

 L'Integrità della Ricerca Biomedica  
 nell'era dell'Evidence-based Health Care


 Gruppo Italiano per la Medicina Basata sulle Evidenze

Bologna, 23 novembre 2001

**Istituti Ortopedici Rizzoli**

---

## La frode scientifica nella ricerca clinica

Antonino Cartabellotta

---

GIMBE® - Gruppo Italiano per la Medicina Basata sulle Evidenze

GIMBE® - © 1996-2001

## La frode scientifica nella ricerca clinica

---

1. Esempi di frode
2. Tassonomia della frode
3. Conseguenze della frode
4. Prevenzione della frode

GIMBE® - © 1996-2001

### 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.  
*BMJ 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*

GIMBE® - © 1996-2001

### 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; 354: 57-61*

GIMBE® - © 1996-2001

### 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 1996;347:1024*
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 1997;315:635*

GIMBE® - © 1996-2001

### Esempi di frode

---

**Plagio: pubblicazione di dati altrui**

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*

GIMBE® - © 1996-2001

## Esempi di frode

### Invenzione-Falsificazione di dati

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*

GIMBE® - © 1996-2001

## Esempi di frode

### Invenzione-Falsificazione di dati

8. AKB, a consultant surgeon was suspended for 1 year by the GMC for publishing a deliberately falsified article about NSAID-induced damage in rats. There was a 6-7 years of delay for the case to get to the GMC, due to the effort of the University of Mr AKB to cover the affair. Recently, the research supervisor of the Department of AKB was "asked to refrain from teaching, supervising and examining students, until he has taken a course in research supervision"

*Gut 1990;31:358  
BMJ 2000; 321:1429  
Lancet 2001;357:780*

GIMBE® - © 1996-2001

## Esempi di frode

### Publication bias

- 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 "ottimistico" dei risultati dei trials che si manifesta nelle meta-analisi con stime esagerate dell'effetto terapeutico, o, meno frequentemente, con risultati falsamente positivi.

GIMBE® - © 1996-2001

*Chalmers I*

## Underreporting research is scientific misconduct

*JAMA 1990;263:1405-1408*

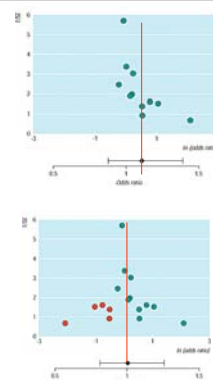
GIMBE® - © 1996-2001

*Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR*

## Empirical assessment of effect of publication bias on meta-analyses

*BMJ 2000;320:1574-7*

GIMBE® - © 1996-2001



GIMBE® - © 1996-2001

*Sutton AJ, et al. BMJ 2000*

## Esempi di frode

### Publication bias: dimensioni del fenomeno

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

Sutton AJ, et al. *BMJ* 2000

GIMBE<sup>®</sup> - © 1996-2001

## La frode scientifica nella ricerca clinica

1. Esempi di frode
2. **Tassonomia della frode**
3. Conseguenze della frode
4. Prevenzione della frode

GIMBE<sup>®</sup> - © 1996-2001

## Tassonomia della frode

BEHAVIOUR	RCP 1991	MRC	US	Denmark 1992	Finland 1994	Norway 1994	Sweden 1997
Inventing a case	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Failing to get consent from an ethics committee	No	Yes	Yes	No	Yes	Yes	?
Publication of <i>post hoc</i> analyses without declaration that they were <i>post hoc</i>	?	Yes	?	?	?	?	?
Gift authorship	?	Yes	?	Yes	?	?	?
Not disclosing a conflict of interest	?	?	?	?	?	?	?
Not publishing completed research	No	?	?	No	No	No	No

COPE Report 2000

GIMBE<sup>®</sup> - © 1996-2001

## Serious research misconduct

- Fabrication: invention of data or cases
- Falsification: 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

COPE Report 2000 (modified)

GIMBE<sup>®</sup> - © 1996-2001

## La frode scientifica nella ricerca clinica

1. Esempi di frode
2. Tassonomia della frode
3. **Conseguenze della frode**
4. Prevenzione della frode

GIMBE<sup>®</sup> - © 1996-2001

## Conseguenze della frode

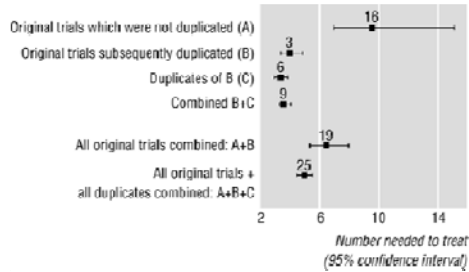
- Sperimentazioni cliniche "fabbricate" o "gonfiate"
- Rassegne elaborate dall'industria e firmate da esperti
- Pubblicazione ripetuta, non dichiarata, di RCTs con risultati positivi
- Mancata pubblicazione di RCTs negativi (publication bias)



**Sovrastima dell'efficacia terapeutica**

GIMBE<sup>®</sup> - © 1996-2001

Number needed to treat to prevent vomiting up to the 24th postoperative hour with intravenous ondansetron 4 mg compared with placebo. The numbers above the symbols are the numbers of reports.



