The Path to Adaptive Drug Regulation:

A Regulator's Perspective on Balancing Benefits, Harms and Related Uncertainties in Practice

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Workshop 2: *Innovation and Adaptive Governance in Biotechnology*
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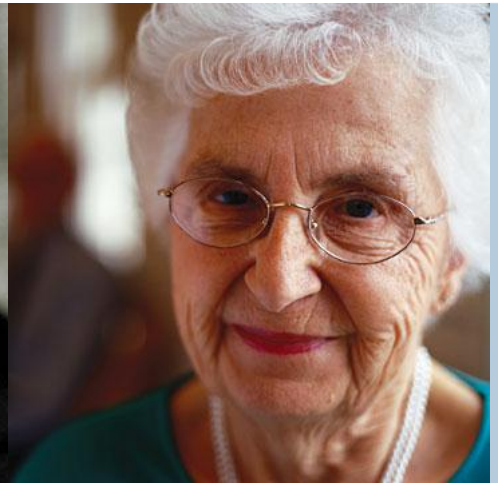

Canada

OBJECTIVES

1 Adaptive Licensing (AL): What is it?

2 Guiding Principles:

- "benefit-risk management" ⟶
- "benefit-harm-uncertainty management"

3 Practical Considerations:

- Health Canada experience

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ADAPTIVE LICENSING (AL): WHAT IS IT?
Different names, same ideas

EMA: staggered approval

FDA: progressive reduction of uncertainty

Health Canada: progressive licensing

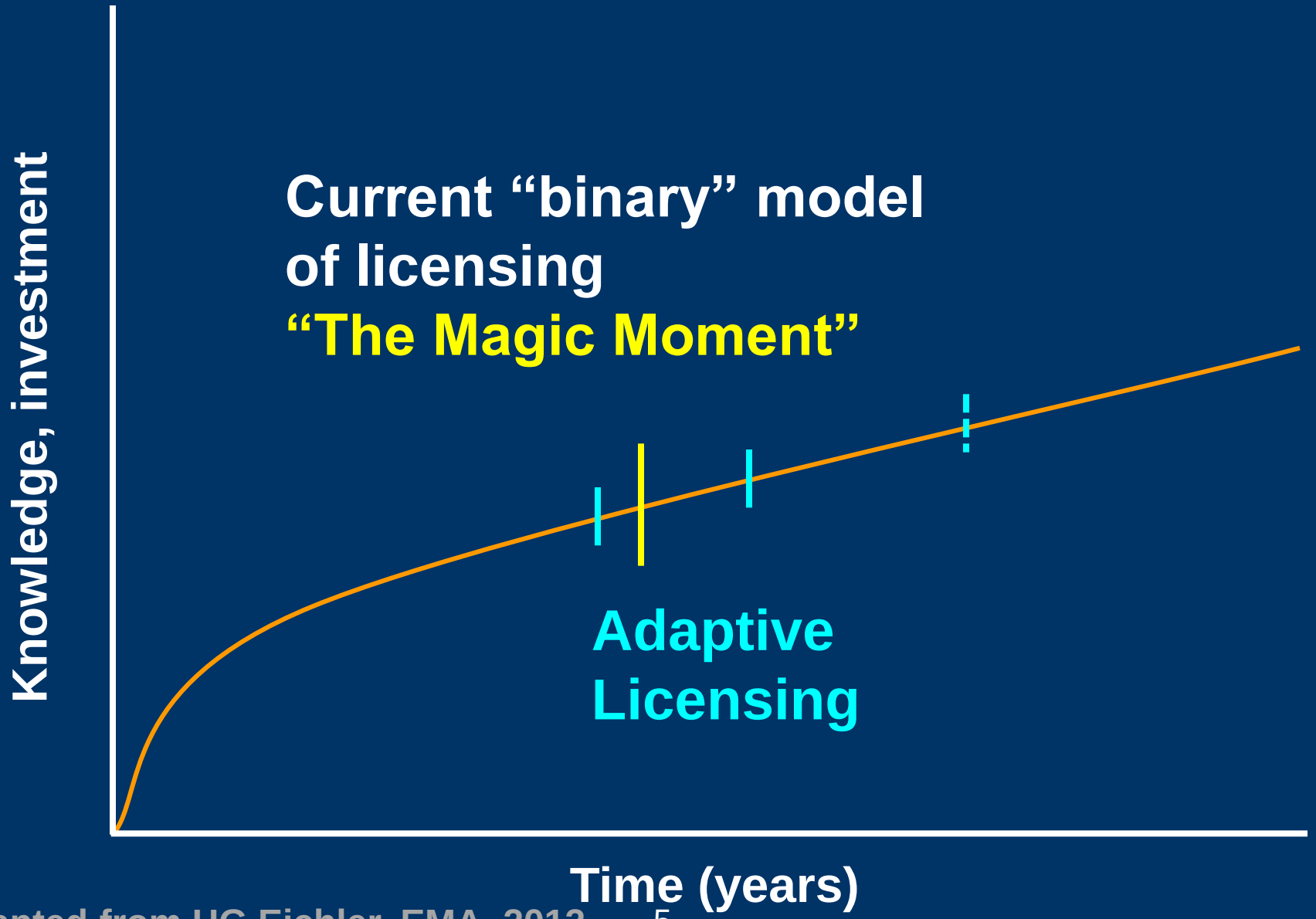
HSA Singapore: test bed for adaptive regulation

