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Adaptive statisticians & the challenges beyond clinical trials

Kit Roes

EFSPI Statistical Leaders Meeting

June 20, 2012

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Structure of presentation

- Rather than a bulleted list, I will wander through topics and approaches I engage(d) in, with an emphasis outside clinical trial statistics.

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…….. our consistent image……..

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- "[Statistics are] the only tools by which an opening can be cut through the formidable thicket of difficulties that bars the path of those who pursue the science of man." Sir Francis Galton

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Industrial statistics

Electronics industry

- Fierce global competition 70s / 80s
- Regulated, but not for statistics
- Quality and efficiency

- I entered this industry in 1985……..at the CQM, Philips

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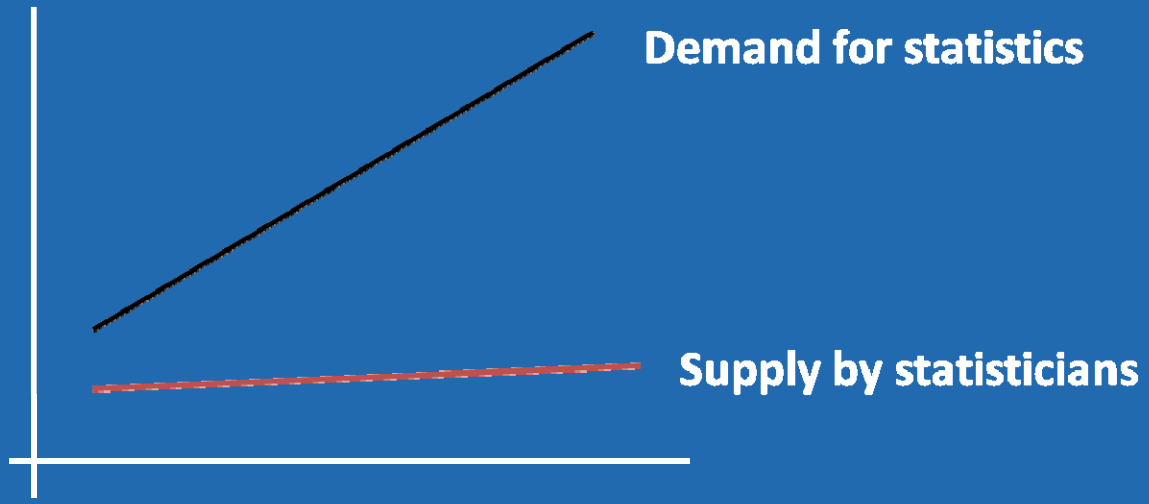
Some projects in the early days

- Design and analysis of accelerated life testing experiments
- Multivariate prediction of batch loss to prevent individual product testing and selection
- Estimating batch size (diodes) by weighing
- And an interesting waiting time model……

Tactical use of statistics

Two connected issues

- Statisticians not impacting the business clearly
- Statisticians in short supply



