Sponsor- vs. investigator-initiated clinical intervention research

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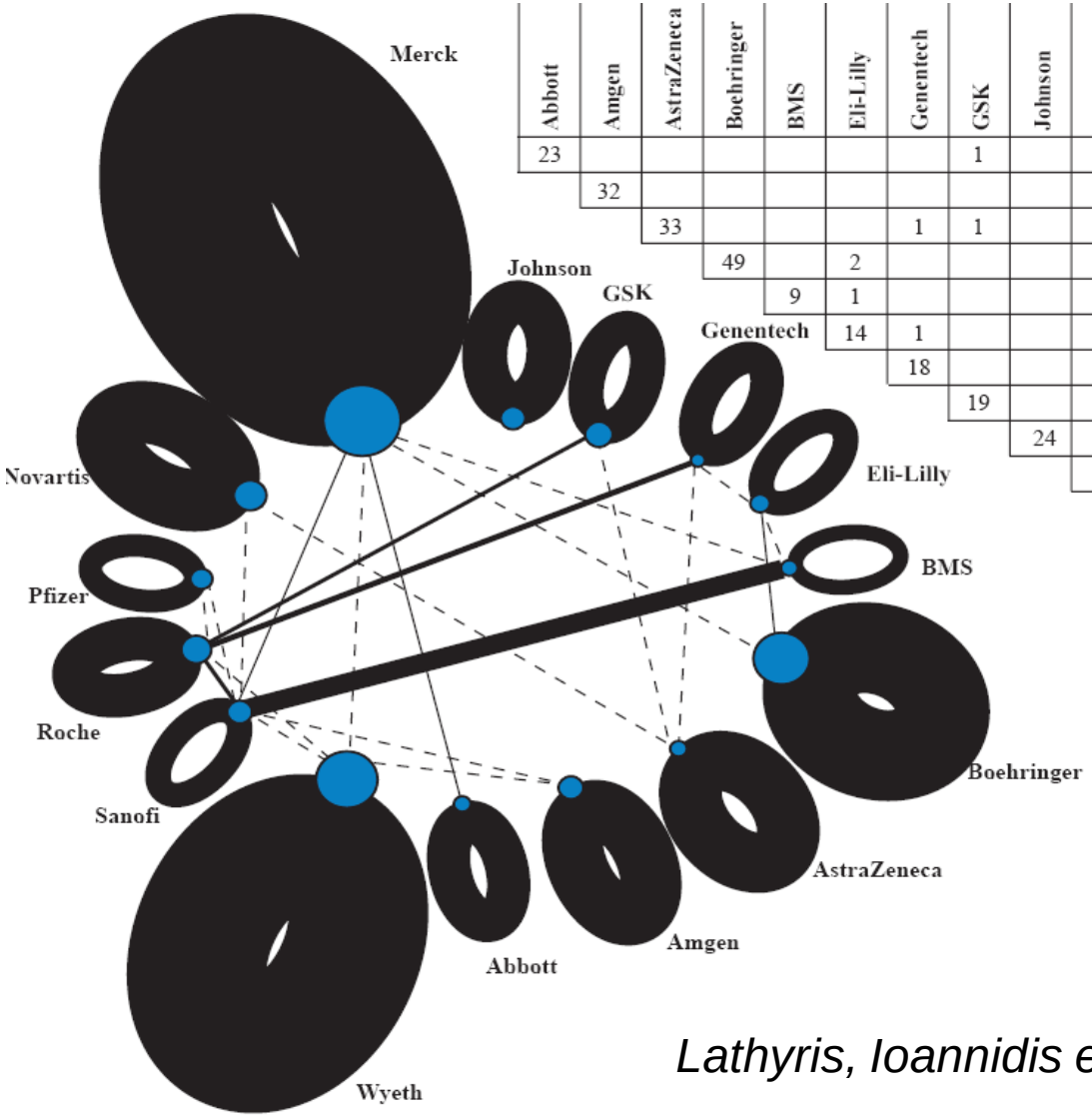
Outline

- The problem with industry-sponsored research
- The problem with investigator-initiated research
- An appraisal
- Proposals for a solution
- Conclusion

Design of clinical research: an open world or isolated city-states (company-states)?



	Abbott	Amgen	AstraZeneca	Boehringer	BMS	Eli-Lilly	Genentech	GSK	Johnson	Merck	Novartis	Pfizer	Roche	Sanofi	Wyeth
Abbott	23							1		2					
Amgen		32												1	1
AstraZeneca			33				1	1			1				
Boehringer				49		2				1					
BMS					9	1				1				11	
Eli-Lilly						14	1								
Genentech							18						4		
GSK								19					3		
Johnson									24						
Merck										87				2	1
Novartis											34		1		
Pfizer												13	1	1	
Roche													24	3	1
Sanofi														14	1
Wyeth															72

Lathyris, Ioannidis et al. Eur J Clin Invest, in press

Head to head comparisons sponsored by one company

- Lead to funny results: *drug A is superior to B, drug B superior to C, and C superior to A*

  Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head-to-head comparison studies of second-generation antipsychotics. Am J Psychiatry 2006)

Pharma-sponsored intervention research (RCTs)

- Is structurally biased – an enormous literature, which I will not review here
- Do not (fairly) address the comparisons that need to be addressed:
  - The comparative effectiveness of interventions
  - Non-pharmacological interventions in comparison to pharmacological

A note of optimism

- From A>B>C paper, and others: the problem of designs with inbuilt bias in favour of sponsored product is perfectly remediable
- RCTs involve subjective design choices; can be made in different ways
- Thus, trials are possible that start from different premises (i.e., not shareholder value) and make different choices

What we need

- Trials set up with an intention to “equipoise”, i.e., that intend to give equal chances to the comparators
- Historically: cannot be done by industry
- We need investigators to set up comparative effectiveness studies

The problem with investigator-initiated intervention research

Amateurish in concepts and design

Anonymised examples (1)

- Two types of “scopy”: invasive (breaks skin, semi-surgical) vs. non-invasive (natural orifice). Used to rule out tumour that is too extensive for surgery.
- Trial:
  - one arm: Invasive
  - other arm: Non-invasive followed by Invasive
- In analysis stage: uncertainty about aims.