Payers (HTAi): managed entry

MIT/NEWDIGS: adaptive licensing project

From Hans-Georg Eichler, EMA, 2012

Adaptive licensing concepts evolve the drug development, regulatory model



Adapted from HG Eichler, EMA, 2012

Adaptive Licensing (AL): definition

AL is a prospectively planned, adaptive approach to regulation of drugs:

Through iterative phases of evidence gathering followed by regulatory evaluation and license adaptation, AL seeks to serve patients' needs by balancing:

- timely access; with
- management - including communication - of benefits and harms as understanding evolves.

Adapted from Hans-Georg Eichler, EMA, 2012

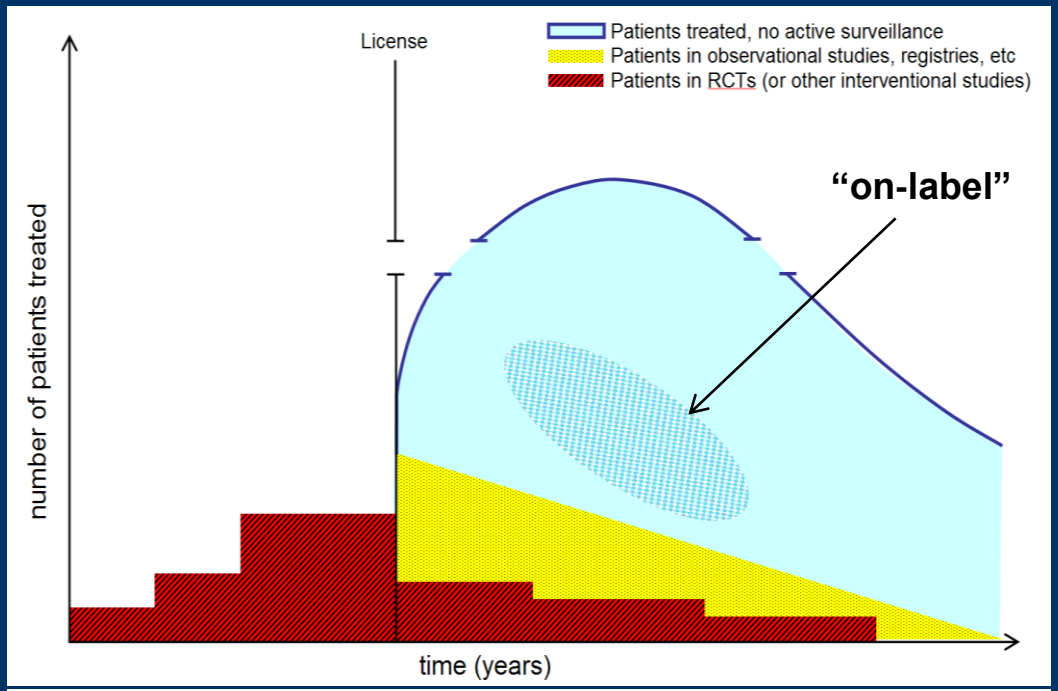
Adaptive Licensing (continued)

