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

(www.interscience.wiley.com) DOI: 10.1002/sim.3933

What is evidence?

Sharon-Lise T. Normand[a,b*†] and Barbara J. McNeil[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 is a net health benefit; does the magnitude of beneficial health effect outweigh the adverse health effects

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Normand S-LT, McNeil BJ. What is evidence? Statistics in Medicine 2010; 29: 1985-1988

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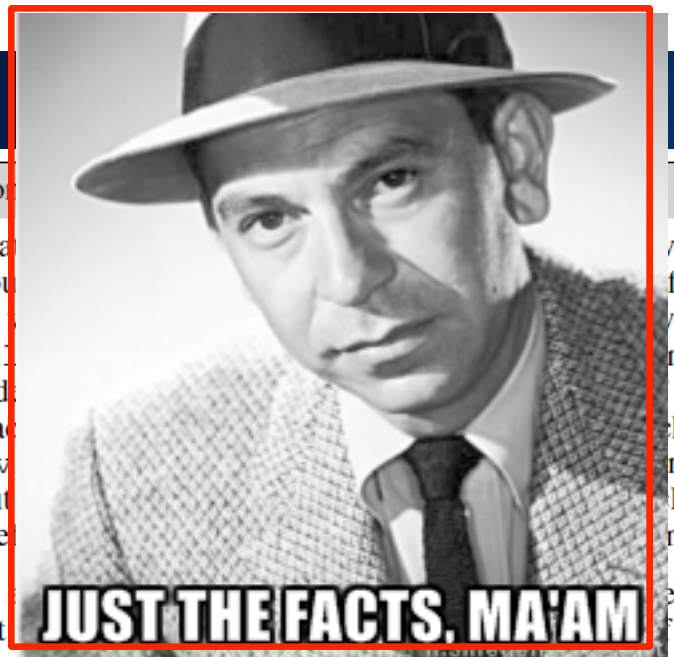

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Current Demands for Clinical Evidence (1)

- 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

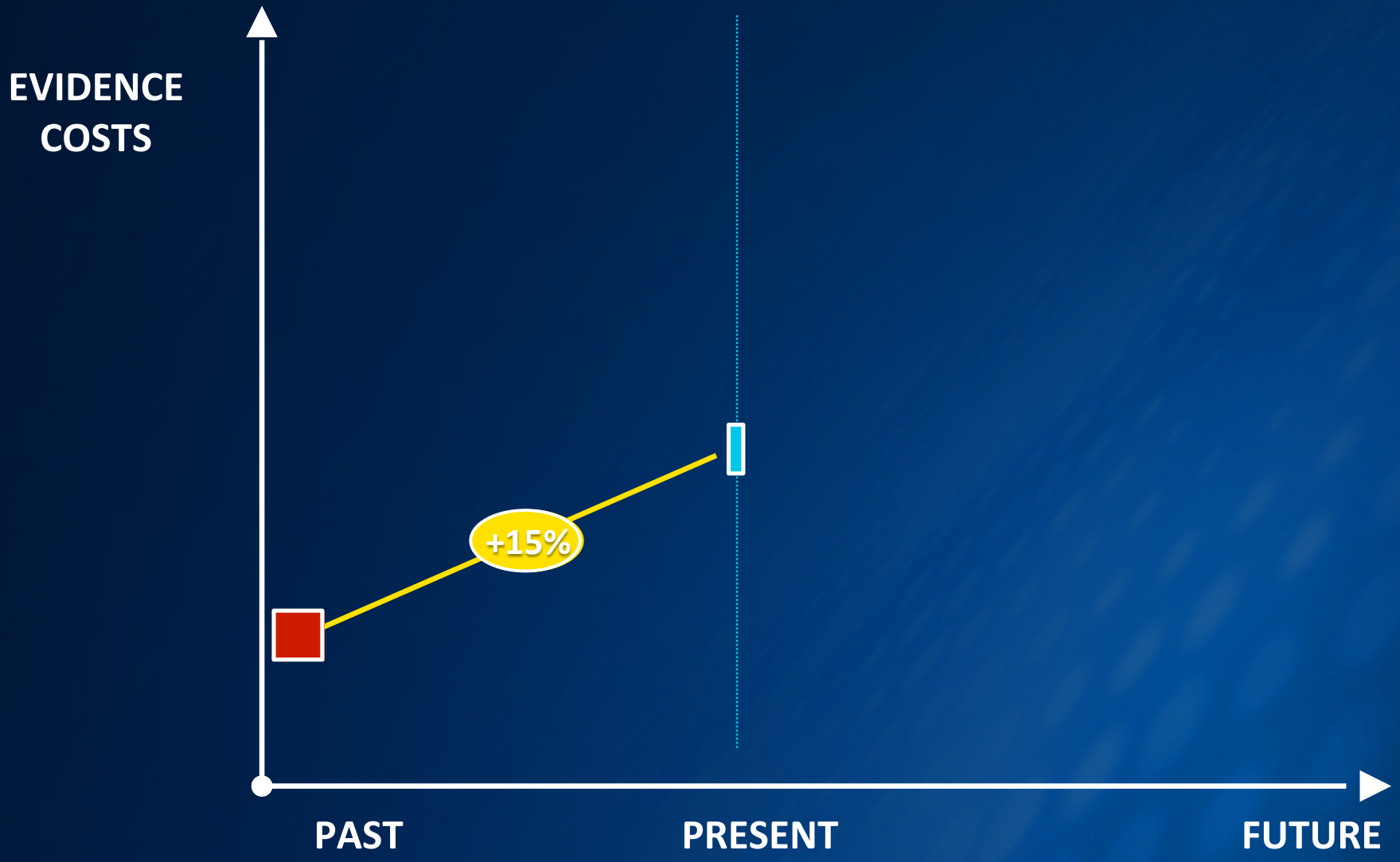
Adapted from "Learning What Works," IOM, 2011