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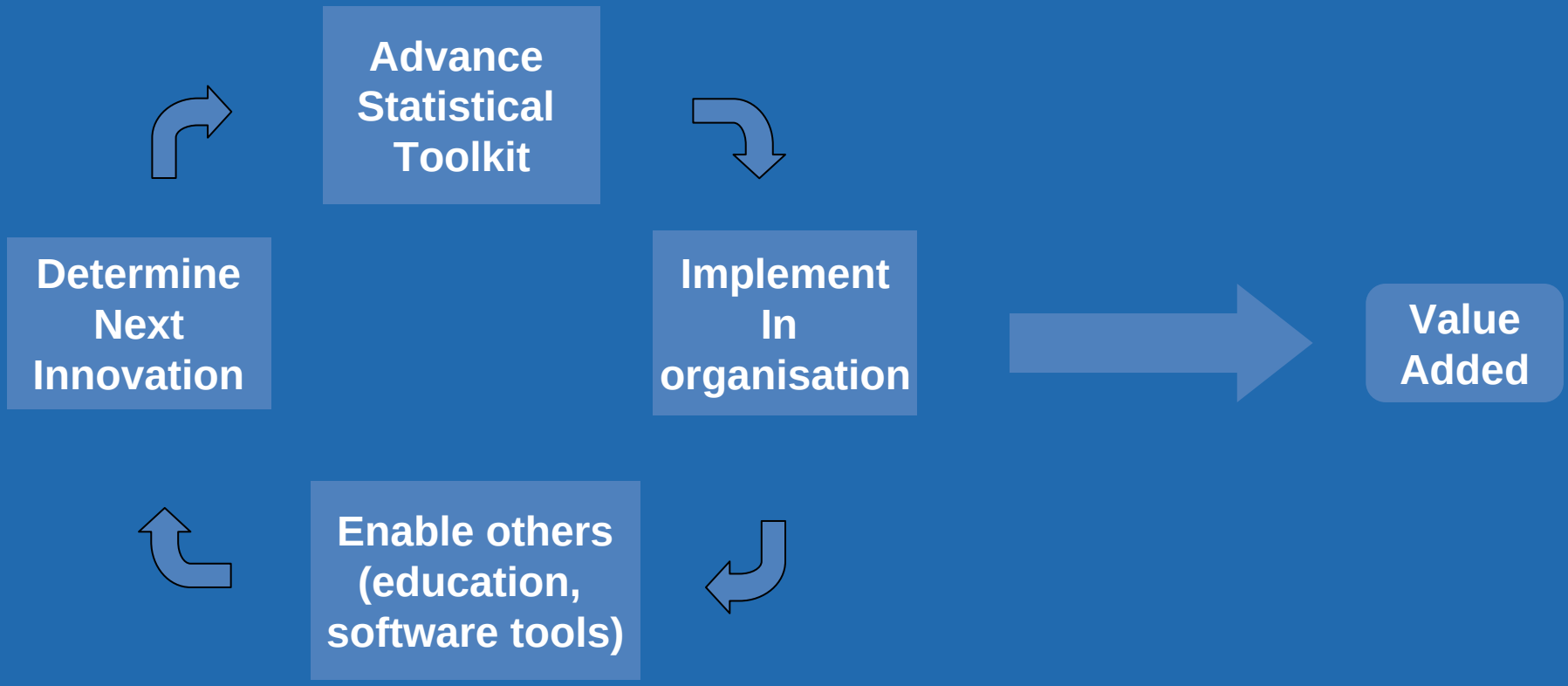
Principle: Innovation Cycle



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"Statistical thinking will one day be as necessary for efficient citizenship as the ability to read and write." H.G.Wells

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Impacting business

Statisticians the lead in quality improvement

- Implementation of Statistical Process Control
- Six Sigma
- Lean Six Sigma

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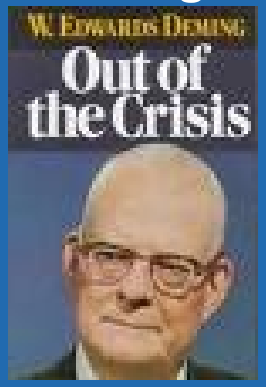
Little Use of Statistics ==>

"Required" use Statistics ==>

Tactical use of Statistics ==>

Strategic use of Statistics



& "Statistical thinking"

1920 **1950** **1988** **Today**

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Key lessons learned

- Entrepreneurial approach to the discipline
- Innovation cycle
- Impact on business

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Arguably, *adaptive design* for clinical trials in drug development has followed a similar path

But so has:

Modeling and simulation, health economics, pharmaco-epidemiology

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Statisticians in pharma industry

Medical / Pharmaceutical Statistics

- (Much) more advanced than industrial statistics

- Huge proven contributions to global health
  - Survival analysis / Cox PH modeling

Arguably the area with the most statistical brains available today (…finance…)

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Current environment

- Global competition in clinical operations statistics
- Drive in innovative methodology
- Many new opportunities
  - *Pharmaco epidemiology*
  - *Comparative effectiveness research*
  - Statistical thinking and methods for decision making at program and portfolio level
  - Early stage R&D

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Are we present?

Pharmaceutical Statistics reviewers & authors

- "clinical trials" returns 118
- "epidemiology" returns 19, of which 3 in companies

Different worlds, also within companies?