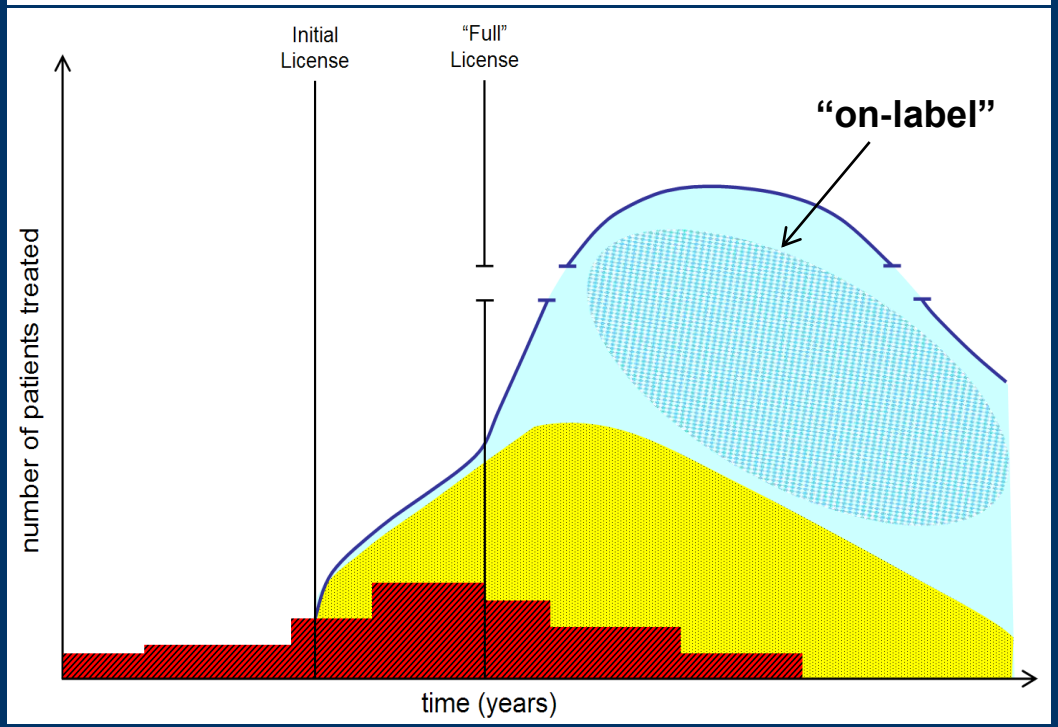
AL builds on existing regulatory processes, including Conditional Authorization and RMPs.

"To achieve the full potential of AL for public health and drug development, licensing decisions should ideally be aligned with coverage and prescribers' decisions…"

…to better coordinate exposure with evidence.

Adapted from Hans-Georg Eichler, EMA, 2012





Exposure vs evidence:

Current scenario:

Post-licensing, treatment population grows rapidly; treatment experience does not contribute to evidence generation

Adaptive Licensing:

After initial license, # treated patients grows more slowly due to restrictions; patient experience is captured to contribute to real-world information

Adapted from Hans-Georg Eichler

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The underlying principle for AL is benefit-harm-uncertainty (BHU) management

AL keywords:

- prospectively planned
- iterative phases evidence gathering
- serve patients', public health needs
- balanced timely access
- benefit-harm management as understanding evolves
- align various decision-makers' needs