Current Demands for Clinical Evidence (2)

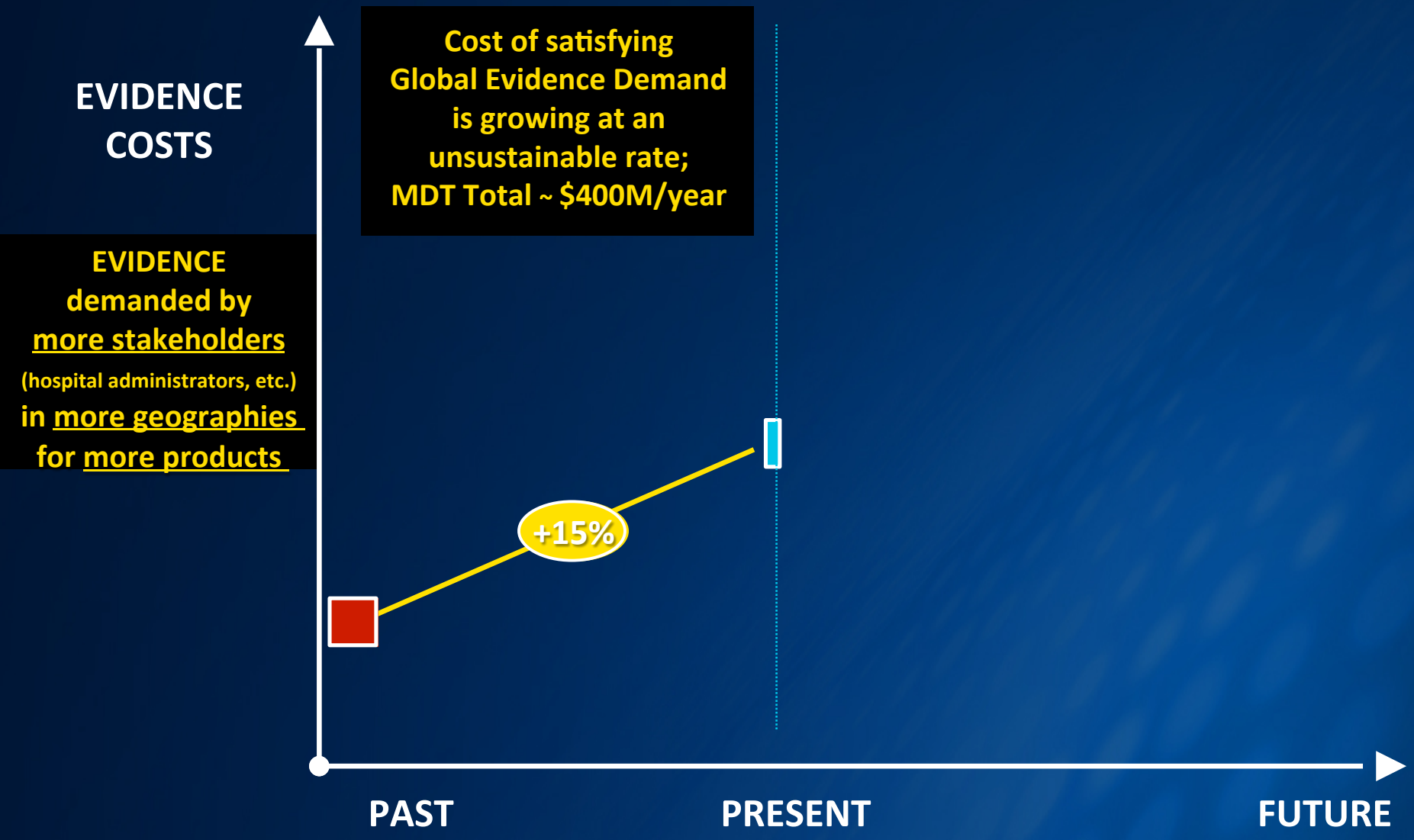
- Comparison of two or more practical alternatives rather than placebo alone
  - Comparative effectiveness research (CER)
- Focus on the unique patient rather than the average population effect
  - Patient-centered outcomes research (PCOR)
- Expanded analysis
  - Systematic reviews
  - Innovative research strategies
  - Clinical registries
  - Coverage with Evidence Development