Lost in translation? Interaction & effect modification, collider stratification, causal inference?

Beyond the RCT.

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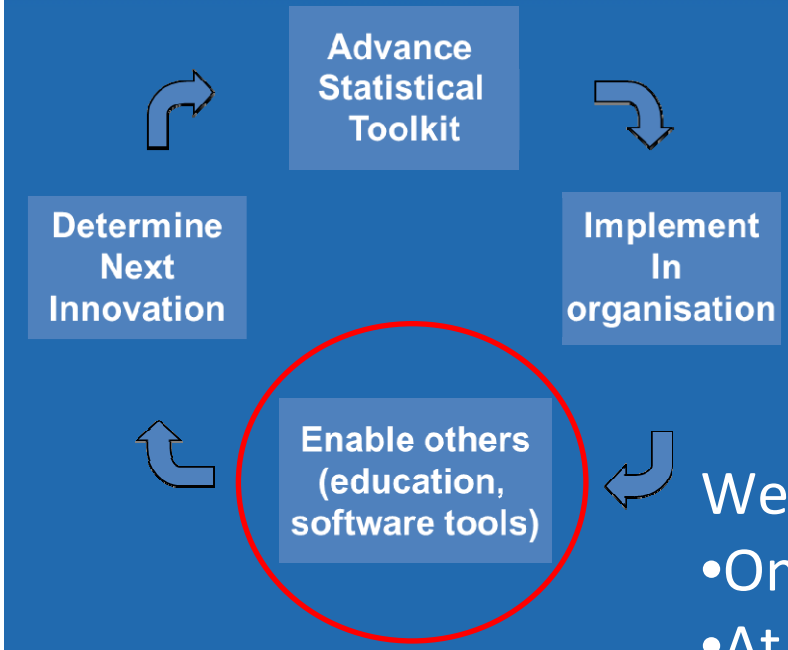

We have enabled Epidemiology
- On average to the benefit of public health
- At the expense of being less involved

- New complexities: need to engage
- Need to rethink our next cycle(s)

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To give you an idea

Julius Center (about 400 – 450, including PhD students)

- Clinical Epidemiology, Primary Care, Health Technology Assessment, Research Ethics, Biostatistics

- Msc Epidemiology, also clinical researchers obtain this Msc

- Epidemiologists “first line” for study design, sample size

- HTA, Research Ethics: perceived as specialists, need to involve

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A predominant clinical trial background may be a blessing as well as curse

- Rigorous methodology
- Pre-disposed to miss out on essentially different paradigms

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New paradigms*

*J.P. Vandenbroucke (2008). Observational Research, Randomised Trials, and Two Views of Medical Science, PLoS Medicine

- Intended effects of therapy
  - RCT
  - Prospective follow-up
  - Retrospective follow-up
  - Case-control
  - Anecdotal
- Discovery and explanation
  - Anecdotal
  - Case-control
  - Retrospective follow-up
  - Prospective follow-up
  - RCT

(Unknown) Adverse effects are “unintended”, usually not associated with indication: no “confounding by indication“-> observational evidence can be strong.

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New paradigms

Axis of multiplicity

SNPs → *Randomized trial*

Prior belief
1 in 100,000

Prior belief
50 - 50

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Data and analyses: pharmaco-epidemiology

PSI SIG on Epidemiology. But also IMI-PROTECT to Strengthen the monitoring of benefit risk of medicines in Europe

A review of risk measures in pharmacoepidemiology with tips for statisticians in the pharmaceutical industry

George Quartey,[a*] Jixian Wang,[b] and Joseph Kim[c,d]

Opportunities for minimization of confounding in observational research

George Quartey,[a*] Maurille Feudjo-Tepie,[b] Jixian Wang,[c] and Joseph Kim[e]

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PROTECT Goal

To strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods

to enhance early detection and assessment of adverse drug reactions from different data sources (clinical trials, spontaneous reporting and observational studies)

to enable the integration and presentation of data on benefits and risks

These methods will be tested in real-life situations.