GIMBE® - © 1996-2001

Tramèr MR, et al. *BMJ* 1997

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

## Conflict of interest in the debate over calcium-channel antagonists

*N Engl J Med* 1998; 338: 101-6

GIMBE® - © 1996-2001

**TABLE 3. AUTHORS WITH FINANCIAL RELATIONSHIPS WITH PHARMACEUTICAL MANUFACTURERS.**

MANUFACTURER	SUPPORTIVE AUTHORS (N=24)	NEUTRAL AUTHORS (N=15)	CRITICAL AUTHORS (N=30)	CHI-SQUARE FOR LINEAR TREND	P VALUE FOR TREND
no. of authors (%)					
Manufacturer of calcium-channel antagonist	23 (96)	9 (60)	11 (37)	22.02	<0.001
Manufacturer of competing product	21 (88)	8 (53)	11 (37)	14.84	<0.001
Any manufacturer	24 (100)	10 (67)	13 (43)	22.68	<0.001

GIMBE® - © 1996-2001

Stelfox HT, et al. *N Engl J Med* 1998

## Conseguenze della frode

- Pubblicazione di dati copiati da lavori pubblicati da altri
- Falsificazione
- Invenzione-falsificazione di dati sperimentali



**Promozione di carriere professionali, in particolare accademiche**

GIMBE® - © 1996-2001

## La frode scientifica nella ricerca clinica

1. Esempi di frode
2. Tassonomia della frode
3. Conseguenze della frode
4. **Prevenzione della frode**

GIMBE® - © 1996-2001

## Prevenzione della frode scientifica

### 1. Nella fase del disegno della sperimentazione

- Comitati Etici
- Osservatorio Nazionale delle sperimentazioni cliniche
- Registri di RCTs

### 2. Durante il corso della sperimentazione

- Organismi di monitoraggio e controllo (eligibilità dei soggetti, applicazione dei trattamenti, end points, etc)

### 3. Dopo la pubblicazione

- "Retraction", pubblicata dalla stessa rivista

GIMBE® - © 1996-2001

## Organismi di monitoraggio e controllo

### 1. Ad hoc organizations

- USA: Office of Research Integrity (ORI)
- UK: Committee on Publication Ethics (COPE)
- National Committees on Scientific Dishonesty in the Nordic Countries
- Italia: Osservatorio Nazionale sulle Sperimentazioni Cliniche (Ministero della Salute)

### 2. Organismi interni delle Istituzioni di ricerca

- Comitati etici, *clinical trial units*

### 2. Industria Farmaceutica

- Organismi per il monitoraggio dei propri RCTs

GIMBE® - © 1996-2001

*Nylenna M, Andersen D, Dahlquist G, Sarvas M, Aakvaag A, on behalf  
National Committees on Scientific Dishonesty in the Nordic Countries*

## Handling of scientific dishonesty in the Nordic countries

*Lancet 1999;354:57-61*

GIMBE® - © 1996-2001



[www.publicationethics.org.uk](http://www.publicationethics.org.uk)

GIMBE® - © 1996-2001

### Contents

COPE moves into the next millennium Michael J.G. Farthing	1
Who will lead on research and publication misconduct in the UK? Michael J.G. Farthing, Richard Smith, Richard Horton	2
Journal membership	3
Constitution of the Committee on Publication Ethics	4
Joint Consensus Conference on Misconduct in Biomedical Research:	6
Consensus Statement	
Position papers	
What is research misconduct? Richard Smith	7
Clinical research fraud and misconduct: how is it diagnosed? Frank Wells	12
Fraud and misconduct in biomedical research: how should we respond? Stephen Kaufman, GRD Catto	17
Abstract presented at the Research on Research Integrity meeting, November 2000	21
Update on cases submitted to COPE	22
Cases submitted to COPE June 1999 to September 2000	25

GIMBE® - © 1996-2001



[ori.dhhs.gov](http://ori.dhhs.gov)

GIMBE® - © 1996-2001



[oss-sper-clin.sanita.it](http://oss-sper-clin.sanita.it)

GIMBE® - © 1996-2001

## Registri di RCTs

Horton R, Smith R.