Adapted from "Learning What Works," IOM, 2011

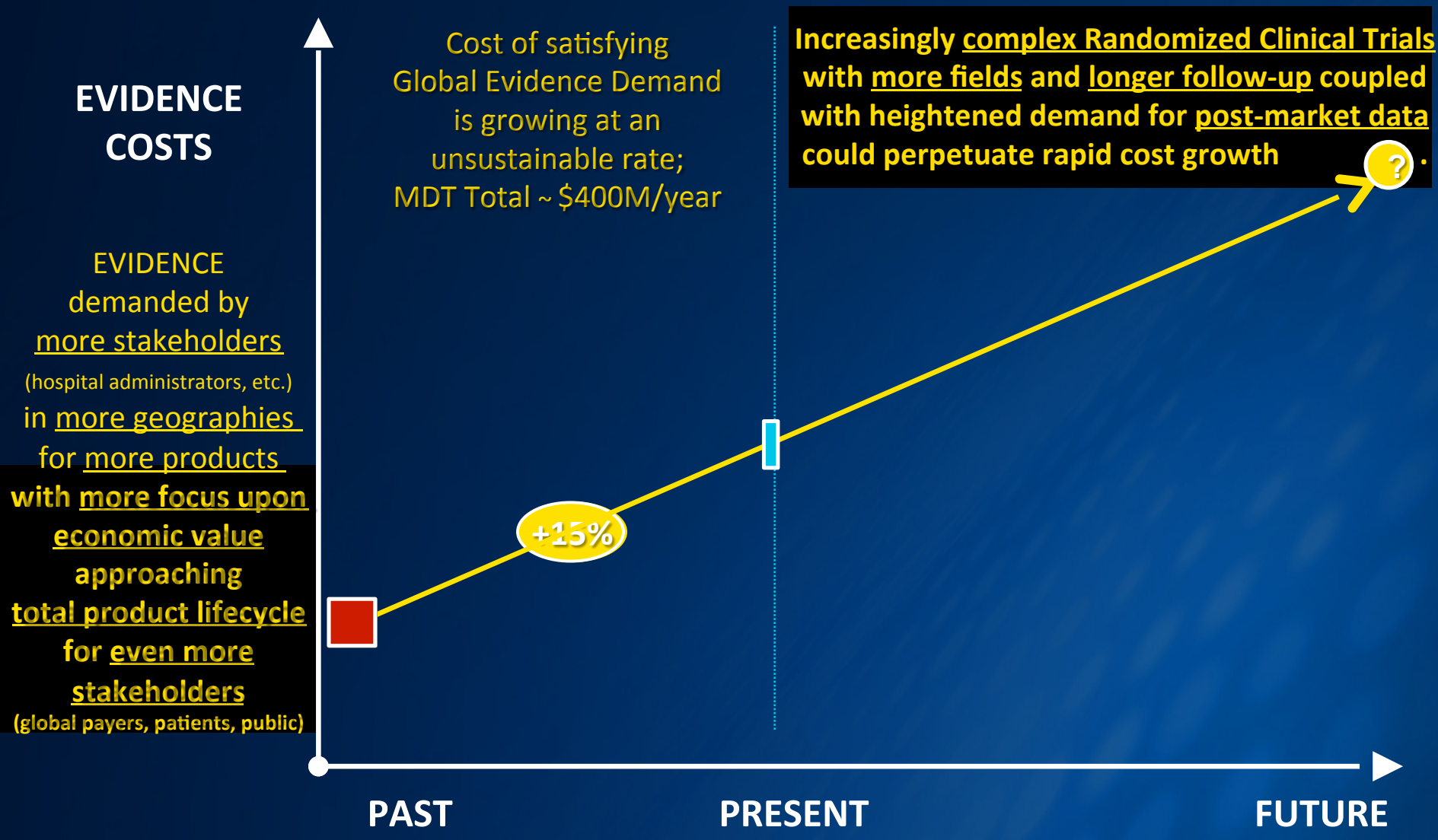
Trends Transforming Clinical Research



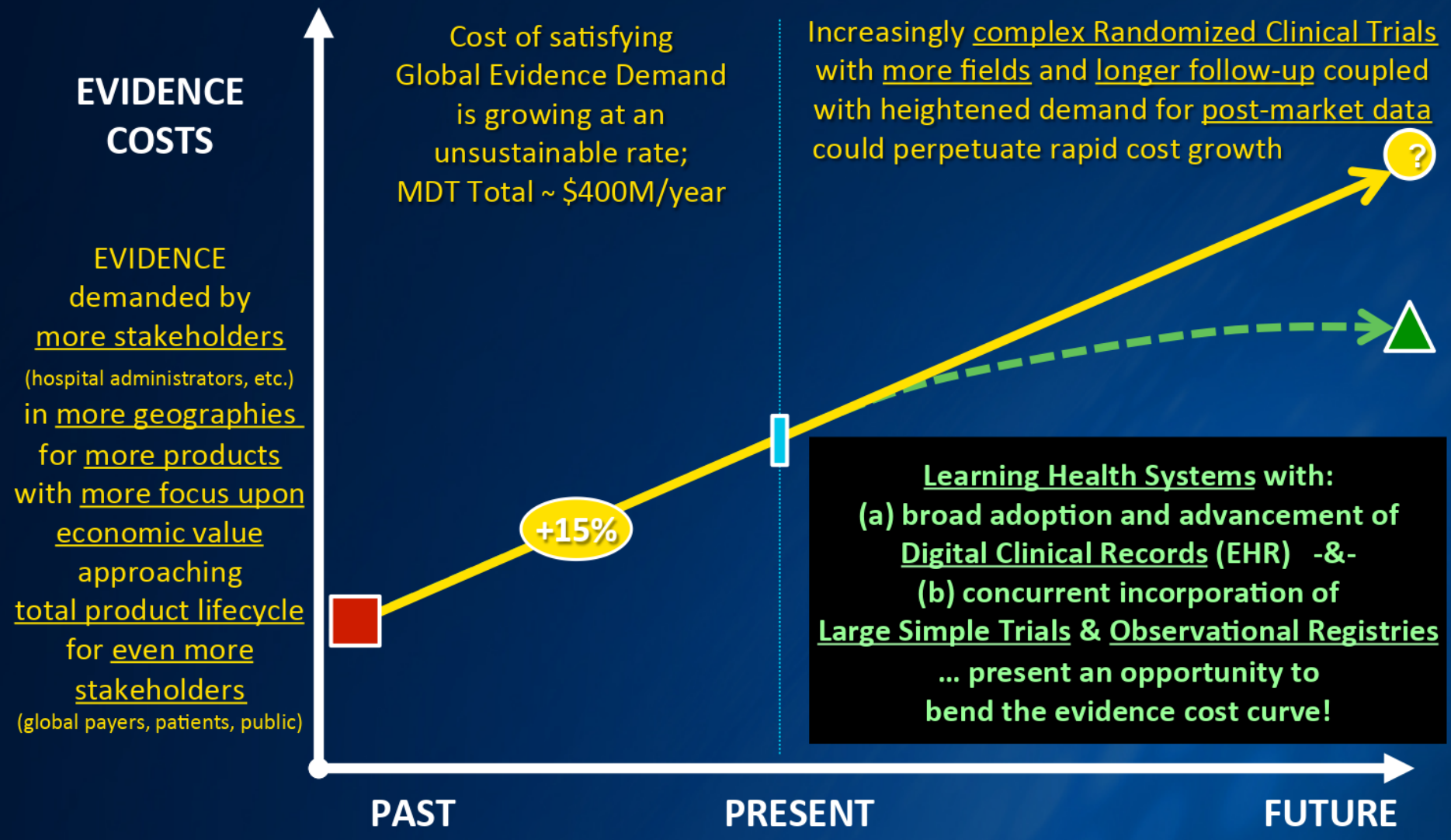
Trends Transforming Clinical Research



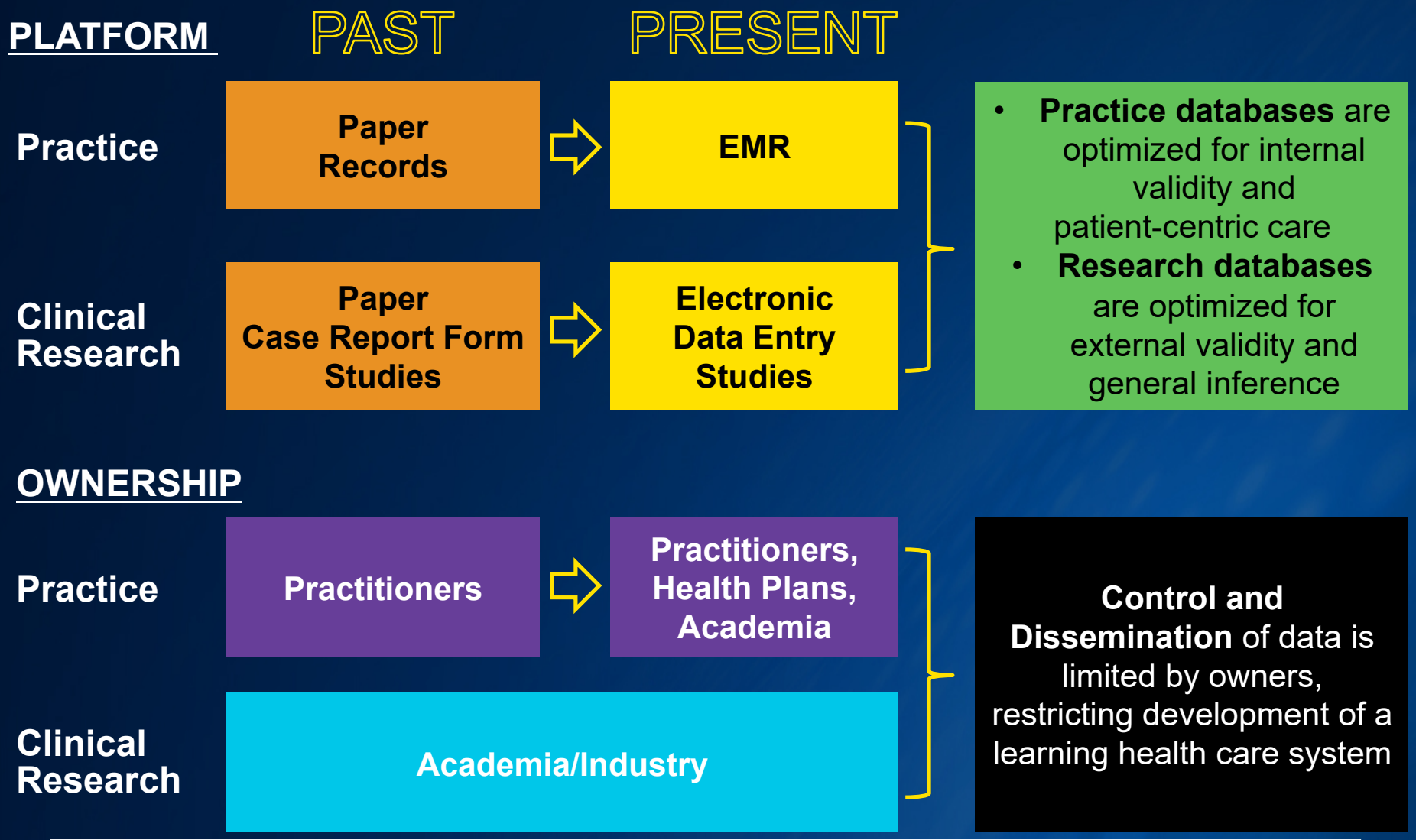
Trends Transforming Clinical Research



Trends Transforming Clinical Research



Clinical Practice & Research Infrastructure Evolution



Transformation of Clinical Evidence Generation

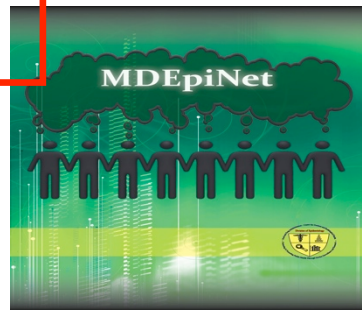
Secular Changes	Past	Present	Future *per current trend*	Desired Future
• **Outcomes**	Placebo Control	Comparative Effectiveness	Cost-Effectiveness & Surveillance	Economic Value