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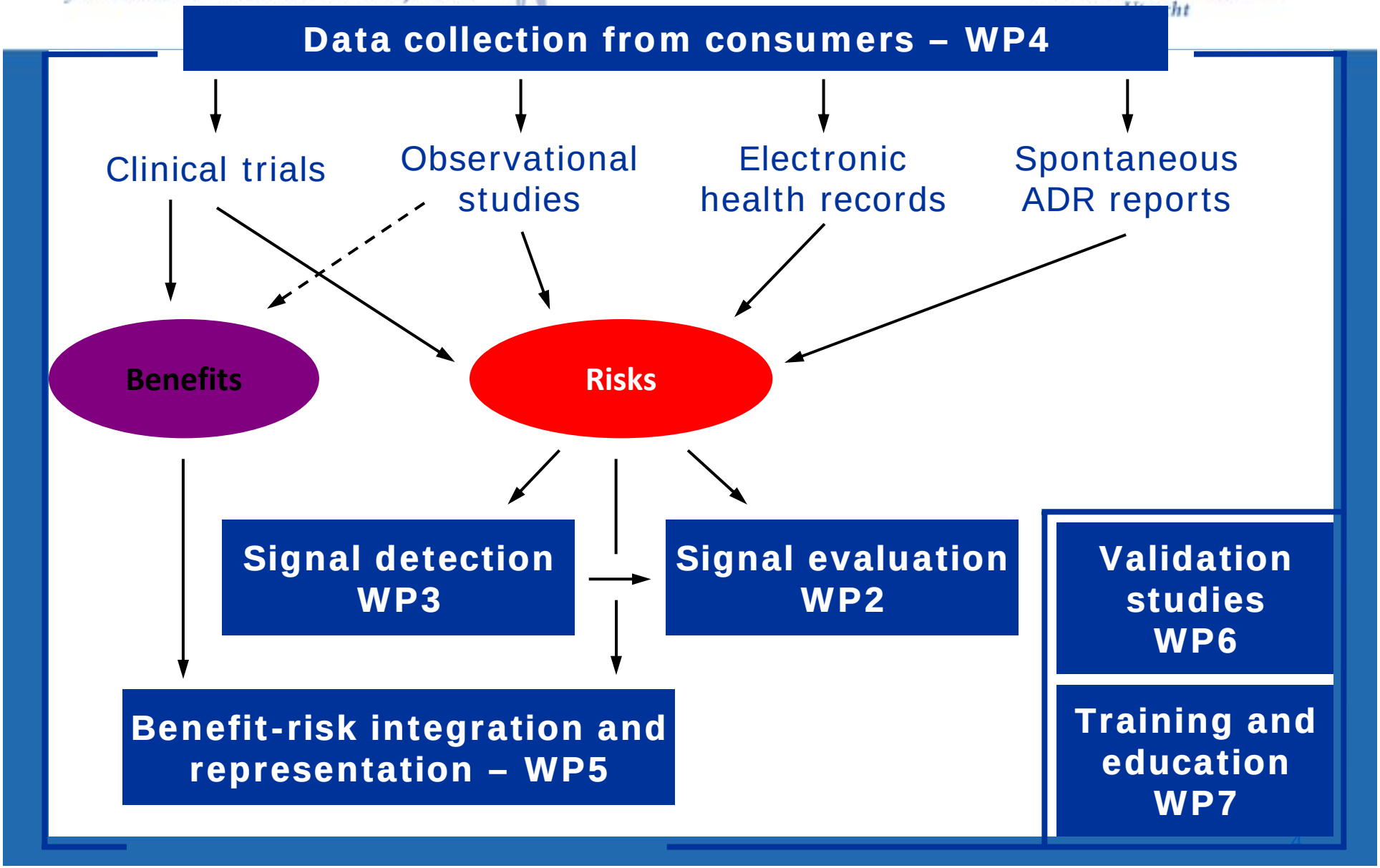

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Partners

Public

Regulators:
EMA (Co-ordinator)
DKMA (DK)
AEMPS (ES)
MHRA (UK)

Academic Institutions:
University of Munich
FICF (Barcelona)
INSERM (Paris)
Mario Negri Institute (Milan)
Poznan University of Medical Sciences
University of Groningen
University of Utrecht
Imperial College London
University of Newcastle Upon Tyne