Benefit-Risk, or
BHU Management

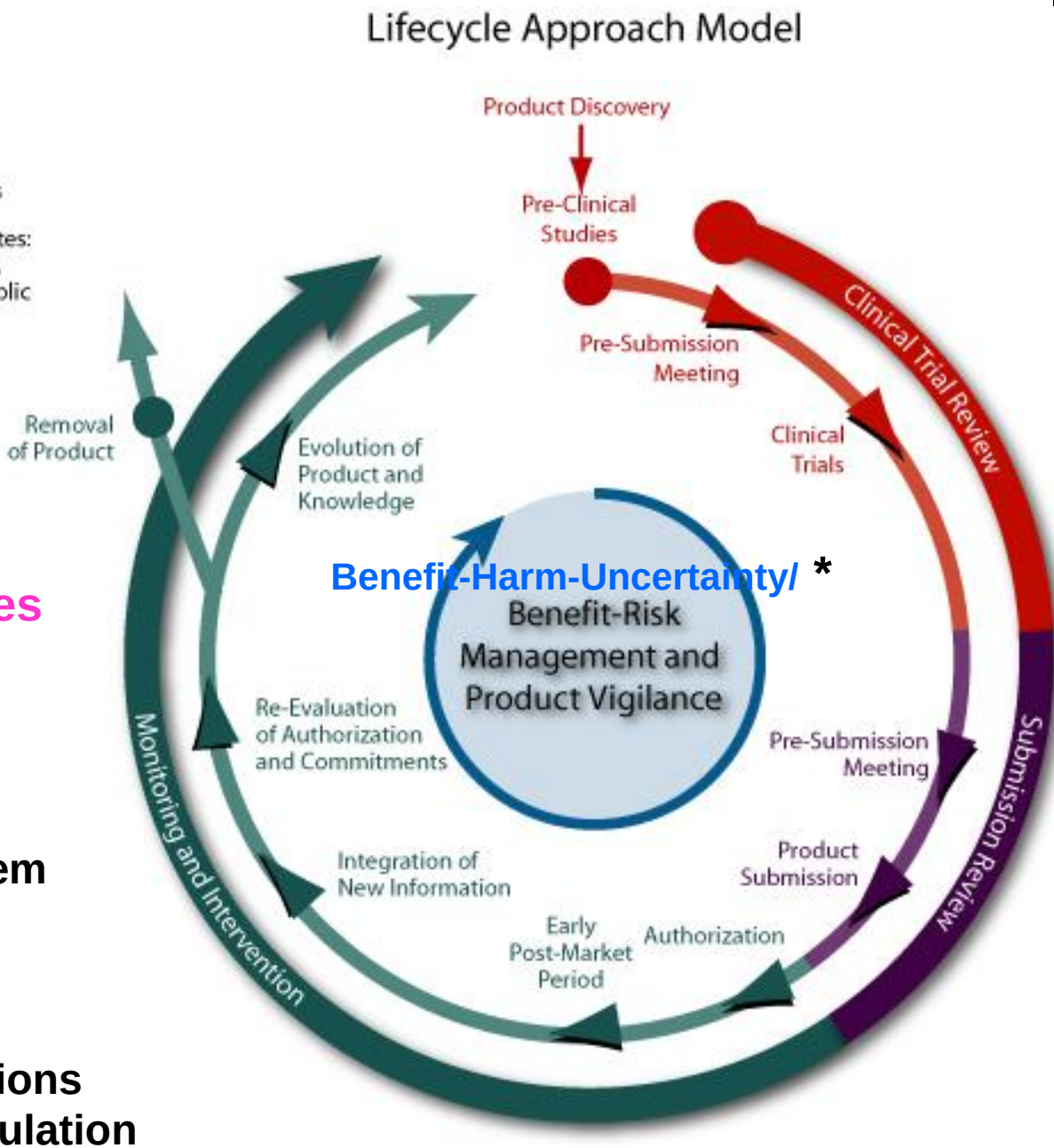
A working definition for BHU Management:

Regulatory science, practices to identify, improve, clarify:

- evidence of (un)favourable effects, uncertainties;
- technical/value judgements (scientific, social);
- decision processes across life-cycle

…to enable better informed, more meaningful, better communicated regulatory decisions so that other healthcare partners - including patients - can make their own best decisions.

