Fraud and misconduct in Medical Research

Research Integrity versus Research Ethics
Research Integrity

What is it?
Defined by the US Commission (DHHS)

• “is significant misbehaviour that improperly appropriates the intellectual property or contributions of others

• that intentionally impedes the progress of research, or

• that risks corrupting the scientific record or compromising the integrity of scientific practices.”
Commonly interpreted

- F
  - Fraud
- F
  - Fabrication
- P
  - Plagiarism
Fraud and misconduct

- The motivations for misconduct are varied and include:
  - Scientific rivalry
  - Competition for research funding
  - the necessity to sustain a publication output
  - But also
    - Greed
    - Vanity or arrogance
    - Sheer boredom of routine clinical practice
    - Emotional disturbance or mental illness

Frank Wells
"I already wrote the paper. That's why it's so hard to get the right data."
Fraud and misconduct

The flagrant examples are:

Fabrication
Falsification
Plagiarism
Theft of data
The High and the Mighty: Cellists Scrotum!

- **1974** - Case Report by John Murphy in BMJ
  - Non-medical husband Elaine Murphy
    - Later to become Baroness Murphy
- **2009**
  - admitted it was all Fabricated
    - Still Honourable(???) member of House of Lords
In an ear infection study, the protocol required subjects to have a certain bacterial infection. Some subjects had no such infection. Fiddes directed study coordinators to purchase the bacteria from a commercial supplier and introduced the infection into the ear, then treated it.
Not only once

• In a contraceptive drug study, Fiddes substituted cervical smears, took blood from staff members (as if they were patients) and completed the records for any patients who dropped out.

• The company monitors and FDA personnel never noticed any problems.

• If it had not been for a disgruntled employee, who complained to the Office for Human Research Protection, this would have gone on ............
Outcome

Robert Fiddes, MD, President of the Southern California Research Institute was sentenced in 1998 to 15 months in prison and ordered to pay $800,000 in restitution for the fabrication and falsification of over 200 studies sponsored by 47 drug companies.
Scientific Misconduct

Researcher Faces Prison for Fraud in NIH Grant Applications and Papers

In the most extensive scientific misconduct case the National Institutes of Health (NIH) has seen in decades, a researcher formerly at the University of Vermont College of Medicine in Burlington has admitted in court documents to falsifying data in 15 federal grant applications and numerous published articles. Eric Poehlman, an expert on menopause, aging, and metabolism, faces up to 5 years in jail and a $250,000 fine and has been barred for life from receiving any U.S. research funding.

Scientists say the falsified data—including work in

for total cholesterol, insulin, resting metabolic rate, and glucose” were falsified or fabricated, said a statement Poehlman signed last week. In an effort to portray worsening health in the subjects, DeNino tells Science, “Dr. Poehlman would just switch the data points.”

After DeNino filed a formal complaint, a university investigative panel looked into Poehlman’s research and uncovered falsified data in three papers. These included a much-cited 1995 Annals of Internal Medicine study that suggested hormone replacement therapy could prevent declines in energy expenditure and increases in body fat during menopause. In that paper Poehlman presented metabolic data on 35 women taken 6 years apart. Most of the women did not exist, according to the statement Poehlman signed. (In 2003 the paper was retracted.) Poehlman left Vermont in 2001, before the investigation ended, for the University of Montreal. He left there in January and now lives in Montreal.
Fraud and misconduct

- The manner in which research is conducted gives rich opportunity for a multitude of less obvious transgressions such as:
  - The omission of inconvenient data
  - Publication of only supportive data
Fraud and misconduct

- Overlooking others’ use of flawed data
- Statistical ‘massage’ of results until a positive test results
- Using another person’s ideas without permission
Clinical research fraud is best defined as:

• The generation of false data with the intent to deceive

Frank Wells
The Rumsfeld Question

The Unknown
As we know,
There are known knowns.

There are things we know we know.
We also know
There are known unknowns.

That is to say
We know there are some things
We do not know.