Others:
WHO UMC
GPRD
IAPO
CEIFE

SMEs:
Outcome Europe
PGRx

Private

EFPIA companies:
GSK (Deputy Co-ordinator)
Sanofi- Aventis
Roche
Novartis
Pfizer
Amgen
Genzyme
Merck Serono
Bayer
Astra Zeneca
Lundbeck
NovoNordisk
Takeda

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WP 2: Framework for pharmacoepidemiological studies

Objectives:

To:

- develop
- test
- disseminate

methodological standards for the:

- design
- conduct
- analysis

of pharmacoepidemiological studies applicable to:

- different safety issues
- using different data sources

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Two studies on the use of statins and the risk of fracture done in GPRD around the same period by two different groups.

	Meier et al., 2000		Van Staa et al., 2001	
Statins only	*Current use*	0.55 (0.44-0.69)	*Current use*	1.01 (0.88-1.16)
	N prescriptions		Time since use	
	- 1-4	0.51 (0.33-0.81)	- 0-3 months	0.71 (0.50-1.01)
	- 5-19	0.62 (0.45-0.85)	- 3-6 months	1.31 (0.87-1.95)
	- 20	0.52 (0.36-0.76)	- 6-12 months	1.14 (0.82-1.58)
			- > 12 months	1.17 (0.99-1.40)
	Recent use	0.67 (0.50-0.92)		
	Past use	0.87 (0.65-1.18)	*Past use*	1.01 (0.78-1.32)
Statins (current) and type of fractures	Femur	0.12 (0.04-0.41)	Hip	0.59 (0.31-1.13)
	Hand, wrist or arm	0.71 (0.52-0.96)	Radius/ulna	1.01 (0.80-1.27)
	Vertebral	0.14 (0.02-0.88)	Vertebral	1.15 (0.62-2.14)
	Other	0.43 (0.23-0.80)		

Why such a difference ?

	Meier et al., 2000		Van Staa et al., 2001	
Source population		370 GPRD practices		683 GPRD practices
Study period		through Sept 1998		through July 1999
Design		Selected case control (3 cohorts)		Conventional case-control
N Cases		3,940		81,880
N Controls		23,379		81,880
Age	*50-69* *70-79* *80-89*	52.2% 28.9% 18.9%	*50-69* *70-84* *≥85*	47.9% 38.9% 13.2%
Sex	*Female*	75.0%	*Female*	75.6%
BMI	*≥25*	57.3%	*≥25*	52.3%

- Different patients (source population, study period, exclusion criteria)
- Study design (e.g. matching criteria for age)
- Definition of current statin use (last 6 months vs. last 30 days)
- Possibly different outcomes (mapping)
- Possibly uncontrolled/residual confounding

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Confounding by indication major focus

Conditional models	Most familiar
Propensity score Instrumental variables	Aim to mimic “randomised” assignment
Marginal structural models	Fundamental different inference

“Causal Inference” somewhat misleading to those familiar with trials

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Implementation of G-computation with complex longitudinal data: Maximizing survival of end stage renal patients by investigating the optimal dialysis treatment switching time

Willem M. van der Wal[1,†], ...