• **Structure & Methods**	Isolated & Confounded Observational Clinical Trials	Complex, Consolidated & Randomized Clinical Trials	Digital Hospital Clinical Records; Systematic Reviews & Controlled Observational Registries	
• **Scope**	Product Performance	Patient Outcomes: Case Studies/Series	Population Outcomes: Evidence-Based Medicine & Large Simple Trials	
• **Hypothesis**	Single Hypothesis / Static Answer		Continuous Update / Bayesian Learning Health System	

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.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologic Evaluation and Research

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

RANDOMIZED, CONTROLLED TRIALS, OBSERVATIONAL STUDIES, AND THE HIERARCHY OF RESEARCH DESIGNS

JOHN CONCATO, M.D., M.P.H., NIRAV SHAH, M.D., M.P.H., AND RALPH I. HORWITZ, M.D.

TABLE 2. TOTAL NUMBER OF SUBJECTS AND SUMMARY ESTIMATES FOR THE EFFECT OF FIVE INTERVENTIONS ACCORDING TO THE TYPE OF RESEARCH DESIGN.

CLINICAL TOPIC	TYPE OF STUDY	META-ANALYSIS*	TOTAL NO. OF SUBJECTS	SUMMARY ESTIMATE (95% CI)†
Bacille Calmette–Guérin vaccine and tuberculosis	13 Randomized, controlled	Colditz et al.[14]	359,922	0.49 (0.34–0.70)
	10 Case–control	Colditz et al.[14]	6,511	0.50 (0.39–0.65)
Mammography and mortality from breast cancer	8 Randomized, controlled	Kerlikowske et al.[15]	429,043	0.79 (0.71–0.88)
	4 Case–control	Kerlikowske et al.[15]	132,456	0.61 (0.49–0.77)
Cholesterol levels and death due to trauma	6 Randomized, controlled	Cummings and Psaty[16]	36,910	1.42 (0.94–2.15)
	14 Cohort	Jacobs et al.[17]	9,377	1.40 (1.14–1.66)
Treatment of hypertension and stroke	14 Randomized, controlled	Collins et al.[18]	36,894	0.58 (0.50–0.67)
	7 Cohort	MacMahon et al.[13]	405,511	0.62 (0.60–0.65)
Treatment of hypertension and coronary heart disease	14 Randomized, controlled	Collins et al.[18]	36,894	0.86 (0.78–0.96)
	9 Cohort	MacMahon et al.[13]	418,343	0.77 (0.75–0.80)

*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.)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Drug-Eluting or Bare-Metal Stents for Acute Myocardial Infarction

