Safety & Risk Management Track

Lessons Learned from Epidemiologic Studies and Clinical Trials

Barcelona, March 5, 2008

S. Perez-Gutthann, MD, PhD, MPD, FISPE, FRCP
Vice-President, Global Head Epidemiology, RTI Health Solutions, Barcelona
Honorary Senior Lecturer, Medicine & Therapeutics, University of Dundee

Outline

- Epidemiology, Decade *Horribilis?*
- Strengths and Limitations of Designs
- Final Remarks

A decade in the limelight

- 1998 Heart and Estrogen-Progestin Replacement Study
- 2002 Women's Health Initiative

Findings from RCTs and Observational Studies

Table 2. Results from Observational Studies of Combined Hormone Therapy and from the Women's Health Initiative and the Heart and Estrogen/Progestin Replacement Study.*

Disease	Women's Health Initiative	Heart and Estrogen/ Progestin Replacement Study	Observational Studies of Estrogen with Progestin
		relative risk (95% confidence interval)	
Breast cancer	1.26 (1.00–1.59)	1.30 (0.77–2.19)	
<5 yr			1.15[7]
≥5 yr			1.53[7]
Colorectal cancer	0.63 (0.43–0.92)	NA	0.66 (0.59–0.74)[8]†
Hip fracture	0.66 (0.45–0.98)	1.10 (0.49–2.50)	0.75 (0.68–0.84)[9]†
Stroke	1.41 (1.07–1.85)	1.2 (1.0–1.4)‡	1.45 (1.10–1.92)[10]
Pulmonary embolism	2.13 (1.39–3.25)	2.8 (0.9–8.7)	2.1 (1.2–3.8)[11]†
Coronary heart disease	1.29 (1.02–1.63)	0.99 (0.80–1.22)	0.61 (0.45–0.82)[12]

* Relative risks are for the women receiving hormone-replacement therapy as compared with those not receiving hormone-replacement therapy. Confidence intervals are nominal. NA denotes not available.
† Estimates are for any hormone use, since there were insufficient data for estrogen plus progestin.
‡ Relative risk is for the combined risk of fatal and nonfatal stroke.

A decade in the limelight

- 1998 Heart and Estrogen-Progestin Replacement Study
- 2002 Women's Health Initiative
- 2002 PROSPER – statins & dementia, cancer
- 2005+ COX2, Avandia…
- 2007 BMJ ;334;179

"**Observational studies should carry a health warning"**

Medical Wisdom, as of Today A great deal of the public-health advice passed down to us is essentially unproved and subject to change. Photograph by Reinhard Hunger for The New York Times.