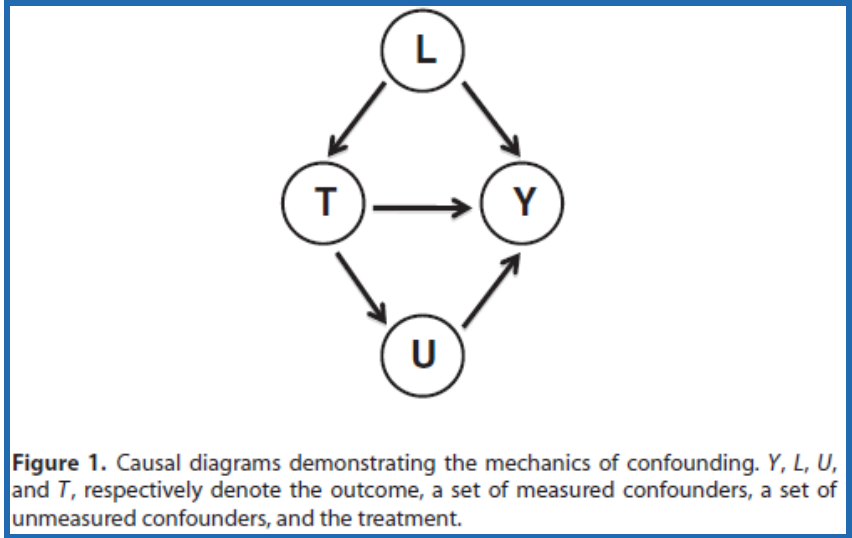
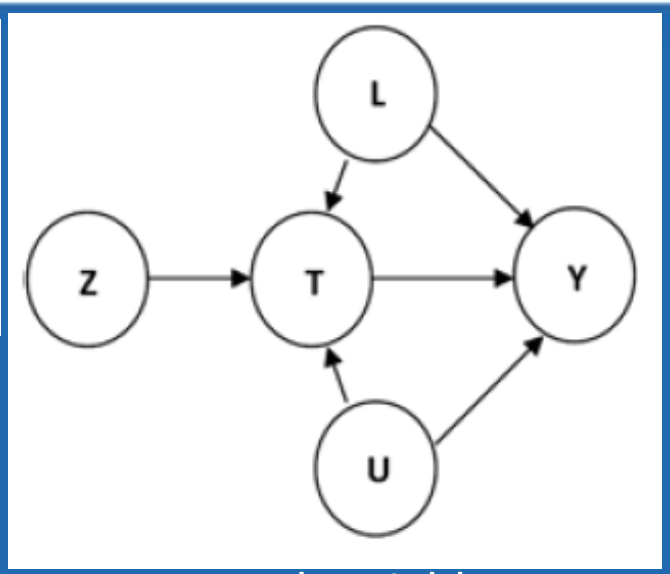


Figure 1. Causal diagrams demonstrating the mechanics of confounding. *Y*, *L*, *U*, and *T*, respectively denote the outcome, a set of measured confounders, a set of unmeasured confounders, and the treatment.



Instrumental variable

Longitudinal data with patterns over time most challenging

Computational issues cannot be ignored (dichotomous outcomes)

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Marginal Structural Models vs Clinical trials

MSM

- Estimate effects at defined population level (& time,..)
- Contrasting counterfactuals:
  - What if all treated by A vs What if all treated by B

Clinical trials

- Estimate effects conditional on trial executed
- Extrapolation to population level separate step
- If study participants would be representative: MSM

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Comparative Effectiveness Research

- Generation and synthesis of evidence
- Compare benefit and harm of alternative methods
- Prevent, diagnose, treat and monitor disease
- ..to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve healthcare at both the individual and population levels.”

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Comparative Effectiveness Research

CLINICAL TRIALS PRESENTATION

Clinical Trials 2012; 9: 6–12

Infusion of statistical science in comparative effectiveness research

Sally C Morton[a] and Jonas H Ellenberg[b]

Beyond the intention-to-treat in comparative effectiveness research

Miguel A Hernán[a,b] and Sonia Hernández-Díaz[a]

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Bridge

- CER triggers thinking across
  - RCTs, observational designs and their synthesis (meta-analysis)
- Rethink RCTs
  - Longitudinal patterns and treatment strategies: design, as-treated, compliance, drop-out
  - Inference to population level (late stage trials)