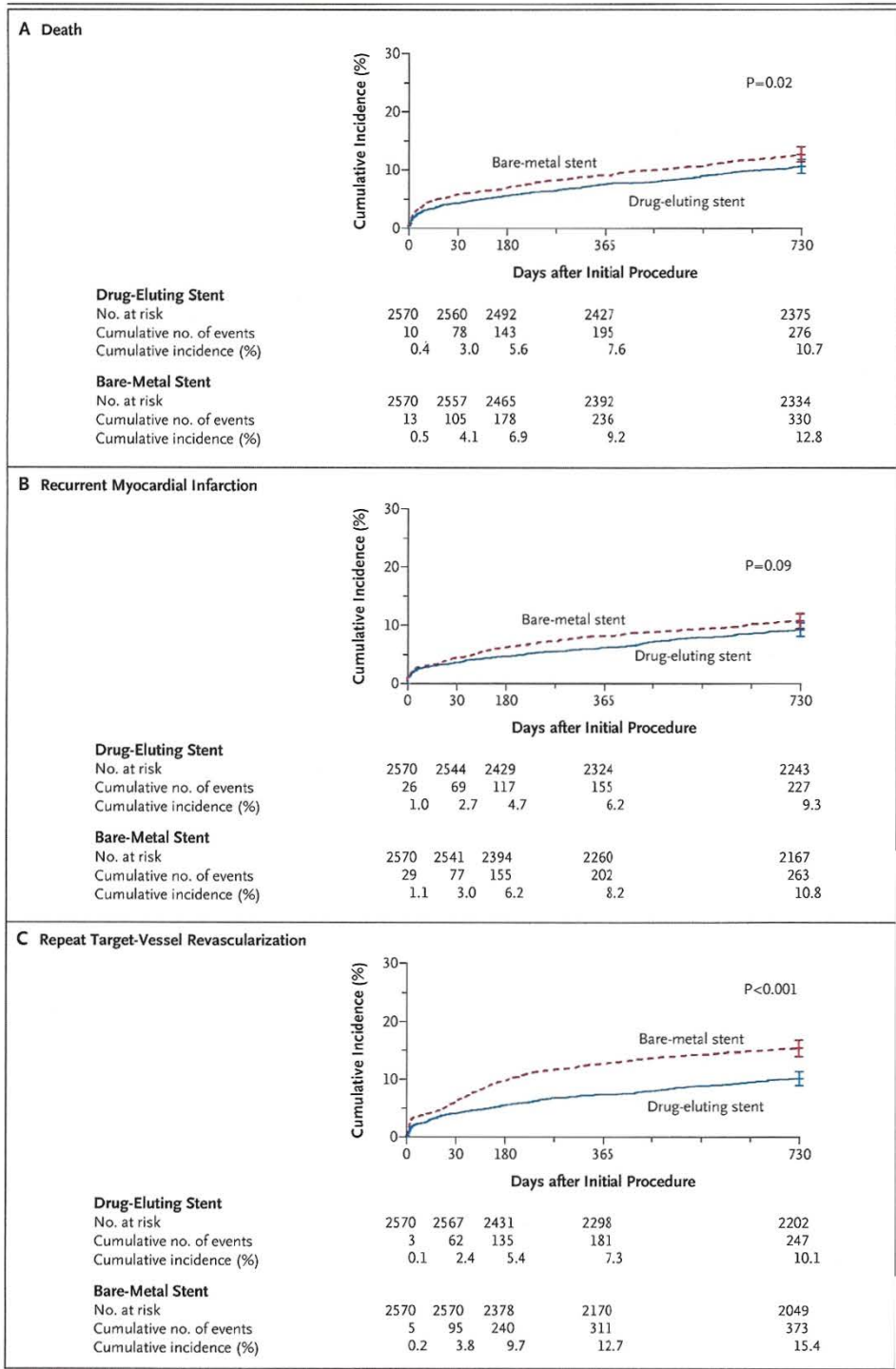
Laura Mauri, M.D., M.Sc., Treacy S. Silbaugh, B.Sc., Pallav Garg, M.B., B.S., M.Sc., Robert E. Wolf, M.S., Katya Zelevinsky, B.A., Ann Lovett, R.N., M.A., Manu R. Varma, B.S., Zheng Zhou, M.D., Ph.D., and Sharon-Lise T. Normand, Ph.D.

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 lmauri1@partners.org.

N Engl J Med 2008;359:1330-42.