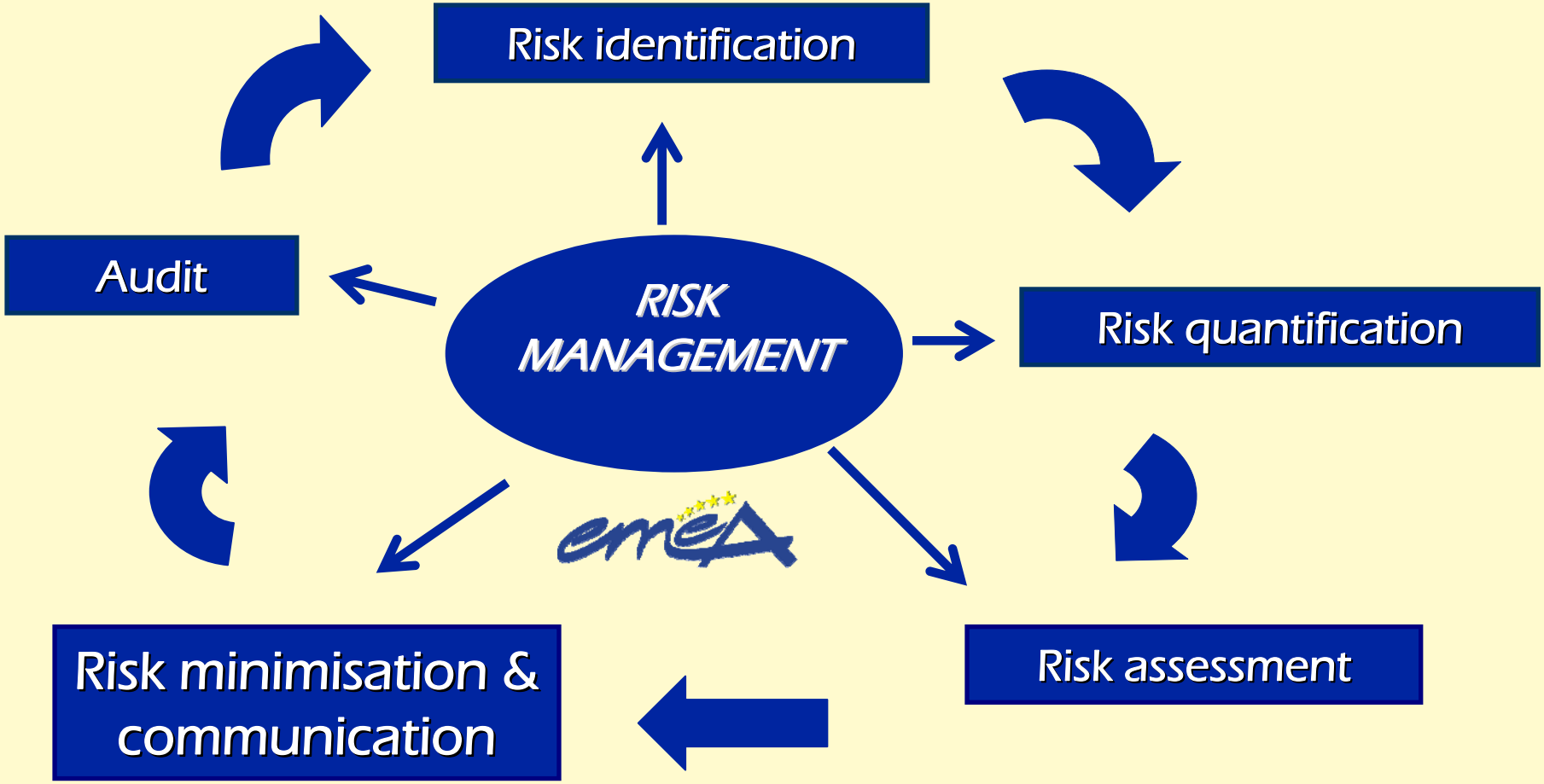
Cover Story 9.16.07

At the same time…

No one questions the value of these epidemiologic studies when they're used to identify the unexpected side effects of prescription drugs or to study the progression of diseases or their distribution between and within populations. One reason researchers believe that heart disease and many cancers can be prevented is because of observational evidence that the incidence of these diseases differ greatly in different populations and in the same populations over time. Breast cancer is not the scourge among Japanese women that it is

THE NEW YORK TIMES MAGAZINE / SEPTEMBER 16, 2007 55

The Age of Risk Management



Risk Management & Epidemiology

- Risk assessment / measurement
  - estimation and evaluation of risk
- Risk confrontation
  - determining acceptable level of risk
- Risk intervention
  - risk minimization action
- Risk communication
  - interactive exchange of risk information
- Risk management evaluation
  - evaluating effectiveness of activities

➔ Epidemiology – population based evidence

➔ Epidemiology – population based evidence

➔ Public Health perspective

➔ Public Health perspective

➔ Epidemiology – population based evidence

EU-RMP Template

1.7 Epidemiology of the indication(s) and important adverse events

Synopsis of ongoing and completed pharmacoepidemiological study programme

European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 27/09/2006
Doc.Ref. EMEA/192632/2006

Annex C: TEMPLATE FOR EU RISK MANAGEMENT PLAN (EU – RMP)

This template provides advice on how the data requested in the Guideline, if available, should be presented. It is anticipated that, particularly in section 1, all the information will not be available for all drugs and that the type of product and where it is in its lifecycle will affect how much information can be provided.