Anonymised examples (2)

- Intervention in newborns: inclusion either birth weight (lower than…), or duration of pregnancy (less than…).
- Randomisation was blocked on birth weight. Baseline difference emerged in duration of pregnancy (perhaps due to the “either/or” inclusion, and small numbers).
- Adjustment? Dual credibility problem.

Anonymised examples (3)

- Intervention based on complete practices: randomisation by time intervals: practice was consecutively either “in” or “out” of active treatment – no placebo; open trial.
- However, not all patients in practice treated: only subgroup of patients. During “in” period, doctors decided which patients to treat. During “out” period doctors had to decide “which patients they would have treated”…

An appraisal

The problem with investigator- initiated trials

- NOT a matter of adhering to GCP, informed consent, data acquisition rules, forms & committees, etc.
- But: lack of conceptual knowledge about comparative research, in particular RCTs.

Solutions for comparative effectiveness research

- Should be done independently from the pharmaceutical industry
- Clinical investigators should be trained in concepts of numerical research – will become possible during residency training in internal medicine from 2011
- Cooperative groups should be built, e.g. at University Medical Centers, to help investigators:
  - Avoid conceptual problems
  - Make the trials fair and balanced
  - Help them with procedural aspects (some form of ‘essential’ GCP)

Cooperative groups exist

- Mostly disease oriented
- One example: Children Oncology Group, under aegis of US National Cancer Institute
- Equipoise achieved in successive randomised trials of new treatments vs. standard treatments

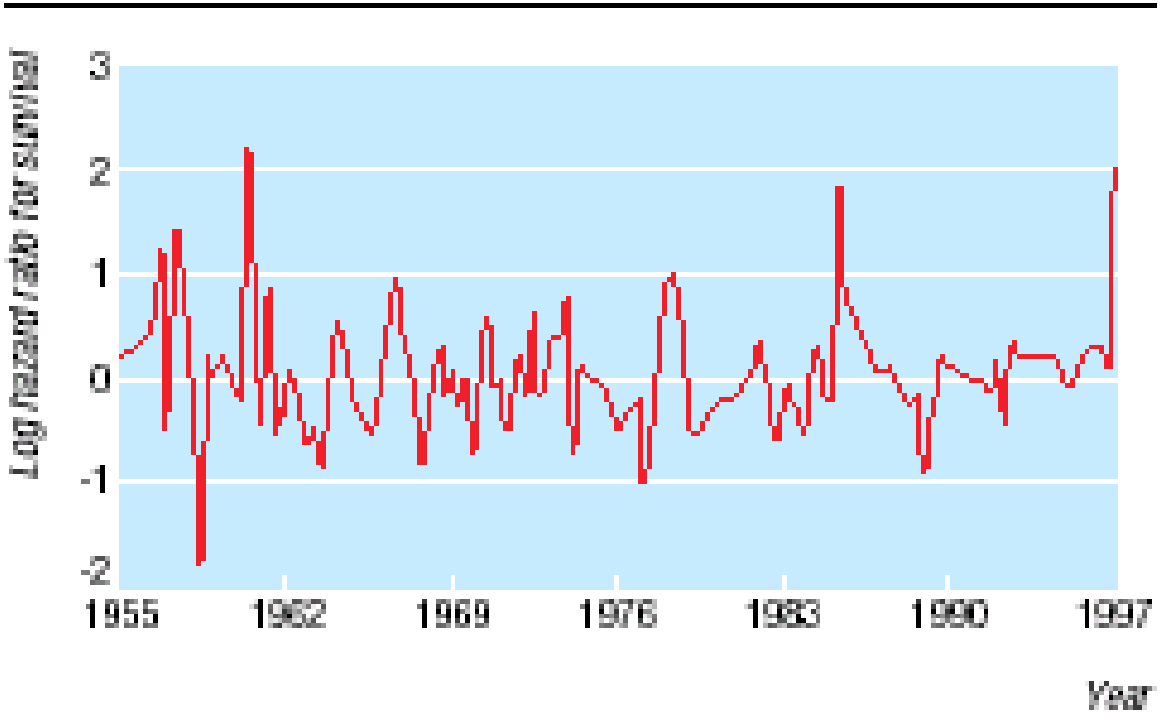


Fig 3 Time series analysis of treatment effect (log hazard ratio) of studies carried out by Children's Oncology Group. White noise pattern indicates no significant autocorrelation between studies carried out at various time intervals. Log hazard <0 indicates superiority of new treatments and >0 a survival advantage for standard treatments

Djulbegovic, BMJ 2005 & Arch Intern Med 2008

In conclusion

- Clinical comparative effectiveness research should be taken over by investigators
- These clinical investigators should be trained in the principles of numerical research
- Leading statisticians & trialists should be retained in academia
- Existing models of investigator-initiated cooperation should be studied
- Obligatory in-depth review of RCTs in clinical trial centers within University Medical Centers