BHU management key elements (HC):



1) Focus on patient needs:

- **personalised to:**
  - **optimize benefits,**
  - **minimize harms,**
  - **manage uncertainties**

Benefit-Harm-Uncertainty/ *

2) Consider context:

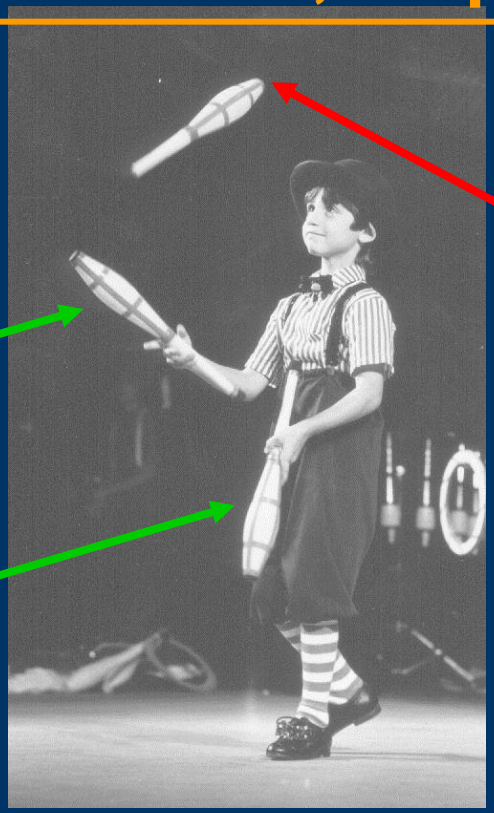
- **e.g.**
  - **burden to patient,**
  - **burden to health system**
  - **available therapy**

3) Recognise life-cycle:

- **integrate emerging innovations into drug development, regulation to reduce uncertainties**

*** http://www.hc-sc.gc.ca/ahc-asc/mod/roadmap-feuillederoute-eng.php**

BHU management helps balance regulator's roles, responsibilities… [1, 2]



Access Facilitator

"ENABLER"

Information Provider

Health Protector

"GATEKEEPER"

…with those of others (industry, payers, HCPs, patients, care-givers)

[1] *Evidence Standards for New Drug Marketing Approval* PLP Discussion Paper, Health Canada Accessible at:
http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/docs/ima-aimm/ima-aimm22-eng.php

[2] *Five Moral Imperatives of Government Regulation.* P. Barton Hutt. Hastings Center Report, February 1980, pp 29-31

BHU language provides direct confrontation of uncertainties in drug evidence / use that would be needed for adaptive licensing

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3 Practical Considerations:

- Health Canada experience –
  - Progressive Licensing, Modernization

Practicalities & lifecycle evidence innovations - what HC statisticians say we need:

Published by Oxford University Press on behalf of the International Epidemiological Association.
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International Journal of Epidemiology 2011;**40**:765–777
doi:10.1093/ije/dyq248

A proposed method of bias adjustment for meta-analyses of published observational studies

Simon Thompson,[1]* Ulf Ekelund,[2] Susan Jebb,[3] Anna Karin Lindroos,[3] Adrian Mander,[1] Stephen Sharp,[2] Rebecca Turner[1] and Désirée Wilks[3]

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Commentary

Creating a demand for bias analysis in epidemiological research

Matthew P Fox

In 2005, Ross and colleagues found a protective association between maternal multivitamin supplementation during the periconceptual period and acute lymphoblastic leukaemia among children with Down's syndrome (OR 0.51; CI 0.30 to 0.89).[1] In their discussion they noted, of research, we are generally left to speculate on or ignore the impact of bias.

In this edition of the journal, Jurek and colleagues[4] use bias analysis to elevate the misclassification discussion in the Ross study from qualitative judgement to quantitative analysis (*see page 168*). Bias

random error), using bias analysis the authors have elevated the discussion of the bias from the qualitative to the quantitative. Although bias analysis may be criticised as subjective, it seems no more subjective than calculating a frequentist confidence interval as if there were no bias. If I disagree with the authors' chosen parameters distributions, I can conduct my own bias analysis. But while qualitative judgments about bias are hard to refute or prove, quantitative assessments of bias can be interpreted, debated and refined.

There is little doubt that bias analysis is a necessary component of epidemiological analysis, but there is currently little incentive for authors to include bias

Press on behalf of the International Epidemiological Association
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International Journal of Epidemiology 2011;**40**:777–779
doi:10.1093/ije/dyq265

Statistics Ready for a Revolution !!!

