Research and Policy

• Building that Relationship
  – Setting aside personal interests
  – Communications: listening and understanding
  – All groups must be interested in the questions, processes, and outputs
  – Understanding and setting expectations

• Constructing the Right Team
  – Picking the right people
  – Scientific excellence coupled with ‘deliverables’ and ‘timelines’ in mind
  – Managing and fostering the team

• Having the Right Infrastructure and Processes
  – Leveraging the infrastructure and balancing the process: being responsive

• Delivering… the ‘Right’ Stuff
  – Leveraging the relationship to ensure end-product relevance to the target audience
  – Communications
"I think you should be more explicit here in step two."