Overview of EU Risk Management Plan Template

Section	
1	Product information
2	Safety specification
3	Pharmacovigilance Plan
4	Evaluation of the need for risk minimisation activities
5	Risk Minimisation Plan
6	Summary of the EU-RMP
	Contact person details
Annex 1	Interface between EU-RMP and Eudravigilance *To be provided in electronic form only*
Annex 2	Current (or proposed if initial EU-RMP) SPC, Package Leaflet
Annex 3	Synopsis of ongoing and completed clinical trial programme
Annex 4	Synopsis of ongoing and completed pharmacoepidemiological study programme
Annex 5	Protocols for proposed and ongoing studies in pharmacovigilance plan
Annex 6	Newly available study reports
Annex 7	Other supporting data
Annex 8	Details of proposed educational programme (if applicable)

To be valid an EU-RMP MUST contain sections 1,2 & 3. With the exception of section 4 (which must be completed if additional risk minimisation activities are proposed) all sections should be provided. Annex 1 should be provided in electronic form only.

Please ensure that the data provided in this document are coded in MedDRA terms where appropriate and are consistent with those submitted electronically in the template attached in Annex 1.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 20
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Principles

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2005; **14**: 589–595
Published online 25 May 2005 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pds.1082

ISPE COMMENTARY

Guidelines for good pharmacoepidemiology practices (GPP)†

Revised: August 2004

- Design and implement activities following Good Pharmacoepidemiology Practices

  http://www.pharmacoepi.org/resources/guidelines_08027.cfm

  Pharmacoepidemiology and Drug Safety 2005; 14(8): 589-595

  - Ethical principles
  - Patient Protection & Data Confidentiality
  - Protocol driven & Statistical Analysis Plan
  - Reporting & Communication
- Referenced in ICH E2E, and FDA, EMEA Risk Management, Pharmacovigilance, and Pharmacoepidemiology Guidances, *internal SOPs*

RCT and Epidemiologic Studies – Notable Differences

	Clinical Trials	Observational Studies
Setting	Standardized approach to treating patients may differ from common practice	Usual clinical practice
Ethics	Must meet ethical standards of human experimentation	Researcher does not offer intervention, which limits ethical concerns mainly to privacy issues
Cost of each study subject	High	Low
Subjects	Selection of patients based on strict inclusion and exclusion criteria that depend on ethics and feasibility	Can readily include all patients, a broad range of patients, or can apply specific inclusion or exclusion criteria
Exposure	Usually 1 or 2 interventions	No limit to the number of interventions or comparisons
Compliance	Can often be measured	More difficult to quantify directly
Confounding control	Randomization addresses known and unknown confounding	Known factors, if measured, can be controlled, but very difficult to control adequately for unmeasured factors
Outcome	1. Standardized measure of both surrogate, soft, and hard endpoints defined by the researcher 2. Blinding is possible	1. Based on routine restriction and mean by hard endpoints 2. No blinding
Rare outcome	Cost is too high for rare outcomes	Much more feasible for rare outcomes

Sørensen HT, Lash TL, Rothman KJ. Beyond Randomized Controlled Trials: A Critical Comparison of Trials With Nonrandomized Studies. HEPATOLOGY 2006;44:1075-1082