1 SEPTEMBER 2010 4,007 VIEWS 2 COMMENTS

Next Generation of Statisticians Must Build Tools for Massive Data Sets

Mark van der Laan, Jiann-Ping Hsu/Karl E. Peace Professor in Biostatistics and Statistics at UC Berkeley, and Sherri Rose, PhD candidate at UC Berkeley

Commentary: Adjusting for bias: a user's guide to performing plastic surgery on meta-analyses of observational studies

John P A Ioannidis

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Drive, S

Biometrika (2011), **98**, 4, *pp.* 845–860
© 2011 Biometrika Trust
Printed in Great Britain

doi: 10.1093/biomet/asr055

Statistical Science
2009, Vol. 24, No. 2, 195–210
DOI: 10.1214/09-STS291
© Institute of Mathematical Statistics, 2009

Relaxation Penalties and Priors for Plausible Modeling of Nonidentified Bias Sources

Sander Greenland

Optimizing randomized trial designs to distinguish which subpopulations benefit from treatment

BY M. ROSENBLUM

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AND M. J. VAN DER LAAN

Division of Biostatistics, University of California, School of Public Health,

Practical considerations of uncertainties - present situation, future needs

Reduce !

Communicate!

Transparency!

ORIGINAL INVESTIGATION

LESS IS MORE

Communicating Uncertainties About Prescription Drugs to the Public

A National Randomized Trial

Lisa M. Schwartz, MD, MS; Steven Woloshin, MD, MS

Background: Many new drugs are aggressively promoted. The public may not realize that even with US Food and Drug Administration (FDA) approval, important uncertainties about the benefits and harms of these drugs remain. We assessed the US public's understanding of the meaning of FDA drug approval and tested how brief explanations communicating drug uncertainties affect consumer choices.

Methods: We conducted an Internet-based randomized controlled trial using a national sample of US adults from a research panel of approximately 30 000 households. A total of 2944 participants were randomized to receive 1 of 3 explanations about a pair of cholesterol drugs (1 approved based only on a surrogate outcome [lower cholesterol] and 1 based on a patient outcome [reduced myocardial infarctions]). Participants were randomized a second time to receive 1 of 3 explanations about a pair of heartburn drugs (1 newly approved and 1 approved 8 years earlier). Controls received no explanation; the nondirective group received explanations (for the cholesterol drugs, surrogates do not always translate into patient outcomes; for the heartburn drugs, it takes time to establish the safety of new drugs); the directive group received explanations plus advice to "Ask for a drug shown to reduce heart attacks or ask for one with a longer track record." The primary outcomes were choice: the cholesterol drug reducing myocardial infarctions, and the older heartburn drug.

Results: Thirty-nine percent mistakenly believed that the FDA approves only "extremely effective" drugs; 25% mistakenly believed that the FDA approves only drugs without serious side effects. Explanations affected choices: 71% of those in the directive group, 71% in the nondirective group, and 59% of controls chose the cholesterol drug that reduced myocardial infarctions (absolute difference, 12% [95% confidence interval, 7%-18%] for each explanation vs control). For the heartburn drugs, 53% of the directive group, 53% of the nondirective group, and 34% of controls chose the older drug (absolute difference, 19% [95% confidence interval, 13%-24%] for each explanation vs control).

Conclusions: A substantial proportion of the public mistakenly believes that the FDA approves only extremely effective drugs and drugs lacking serious side effects. Brief explanations highlighting uncertainties about the benefit of drugs approved based on surrogate outcomes and the safety of new prescription drugs improved choices. Nondirective explanations worked as well as directive ones.