But there are also unknown unknowns,
The ones we don't know
We don't know.
Fraud and misconduct

• A survey reported that 33% of 3,247 early- and mid-career scientists funded by the USA NIH admitted to one of ten types of misconduct

### Examples of Cases in the UK since 1974

With thanks to Dr Frank Wells

<table>
<thead>
<tr>
<th>Year</th>
<th>Name</th>
<th>Occupation</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>J P Sedgwick</td>
<td>GP, High Wycombe</td>
<td></td>
</tr>
<tr>
<td>1977</td>
<td>Robert Gullis</td>
<td>Biochemist, Birmingham University</td>
<td></td>
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<tr>
<td>1981</td>
<td>Michael Purves</td>
<td>Physiologist, Bristol University</td>
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<tr>
<td>1986</td>
<td>Art Connolly</td>
<td>Medical student, Oxford Univ.</td>
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<tr>
<td>1988</td>
<td>Uzair Siddiqui</td>
<td>Psychiatrist, Durham</td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td>K Francis</td>
<td>GP, Coventry</td>
<td></td>
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<tr>
<td>1991</td>
<td>David Latta</td>
<td>GP, Glasgow</td>
<td></td>
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<tr>
<td>1992</td>
<td>Drs Chandnani and Vishin</td>
<td>GPs, Leeds</td>
<td></td>
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<tr>
<td>1994</td>
<td>John Anderton</td>
<td>Nephrologist, Edinburgh</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>Jyoti Agarwala</td>
<td>GP, Salford</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>Paul Presley</td>
<td>Gloucester GP, deceased</td>
<td></td>
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<tr>
<td>1996</td>
<td>Geoffrey Fairhurst</td>
<td>GP, St Helens</td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>Malcolm Pearce</td>
<td>Obstetrician, St George’s</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Richard Wilson</td>
<td>Endocrinologist, Sheffield</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Robert Adams</td>
<td>GP, Letchworth</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>Kevin Gangar</td>
<td>Gynaecologist, Weybridge</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Goran Jamal</td>
<td>Neurologist, Glasgow</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>Tonmoy Sharma</td>
<td>Psychiatrist, London</td>
<td></td>
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</table>
Lessons from the UK

The Siddiqui case
(British Medical Journal 1988; 296: 306)
12 patients with fabricated biochemistry
1 non-existent patient
Blamed his junior colleague

The sponsor was reluctant to take any action

The doctor was erased from the medical register
Some examples in the UK:

- **Fabricating Ethics Committee Approval**
  - A general practitioner fabricated research ethics committee approval, twice.
  - Erased from the Medical Register.
  - A second general practitioner committed suicide after, amongst other fraudulent activities, forging REC approval.
  - An academic consultant forged REC approval twice for the same study. Admonished and registration conditional upon his conducting subsequent research under supervision.
Patients who do not exist

• An academic consultant surgeon purported to
  – have assessed a patient in a study for six months after the patient’s death and to having assessed
  – other patients not attending the hospital.

• Found guilty of serious professional misconduct
Studies that did not take place

• Two consultant gynaecologists, one academic and one non-academic, published articles purporting to report events that did not occur
• as well claimed to have carried out studies known not to have been conducted,
• reporting on findings known not to have occurred.
• One was erased from the medical register,
• the other is under investigation.
Compelling others to behave dishonestly

- An academic consultant physicians fabricated laboratory data
- Made secretary “witness” non-existent signatures.
- Erased from medical register.
Multiple use of same material

• A general practitioner (on his own Local Research Ethics Committee)
  – took large amounts of blood from his elderly patients which he then divided into several aliquots
  – purporting to come from different patients.

• Erased from the medical register.
Forging the handwriting of patients

- An investigator forged multiple patient signatures (191 forgeries)
- Other data in 21 studies.

- Found dead in swimming pool after submission of 2 statutory declarations to the GMC.

- Another investigator completed the diary cards of all the patients taking part in a clinical trial
- Used members of his family to do so.
Bribery

- A general practitioner offered a patient a bribe not to co-operate with MLI when he realised he was being investigated.

- Erased from the medical register.
  - *The bribe was for £2,000 (2,320€)*
Not only in UK

- France
- In 1993, Lagarde and Maisonneuve wrote: “The borders between negligence, misconduct and fraud are difficult to assess. There are cases of misconduct and fraud in France but owing to the Latin mentality, and to the way French journals are run, these cases are never disclosed.”
# Examples of Cases in Germany since 1974

<table>
<thead>
<tr>
<th>Year</th>
<th>Case Study</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1974</td>
<td>Hasko Paradies (Cell biologist, Free University of Berlin)</td>
<td>1977 Robert Gullis (Biochemist, Max-Planck Institute)</td>
</tr>
<tr>
<td>1995</td>
<td>Benzol study (Southern Germany)</td>
<td>1997 Guido Zadel (Chemistry student, Bonn University)</td>
</tr>
<tr>
<td>1999</td>
<td>Thomas Lenarz (ENT specialist, Hannover University)</td>
<td>1999 Peter Seeburg (Gene-cloning research, Max-Planck Institute, Heidelberg)</td>
</tr>
</tbody>
</table>
Threats to German Misconduct Governance

- German data protection law prohibits REC discovery

- Research Participant protection must be paramount
Research scam makes waves

A Norwegian doctor's fabrication of cancer research is making waves far beyond Norway's borders. The fraudulent research may have led to faulty treatment of cancer patients, international investigations have been launched into how the fraud could have occurred, and top Norwegian officials all the way up to the ministerial level are desperately trying to control the damage.