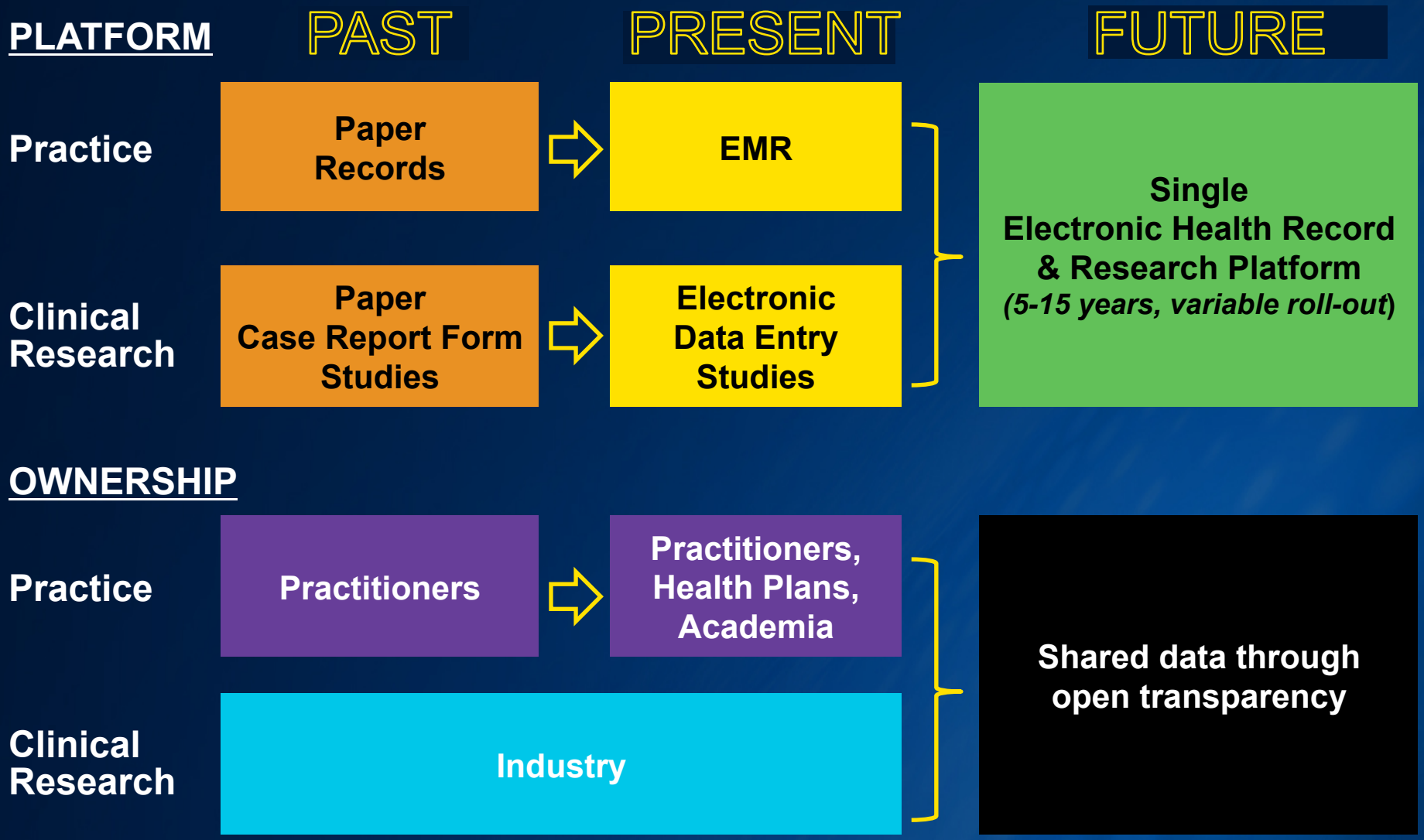
Figure 1 (facing page). Clinical Outcomes after Stenting for Myocardial Infarction.

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

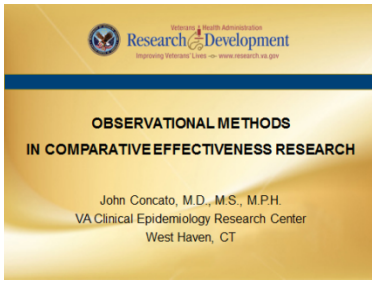
Clinical Practice & Research Infrastructure Evolution



‘SCIENCE AS EXPERIMENT; SCIENCE AS OBSERVATION’

“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



Veterans Health Administration
R&D
www.research.va.gov

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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