Trial Registration: clinicaltrials.gov Identifiers: NCT00950157, NCT00950131

Arch Intern Med. 2011;171(16):1463-1468

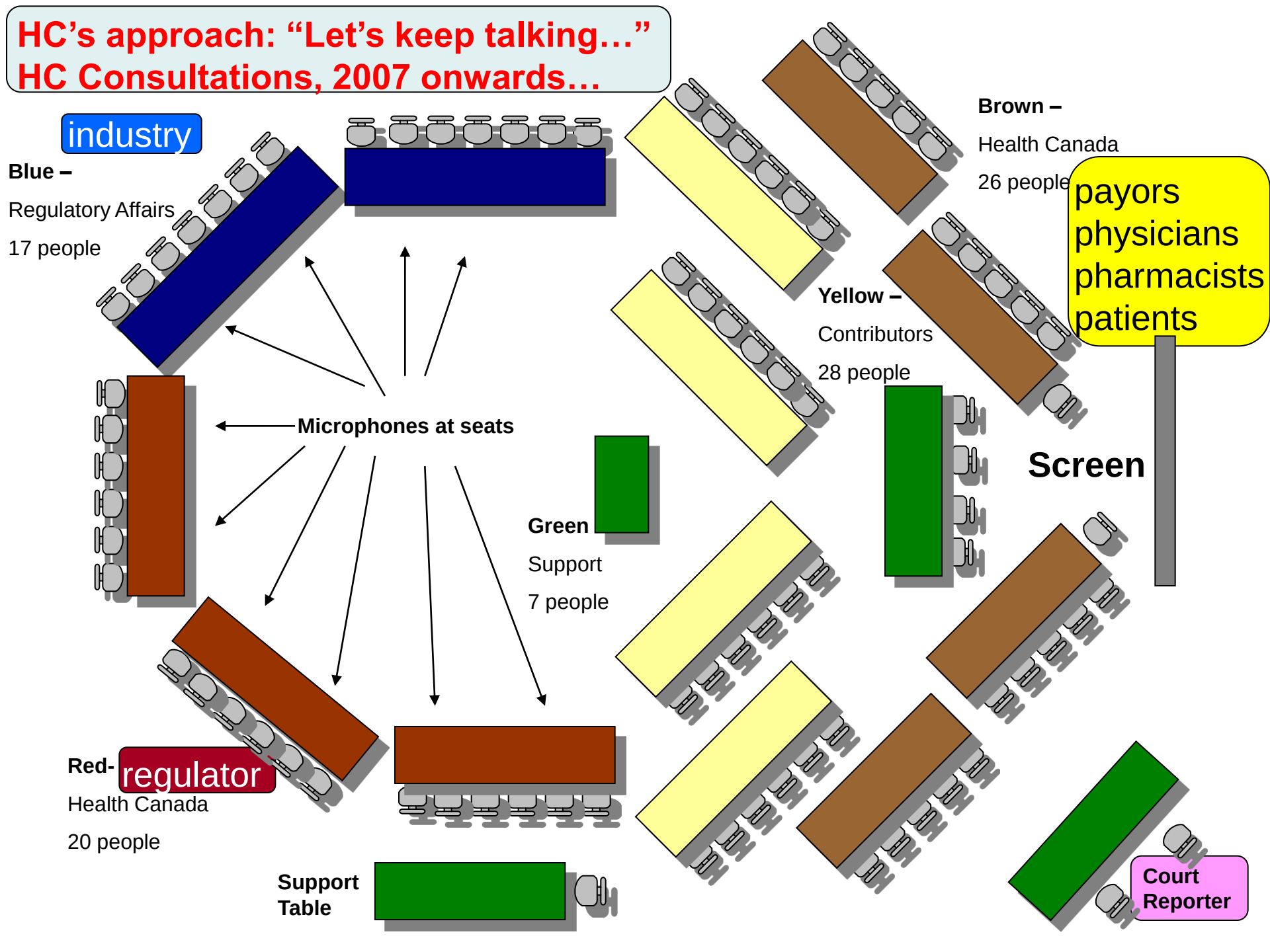
Practical considerations: AL will need a broad social contract to align behaviours

- **Socially and scientifically responsible drug regulation requires:**

- **…agreement (mandate?) among healthcare system partners/decision-makers (e.g. regulators, industry, payers, pharmacists, prescribers, caregivers, patients) to act upon - and respect each other's – roles, responsibilities…**

……TRANSPARENCY!

HC's approach: "Let's keep talking…"
HC Consultations, 2007 onwards…



Practical considerations: present vs future decision and information flow paths

Can we improve flow to enhance evidence, decisions?

CONCLUSIONS…?

Adaptive Licensing not a panacea, not necessarily a route for *all* drugs, one size doesn't fit all,

but might help regulators avoid the reputation trap,

if properly managed and *communicated*, may be the best (or only?) option to balance the regulators' *gatekeeper* and *enabler* roles.

From Hans-Georg Eichler, EMA, 2012