Strengths	Weaknesses
Randomized, controlled trial	
Study groups very similar before treatment	Costly, cumbersome
Conducted by well-established methodologic rules	Involve limited number of participants
Considered gold standard for assessing efficacy	Often underrepresent key patient groups
Can be registered to prevent selective reporting	Short duration
	Comparator (or placebo) often irrelevant
	May measure surrogate end points rather than clinical outcomes
	Protocol may not reflect typical care
Observational study	
Can involve large numbers of typical patients in settings of routine care	Susceptible to confounding caused by underlying differences among patients treated with different drugs
Can focus on specific vulnerable populations	Confounding (especially due to patient selection and differences in compliance) can generate drug–outcome associations that are not truly causal
Can be performed relatively quickly and at modest cost	Methodologically difficult to do well
Can identify rare adverse events	Difficult to identify selective reporting of findings
Can follow patients over many years	Difficult to require registration
Can compare outcomes of several treatment alternatives	

Avorn J. In Defense of Pharmacoepidemiology - Embracing the Yin and Yang of Drug Research. N Engl J Med 2007 357;22:2219-21

Experimental Studies - Considerations

- Gold standard for efficacy
- Important limitations for safety
- Most are aware of some limitations:
  - Too Short to identify mid to long term effect
  - Too Small to identify moderately infrequent events
  - Too Narrow Populations to allow generalization to final patient population of users
- Not discussed limitations:
  - Differential drop outs, and other sources of bias
  - Misuse of p-values as decision criterion
  - Impact of Intention- to-treat analysis

RCT: p-values and safety findings

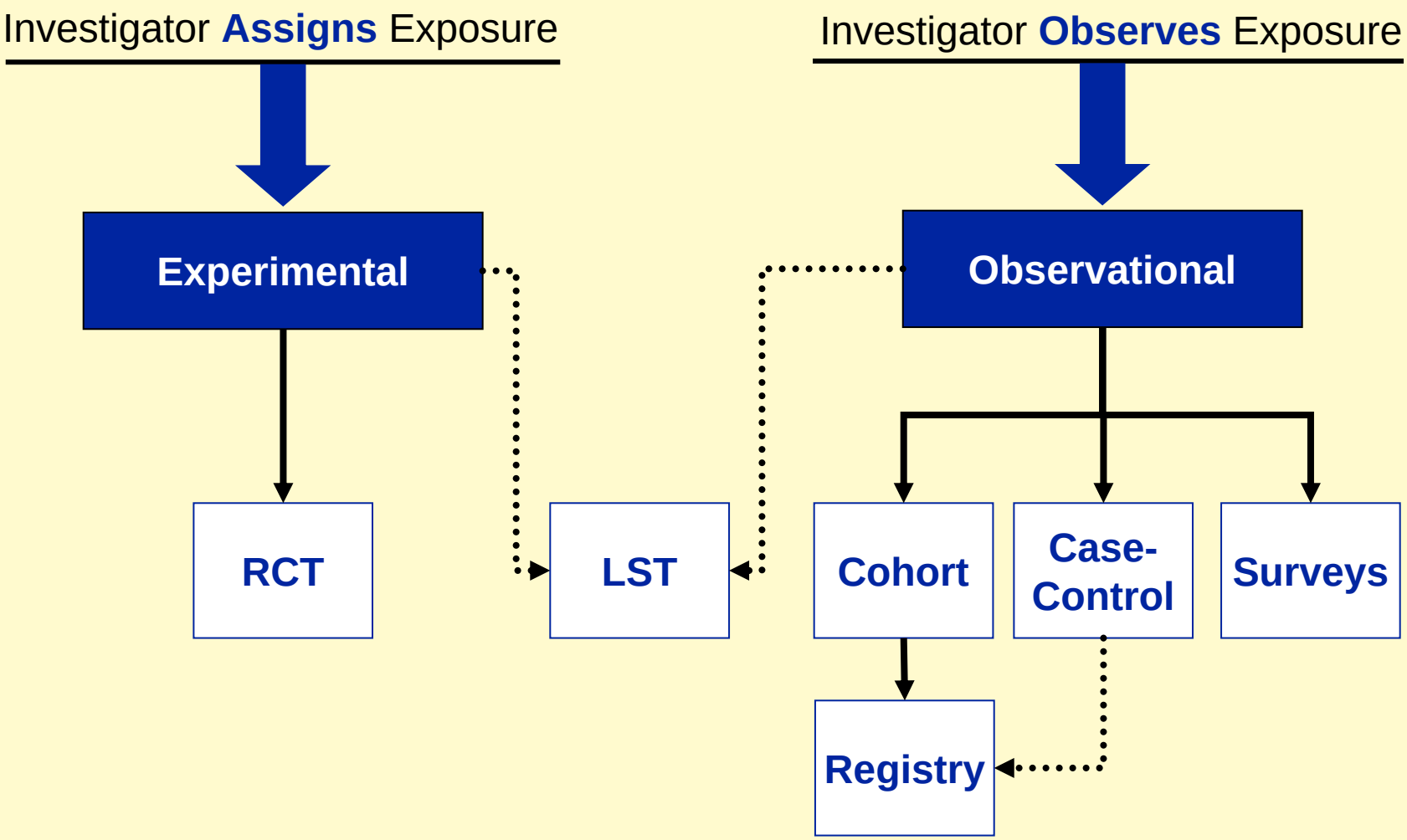
Safety event	RR	p-value
Aaaaa	2.3	0.08
Bbbbb	1.0	0.08
Ccccc	0.5	0.08