The editor of the respected magazine, The Lancet, in which the fabricated article was published, calls the fraud "the worst the research world has seen."

Richard Horton told Oslo newspaper Aftenposten that he also can't understand how the Oslo doctor's 13 co-authors and colleagues on the fraudulent cancer research project could have been duped as well.

Horton claims at least six of the doctor's co-authors corresponded with The Lancet, and were highly involved with the substance of the article.
Registration of Clinical Trials

• Researchers who under-report their results are guilty of scientific and ethical misconduct

• Science is cumulative, and researchers must cumulate more scientifically

• The human costs of not paying attention to these issues can be substantial

Iain Chalmers @ EMRC Standing Committee Meeting, Reykjavik. April 2000
Autologous myoblasts and fibroblasts versus collagen for treatment of stress urinary incontinence in women: a randomised controlled trial

Hannes Strasser, Reiner Marklmaier, Eva Margreiter, Gernot Michael Piringer, Michael Mitterberger, Ferdinand Preuschl, Hans Ulmar, Martin Fussenegger, Kurt Kepfler, Georg Bartsch

Summary
Background Preliminary studies have suggested that transurethral injections of autologous myoblasts can aid in regeneration of the rhabdosphincter, and fibroblasts in reconstitution of the urethral submucosa. We aimed to compare the effectiveness and tolerability of ultrasonography-guided injections of autologous cells with those of endoscopic injections of collagen for stress incontinence.

Methods Between 2002 and 2004, we recruited 60 eligible women with urinary stress incontinence. 42 of these women were randomly assigned to receive transurethral ultrasonography-guided injections of autologous myoblasts and fibroblasts, and 21 to receive conventional endoscopic injections of collagen. The first primary outcome measure was an incontinence score (range 0–6) based on a 24-hour voiding diary, a 24-hour pad test, and a patient questionnaire. The other primary outcome measure was contractility of the rhabdosphincter and thickness of both the urethra and rhabdosphincter. Analysis was by intention to treat. This trial is registered with Controlled-Trials, number CCTNAPN-16630.

Findings At 12 months' follow-up, 38 of the 42 women injected with autologous cells were completely continent, compared with two of the 21 patients given conventional treatment with collagen. The median incontinence score decreased from a baseline of 6.0 (IQR 6.0–6.0) to 0.0 (IQR 0.0–6.0) for patients treated with autologous cells, and 6.0 (3.5–6.0) for patients treated with collagen (p<0.0001). Ultrasoundographic measurements showed that the mean thickness of the rhabdosphincter increased from a baseline of 2.13 mm (SD 0.39) for all patients to 2.48 mm (SD 0.28) for patients treated with collagen (p=0.0001). Contractility of the rhabdosphincter increased from a baseline of 0.56 mm (SD 0.32) to 1.56 mm (SD 0.28) for patients treated with autologous cells and 0.67 mm (SD 0.51) for controls (p<0.0001). The change in the thickness of the urethra after treatment was not significantly different between treatment groups. No adverse effects were recorded in any of the 63 patients.

Interpretation Long-term postoperative results and data from multicentre trials with larger numbers of patients are needed to assess whether injection of autologous cells into the rhabdosphincter and the urethra could be a standard treatment for urinary incontinence.

Introduction
The most common causes of urinary incontinence are excessive activity of detrusor (neurogenic and idiopathic), which is known as urge incontinence, and incompetence of the urethral sphincter complex, which causes stress incontinence. Because 78% of incontinent women suffer from stress or mixed urinary incontinence, the target of treatment in most women is the urethral sphincter complex—i.e., the urethra and striated rhabdosphincter.