### Time to register randomised trials The case for registering all clinical trials is now unanswerable

BMJ 1999;319:865-6  
Lancet 1999;354:1138-9

GIMBE<sup>®</sup> - © 1996-2001

## Registri di RCTs

### mRCT metaRegister of Controlled Trials

### ISRCTN International Standard Randomised Controlled Trial Number

GIMBE<sup>®</sup> - © 1996-2001

## Retraction of publication

- Dichiarazione di "misconduct" e pertanto di non validità di studi già pubblicati

*"The retraction [of a fraudulent work published by a journal], so labeled, should appear in a prominent section of the journal, be listed in the contents page, and include in its heading the title of the original article"*

International Committee of Medical Journal Editors.  
Retraction of research findings.  
Ann Intern Med 1988

GIMBE<sup>®</sup> - © 1996-2001

### Retraction: Interferon alfa-2b. . . in Behçet's disease

Lancet 2000;356:1292

The Feb 16, 2000, The Lancet published an article by Hattji Deming and colleagues reporting the results of a randomised trial of interferon alfa-2b, sulphur, and benzathine penicillin among patients with Behçet's disease. In a letter to the Editor, the Dean of Hacettepe University Medical School, Prof Iskender Nettek, writes to state, according to the findings of an "Investigational Committee", and contrary to statements made in the published paper, there was no ethics committee approval for the study and informed consent was not obtained from participating patients. The corresponding authors, Dr Deming, wrote to three laboratories.

The journal was alerted to problems with this paper by letters, also published in our Correspondence column, from alleged co-authors Dran Kildan, Nuzur Dincel, and Chaman Shukla. They do not accept responsibility for the published article. The Hacettepe committee found, and Dr Deming's co-edited that the signatures of an author on the submitted manuscript were forged by Dr Deming's team.

Taken together, these allegations, and the serious ethical transgressions they state, mean that the paper by Deming and colleagues must be retracted from the published record. In a letter to the journal, also published this week, Dr Deming disputes the accuracy of this statement, that I am satisfied that his admission readily allows the decision to retract. Full statements about patient consent and ethics committee approval cannot be obtained by pointing to the importance of the study question or its final result. In short, the end cannot justify the means.

I finally, there is remaining uncertainty about the validity of the reported data. Professor Nettek notes that "the investigational committee believed that some deception and falsification might have taken place". Dr Deming denies the allegations. The Higher Educational Council of the University does not appear to consider this matter further but could not reach a final conclusion. Further investigations are in progress.

Hacettepe University declares itself for moving to resolve this matter quickly, carefully, and openly.

Richard Peto  
The Lancet, London WC2A 3NH, UK

© Copyright © 2000 by Elsevier B.V. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or by any information storage and retrieval system, without the prior written permission of Elsevier B.V. or its publisher, North-Holland Publishing Co.

GIMBE<sup>®</sup> - © 1996-2001

## Retraction of publication

### La "retraction" è tempestiva?

- L'intervallo medio intercorso fra la pubblicazione dell'articolo e la sua "retraction" nei 25 casi registrati dall'ORI è stato di 83 mesi

Parrish DM. Acad Med 1999.

### La "retraction" è efficace?

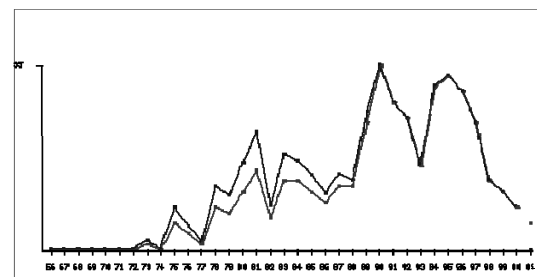
- Dopo retraction, le citazioni degli articoli affetti da "misconduct" si riducono del 35% circa, ma non si azzerano

JAMA 1990

- Qual è l'entità del fenomeno "retraction"?

GIMBE<sup>®</sup> - © 1996-2001

## Retracted publication: MEDLINE 1966-2001



GIMBE<sup>®</sup> - © 1996-2001

## Conclusioni

---

- Esistono in letteratura numerosi esempi di frode che vanno dalla completa invenzione di uno studio, alla sua parziale falsificazione, al "gonfiamento" dei dati, alla duplicata pubblicazione dei risultati di un singolo RCT, alla mancata pubblicazione dei RCTs negativi
- La prevenzione e la correzione della "misconduct" richiedono la collaborazione tra ricercatori, sanità pubblica, industria ed editori.

GIMBE® - © 1996-2001

## RINGRAZIAMENTI

Si ringrazia il Prof. Luigi Pagliaro dell'Università degli Studi di Palermo per il materiale fornito ed i preziosi suggerimenti

GIMBE® - © 1996-2001