- p-value 0.05, a standard but arbitrary, and often misleading decision making tool
- Particularly non-applicable to study events for which the study was not powered for
- In general, confidence intervals are the most informative regarding statistical variability

RCT: ITT and safety findings

- To gain the full benefits of random assignment, one must compare groups according to their randomly assigned treatment (intent-to-treat).
- On the other hand, if patients do not follow their assigned treatment, bias from non adherence results.
- This bias underestimates the effect of actually taking the treatment = conservative
  - Benefit findings, barrier to entry (standard)
  - Equivalence studies, can lead to the false inference of comparability when real differences exist (inappropriate)
  - Safety findings, underestimated (inappropriate)

What Are the Options



Lessons learned

Trials

- Aware of ITT impact
- Avoid p-values in general, and specially for safety events. Focus on point estimates and measure of variability
- The longer a trial, the more susceptible to biases, and epidemiologic methodology is required for analysis

Observational

- Never forget the effect of missing data, bias, confounding (do not use the terms lightly either…)
- New user designs
- Endpoint definition and validation
- Beware of multivariable modeling without accompanying stratified analysis (black box approaches)

Role of Epidemiology in Transition

"Nice to have"

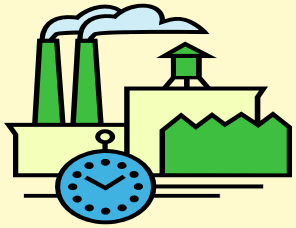
Regulatory requirement

Strategic advantage

Core discipline for R&D

Critical in filing, peri/post-approval

Move to large volume systematic "production mode"



In conclusion

- [We] should not denigrate the observational nature of the data. Most of what we learn, and will continue to learn, about adverse drug effects are from observational studies.

  Stampfer, Walker, Lancet 1996

- Observational studies cannot replace trials, nor do trials make observational studies unnecessary. Both designs are susceptible to particular bias, so neither provides perfect information.

  Sorensen, Lash, Rothman, Hepatology 2006

- This is a nonchoice: to understand everything we should know about a drug, we must do both kinds of research [trials, observational] with rigor and with humility.

  Avorn, N Engl J Med 2007

THANK YOU
GRACIAS, GRÀCIES

Susana Perez-Gutthann, MD, MPH, PhD, FISPE, FRCP
Vice President, Global Head Epidemiology, RTI Health Solutions
Trav. Gracia 56, Atico 1, 08006 Barcelona
Office: +34 93 241 7760
Email:sperez@rti.org
www.rtihs.org