Factors that affect closure of the urethra include urethral smooth and striated muscle tone and the supportive properties of the urethral muscles and submucosa, especially the vascular submucosal layer. Poor mucosal function, due to atrophy and reduced vascularisation, might contribute to stress incontinence, especially in elderly women with low oestrogen. The role of the submucosal layers of the rhabdosphincter is integral to the urethral closure mechanism. The resting tone and contractility of the rhabdosphincter are noticeably reduced in incontinent patients, and the urethra does not close completely. Damage to this muscle can result from maternal injury during childbirth or from surgical injury. Spontaneous apoptosis also contributes to an age-dependent loss of the striated muscle cells of the rhabdosphincter. Conventional surgical procedures to treat urinary incontinence produce a mean rate of up to 70% continence 1 year after surgery, but this continence rate has been shown to decrease with time. Injection of a bulking agent, such as collagen, into the perurethral tissue to compress the urethra and thus occlude the urethral lumen is one of the standard techniques for treatment of urinary incontinence. Injection of bulking agents is less invasive than other surgical treatments, but overall success rates are poor. Implantation or injection of material into the lower urinary tract can also cause severe side-effects.
The Lancet paper

Austrian stem cell trial

• Stress urinary incontinence study
• Muscle biopsy upper arm
• 250 mL blood
• *In vitro* cultivation autologous myoblasts and fibroblasts
• Trans-urethral injections
• Similar study rejected in NL in 2006
A few weeks later

Expression of concern—autologous myoblasts and fibroblasts for treatment of stress urinary incontinence: a randomised controlled trial

On April 22, it was brought to our attention that the published trial registration number provided by the authors of this study is incorrect. We have also been made aware of concerns about the ethical approval and conduct of this study, which are currently subject to investigations in Austria. Pending the outcome of these investigations, we issue an expression of concern about the article by Dr Hannes Strasser and colleagues.

The Editors of The Lancet

Report finds grave flaws in urology trial

A clinical trial of a stem-cell procedure for urinary incontinence by urologists at the Medical University of Innsbruck, Austria, was full of serious procedural and ethical problems, finds a report by the government's Agency for Health and Food Safety.

The study by Hannes Strasser and his colleagues, to determine the experimental therapy's efficacy, was published last year (H. Strasser et al. Lancet 369, 2179–2186; 2007). A partial study was published a few months after (H. Strasser et al. World J. Urol. 25, 385–392; 2007).

The agency's report says that the urologists failed to get appropriate approval for the trial from authorities, including an ethics committee, and failed to adequately inform patients about the nature of the procedures and to insure them. Other problems outlined in the report include poor study design, inconsistent handling of patients and failure to randomize patients properly.

The report also says that many of the documents relating to the trials that were presented for inspection may have been forged, including supposed insurance certificates and e-mail correspondence with The Lancet.

The therapy involves removing tissue from a patient's arm to create muscle stem cells, then injecting these cells into the same person's urinary sphincter muscle.

Strasser, who is head of the urology department's incontinence division, designed and led the stem-cell project and is implicated throughout the report. The university hospital has now forbidden him from treating patients. But, controversially, the report exonerates the head of the urology department, Georg Bartsch, even though he signed many of the documents related to the therapies and is listed as a co-author on the publications.

Meanwhile, the university rector, Clemens Seger—who has been outspoken about his intention to act on any scientific misconduct exposed by the inspection, and who asked the Austrian Academy of Sciences to investigate the situation — has been threatened with the sack.

Strasser declined to comment on the case. But he has written an open letter to university authorities denying wrongdoing.

Bartsch, an oncologist, dissociates himself from all parts of the trial, saying that he was unaware of the problems developing until the rector informed him of concerns in November 2007. Although the Lancet paper lists him as one of five co-authors who did "all investigations and treatments", and includes...
Scandalous behaviour

Austria’s most serious report of scientific misconduct in recent memory must be handled properly.

The academic community in Austria often seems to be a closed, elite set, especially in the sphere of medicine. The power and influence wielded by a professor are hard to understand from the outside, and the rigid hierarchy of the academic system has been hard to dismantle from the inside, despite reformers’ best efforts.

The upper echelons of that community also seem to know how to close ranks. Witness an example now threatening to emerge from the Medical University of Innsbruck, where there are worrying signs that investigations into a scandal of unprecedented dimensions in this small country may be thwarted.

