Possiamo sempre fidarci delle “migliori evidenze”? L’integrità della ricerca tra bias di pubblicazione, frodi scientifiche, etica e conflitti d’interesse

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L’integrità della ricerca

1. Bias di pubblicazione
2. Frodi scientifiche
3. Etica
4. Conflitti d’interesse

1. Bias di pubblicazione
• I trials con risultati negativi hanno minori probabilità di essere pubblicati rispetto a quelli con risultati positivi.
• Il publication bias determina una distorsione in senso “optimistico” dei risultati dei trials che si manifesta nelle meta-analisi con stime esagerate dell’effetto terapeutico, o, meno frequentemente, con risultati falsamente positivi.

Chalmers I
Underreporting research is scientific misconduct
JAMA 1990;263:1405-1408

Empirical assessment of effect of publication bias on meta-analyses
BMJ 2000;320:1574-7
1. Bias di pubblicazione

Dimensioni del fenomeno

- Possibile sino al 50% delle meta-analisi pubblicate
- Molto probabile nel 20% dei casi
- In grado di determinare una modifica dei risultati in meno del 10% dei casi


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Serious research misconduct

- Fabrication: invention of data or cases
- Falseification: wilful distortion of data
- Plagiarism: copying of ideas, data or words without attribution
- Failing to get consent from an ethics committee for research
- Not admitting that some data are missing
- Ignoring outliers without declaring it
- Not including data on side effects in a clinical trial
- Conducting research in humans without informed consent or without justifying why consent was not obtained from an ethics committee
- Publication of post hoc analyses without declaration that they were post hoc
- Gift authorship
- Not attributing other authors
- Redundant publication
- Not disclosing a conflict of interest
- Not attempting to publish completed research
- Failure to do an adequate search of existing research before beginning new research

Minor research misconduct

- Publication of post hoc analyses without declaration that they were post hoc
- Gift authorship
- Not attributing other authors
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- Not disclosing a conflict of interest
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Esempi di frode

Pubblicazione di dati “fabbricati”
1. JA, a senior Consultant Physician, pleaded guilty for conducting a sham trial of a calcium-channel antagonist: he had forged consent forms for 17 pts who were never given the drug, and invented EchoCG and MR imaging of the patients.

Lancet 1997;315:205

Pubblicazione di dati “gonfiati”
2. Two clinical scientists distorted their research results. They reported a larger n° of patients and a longer follow up than what could be reconstructed from independent registers.

Lancet 1999;354:57-61

Esempi di frode

Pubblicazione di review apparentemente imparziali, orientate a promuovere un farmaco (scrive un “ghost writer” dell’industria e firma un esperto indipendente)
3. An American Information Company offered a Nordic expert the authorship of a completed review paper recommending a certain drug. The Company aimed to give the impression that the review was impartial

Lancet 1999; 254: 57-61

Esempi di frode

Pubblicazione ripetuta dei dati di un singolo RCT, in articoli firmati da Autori diversi
4. A single RCT of risperidone was reported “not transparently” in 6 different publications with different Authorship

Lancet 1999; 354: 57-61

5. Nine RCTs of ondansetron were published a total of 23 times. There were 4 pairs of almost identical reports with completely different authors

BMJ / 315: 635
6. The Author of a paper discovered that his paper had been plagiarised. Later on, more than 20 papers were found to be plagiarised by the same person, who was dismissed from his professorship.

Lancet 1999; 354: 57-61

7. HD, a clinician, reported that treatment with IFN, colchicine and benzathine penicillin was useful in Behcet disease. The Investigational Committee of the University found that:
- the no. of pts had been inflated;
- contrary to statements in the paper, neither ethics committee approval nor written informed consent had been obtained;
- HD had forged the signatures of alleged co-authors, who denied their participation.

Lancet 2000; 356: 1292 & 1351

1. Placebo orthodoxy
Placebo should be used as a control unless there is an increased risk of death or irreversible morbidity associated with its use.