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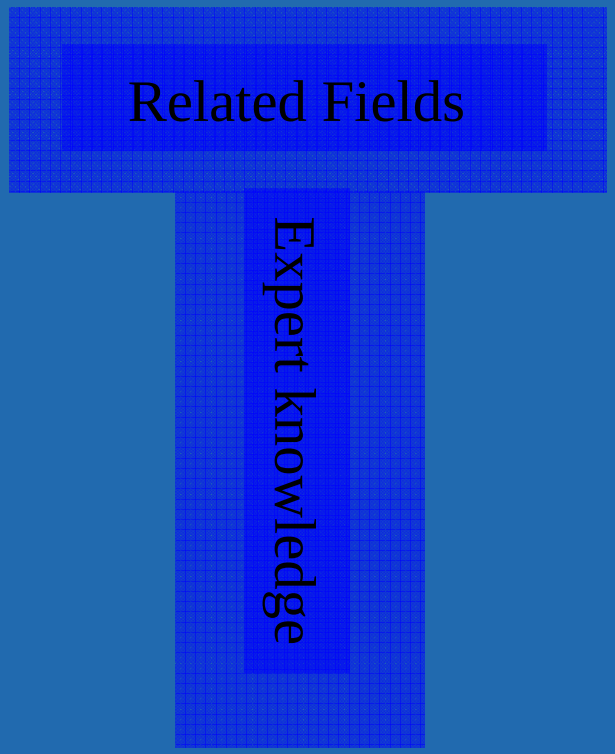
T-model Statistician



'…Become an expert in the subject matter area within which he or she is working.'

'… combining statistical reasoning with knowledge of the real scientific problems, statisticians can and have made high-profile contributions both to the science and to the policy'

Molenberghs, Biometrics 2005

'……..Much harder to copy or improve upon by I model…….'

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"It is not the strongest of species who survive, nor the most intelligent, but the ones most responsive to change."

Charles Darwin

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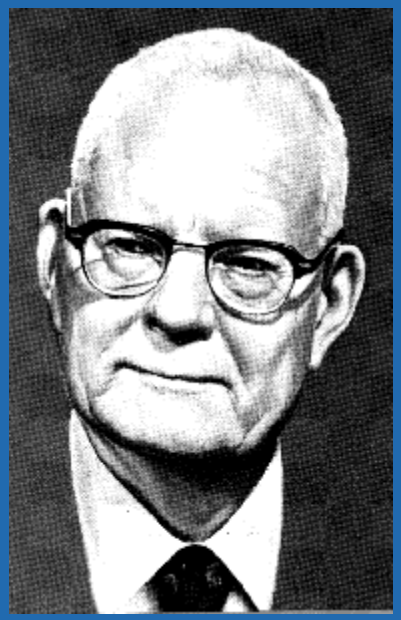
Change is not
essential……survival is not
mandatory.

W.E. Deming



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Some things that can be done

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Some things that can be done

- Diversify (as a group) and specialize (as individual)
- Start careers with broad perspective early
  - Clinical trials is NOT an optimal learning environment for statisticians
- Adopt the innovation cycle
  - Towards data management and statistical programming
  - Towards discovery, epidemiology,..
  - Towards decision makers
  - Towards “off-shoring”
- Entrepreneurial (involved because of added value, not because of regulations or procedure)

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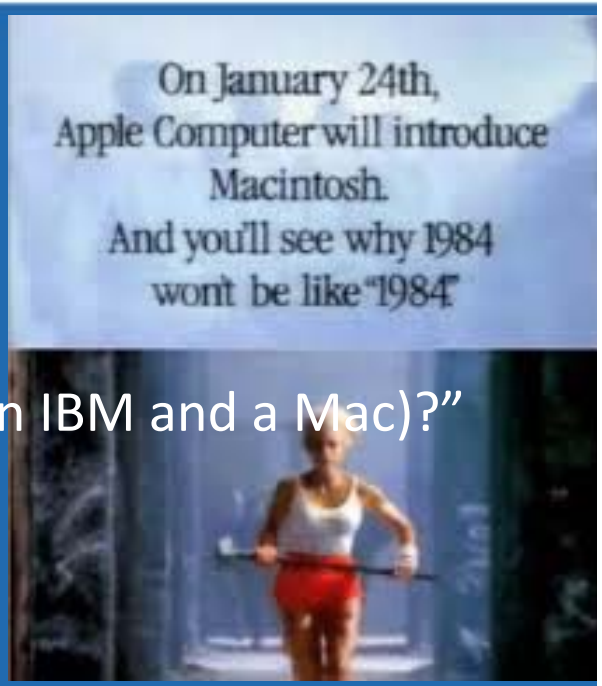
And an old commercial



"What's the most powerful computer (looking at an IBM and a Mac)?"

"That's easy, the one with the highest processor speed, memory, etc."

"No, I don't think so. Its the one that is used the most."