According to a report from the Austrian Agency for Health and Food Safety, a urologist at the university, Hannes Strasser, has conducted a high-profile clinical trial so inappropriately that it must be considered entirely invalid (see page 922). Moreover, that trial

Austria is a small country, and networks between power-brokers are small and tight. But something, it seems, is rotten in the state of Austria, and it needs to be faced and dealt with openly.
Austria

- Falsified Insurance documentation
- Research not authorised by REC
- Patients not informed it was a study
- Charged for so called “treatment”
- Subjected to degrading and invasive procedures
- Institutional influence
<table>
<thead>
<tr>
<th>Problem/Dilemma</th>
<th>Count</th>
</tr>
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<tbody>
<tr>
<td>Duplicate/redundant publication</td>
<td>58</td>
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<tr>
<td>Authorship issues</td>
<td>26</td>
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<tr>
<td>No ethics approval</td>
<td>25</td>
</tr>
<tr>
<td>No or inadequate informed consent</td>
<td>22</td>
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<tr>
<td>Falsification or fabrication</td>
<td>19</td>
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<tr>
<td>Plagiarism</td>
<td>17</td>
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<tr>
<td>Unethical research or clinical malpractice</td>
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<tr>
<td>Undeclared conflict of interest</td>
<td>8</td>
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<tr>
<td>Reviewer misconduct</td>
<td>6</td>
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<td>Editorial misconduct</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>39</td>
</tr>
</tbody>
</table>

*More than one possible*
Fraud and misconduct

• S Korea: stem cells
• Woo Suk Hwang
  – Fabrication
  – Coercion
• USA: Nature Medicine 2006:12;491-492
  (best-endowed centres report most cases of fraud)
Who finds fraud?

• Most commonly monitors
  • Patterns or trends
  • Wrong “feeling”

• Auditors

• Data monitors

• Statisticians
Why have cases been ignored?

• Fear
  • Recrimination
  • Adverse publicity,
  • Loss of favour and support
  • Loss of prescriptions
  • Asking embarrassing questions

• Institutional connivance
Warning signs (1)

Forensic Examination

- Immaculate CRFs or electronic data records
- Difficulty in arranging meetings
- Differences from other sites
  Faster recruitment
  Fewer adverse events
  Fewer withdrawals
- Odd hours worked
- Odd days of week/month worked
Warning signs (2)

- Separate (manual or electronic) pages made for hospital notes
- Separate (manual or electronic) folders for GP notes
- Marks on visual analogue scales
- Clean diary cards, or completed with the same pen
Forensic Examination
Patient signatures on the study consent forms were not consistent with patient signatures elsewhere in the hospital notes.

Treatment randomisation numbers were allocated *after* visit 2 instead of *at* visit 2.

Patients were purported to have been seen on three separate Bank Holidays.

Patient visits were purported to have taken place when the investigator was on holiday but there was no evidence of recorded cover during this period.
Echocardiogram and nuclear medicine data for all patients were provided on forms that were no longer used in their respective departments.

“Bogus” data were attributed by the investigator to another doctor who he alleged was his "research fellow" at the time, and whose qualification as a medical practitioner was never able to be verified.

Letters to GPs indicated that certain patients were not stabilised on treatment, and thus ineligible to enter the study, even though they were entered into the study and the CRFs indicated that they were stabilised.
The hospital out-patient register verified the appointments for the patients in the study for their first and fourth visits, but their attendance for visits 2 and 3 could not be so verified.

For ECG traces and X-rays either the date on which they were taken, or the patient identification, or both, had been cut off.

Drug accountability for patients who were withdrawn from the study at an earlier stage were completed *in advance* and then scored out when it was realised that the patients had withdrawn.
(Notwithstanding any research governance procedures that may be in place) sponsors and research ethics committees have a responsibility to check that investigators who are

too busy

too arrogant

too tired

too lazy

too greedy

too careless

..... are not recruited
Can RECs do more to detect Fraud?

EFGCP Annual Conference 2009 on
Research Integrity: A European Perspective

Workshop 3: The role of research ethics committees in preventing misconduct

27 January 2009
Diplomat Hotel, Prague, Czech Republic
What can RECs Do?

Influence of Ethics committees?
Preventive, reactive?
Protocol (Risk factors?)
Investigator (Any previous training in GCP?)
Conflict of interest?
Site
Connection between misconduct and fraud?
Communication between inspectors and ethics committees?

REC: review, process, accountability, transparency?
RECs – Naïve?

• REC training
  – Fraud detection
  Forensic examination
• Site assessments?
• Suitability investigator
• Legal expertise
• Policy
• SOP - How to deal with misconduct
Remember

Uncle Sam will be after you
What more can we do?

• Dites-moi!
• Education and training
  – Obligatory?
• GCP+++