2. Active-control orthodoxy
If an effective therapy exists, the use of a placebo should be prohibited.

4. Etica

- Dimostrare la superiorità di nuovi farmaci rispetto ai vecchi (interesse legittimo dal punto di vista dell'industria, ma non necessariamente coincidente con quello della salute pubblica) può facilitare il pianificare RCT dove il nuovo farmaco viene confrontato:
  - con il placebo
  - con farmaci non molto efficaci
  - oppure attraverso "il gioco delle dosi"

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Il gioco delle dosi

- Aumento, o diminuzione delle dosi del farmaco "nuovo" o di quello di confronto.
- Si potrebbero, ad esempio, diminuire le dosi del farmaco di controllo (quando si vogliono aumentare le probabilità che il farmaco sperimentale risulti più efficace), o aumentarle al di sopra delle dosi standard, quando si vuole dare più chance al farmaco sperimentale di risultare, a parità di effetto terapeutico, meglio tollerato e scevro da effetti collaterali.

Stelfox HT, Chua G, O'Rourke K, Detsky AS.

Conflict of interest in the debate over calcium-channel antagonists


Trombosi venosa
Novità terapeutica dimezza rischio

04.04.2003
Una assoluta novità terapeutica, il fondaparinux, dimezza il rischio di trombosis venosa rispetto ai farmaci finora utilizzati. Il farmaco è disponibile in Italia, in fascia H-A, a carico del Servizio sanitario nazionale.

I risultati del Fondaparinux sono stati messi in luce da quattro studi clinici condotti in 24 Paesi e in 300 Centri in tutto il mondo.

Questi studi clinici - pubblicati su Lancet e New England Journal of Medicine - hanno reclutato 7,344 pazienti (metà in USA e Canada, il resto in Europa, America latina, Sudafrica e Australia) sottoposti a interventi di chirurgia ortopedica agli arti inferiori.

Nel prevenire la trombosi hanno dimostrato una efficacia superiore del 55% rispetto alla tradizionale eparina a basso peso molecolare.

Fondaparinux was compared with enoxaparin, in four randomised controlled trials of major orthopaedic surgery

- Hip-fracture
- Major knee surgery
- Elective hip replacement
  - EPHESUS Lancet 2002;359:1715-20
  - PENTHATLON Lancet 2002;359:1721-26

Fondaparinux and conflict of interest?

- In the recruitment of patients, the two NEJM papers were oriented internationally and towards the USA, whereas the Lancet papers had European slant.

  All four trials had virtually identical paragraph in their methods section, describing that the trial was designed, supervised, and the paper written by a committee of 10 (one time 11) people, of whom six (one time seven) were employees of the sponsoring companies.

Vandenbroucke JP

Do editors live up to the Sept 10, 2001, expectations?

Lancet 2002;360:1605-6
The sponsor did the analysis for all four papers.

The Lancet papers described that the sponsor also collected the data.

In these arrangements, the sponsors had a majority vote on all aspects of design, interpretation and reporting, and they were the sole analysts.

All authors are consultants for the sponsoring companies!

3/4 of systematic reviews was signed by same author(s)

- Turpie AG. Haematologica 2001;86 (suppl II):59-62
- Turpie AG, Bauer KA, Eriksson BI, Lassen MR. Arch Intern Med 2002;162:1933-40

Indeed, the impression one gets is that the series of publications and associated meta-analyses by investigators who were also involved in the design and undertaking of the original fondaparinux studies has been part of a well orchestrated plan aimed at with introduction of this antithrombotic agent to the market. All involved, including investigators well respected in the specialty and medical journals have been, willingly or not, part of this aim.

Scientific harassment by pharmaceutical companies: time to stop

Hailey D
CMAJ 2000;162:212-213

Is academic medicine for sale?

Angell M
Bodenheimer T

Uneasy alliance. Clinical investigators and the pharmaceutical industry


Commens CA

Truth in clinical research trials involving pharmaceutical sponsorship

MJA 2001;174:648-649

De Maeseneer JM, van Driel ML, Green LA, van Weel C

The need for research in primary care

Lancet 2003, 18 October

We have a mismatch between primary care-based questions and hospital care-based answers.

Explanatory RCTs
Condizioni sperimentali ideali

Validità interna
(efficacy)

Pragmatic RCTs
Setting assistenziali reali

Applicabilità clinica
(effectiveness)