How to Avoid the Jail; Clinical Trial Fraud.
Lessons from the past: detection, consequences and prevention.

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Aims of Talk

- Define fraud & research misconduct
- Review legislation around clinical trial fraud
- Reference local policies and guidelines
- Case examples of individual’s clinical trial fraud & research misconduct
  - Detection, consequences and prevention
- Thoughts on the cases presented
- Lessons we can learn
The Jail!

Fury as killers, gangsters and drug dealers get medals for their own prison Olympic Games
Fraud v Research Misconduct

• Fraud is the use of deception with the intention of obtaining personal gain, avoiding an obligation or causing loss to another party\(^1\).

• Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results\(^2\).

2. [https://ori.hhs.gov/definition-misconduct](https://ori.hhs.gov/definition-misconduct)
Legislation

Medicines for Human Use (Clinical Trials) Regulations Statutory Instrument 2004 No. 1031

UK legislation for CTIMPs:
• 14 Principles & Conditions of GCP
Local NHS and University Policies

- NHS Tayside
- NHS Tayside Whistleblowing Policy
- Code of Corporate Governance: The Fraud Standards
- Fraud Liaison Officer

- University
- Research Concordant
- Code of Policy and Procedures for Investigating and Resolving Allegations of Misconduct in Research
- Whistleblowing Code
The guilty parties
Case 1: Dr Anne Kirkman Campbell (2001-02)

• Post Marketing Safety study of Ketek (oral antibiotic) for Community acquired pneumonia, bacterial sinusitis and URTI
  • Concerns regards liver toxicity, drug interactions, visual acuity problems
  • 24000 patients: 1800 sites

• Sponsor: Aventis, CRO- PPD

• July 2002- FDA routine validation of data:
  • Failure to ensure regulatory compliance, serious protocol violations, lack of site knowledge of AESIs, SAE reporting, AEs not reported

• Target of 5-50 patients per site approved
Case 1: Details

• Dr Kirkam Campbell- weight loss clinic – single practitioner – 3 co-ordinators
• Enrolled 400+ patients *(over 3 months)*
• Recruited up to 30 patients a day : $400 per pt
• Only 50 could be proven to exist
  • Family members,
  • forged signatures,
  • non-existent patients,
  • Falsified data
  • No history of infection,
  • AEs of four types only, Blood results suspicious
  • 10% only received drug.
• Concerns raised by monitors and auditors- not reported to FDA
  • Explained by notes to file post close of study
Case 1: Consequences

• Dr Kirkman Campbell- 57 months Federal Jail for Mail Fraud
  • $500k fine & $900k damages to sponsor.

• Subsequent Congressional Investigation of FDAs handling of case

• conduct of 18 other Investigators on study raised concerns also
  • One was suspended BEFORE study for gross negligence, inability to maintain adequate and accurate records
  • Other no record of written consent for 30 patients: Had chronic cocaine addiction and was arrested for holding gun to wife’s head

• Liver toxicity (57 cases) and deaths (at least 4)

• FDA removed licence for 2 of 3 indications in 2007 after much controversy and day before Congressional hearing

• Dr KM, whilst under FDA investigation, was proven to have falsified records on a further GSK study
Case 2: Steve Eaton (2013)

- Clinical Scientist at Aptuit in Riccarton
- preclinical trials in animals to assess the efficacy of new treatments on behalf of several major drug companies
- Prosecuted under GLP Regulations
- Convicted of selectively reporting data between 2003 and 2009 on drug concentrations in blood
- 3 months jail- 1st conviction under GLP regulations
Case 2: Detection & Actions

• Quality control audit raised concerns about irregularities in one assay
• added extra blank washes during calibration, but removed them when running analyses on test sample
• Subsequent review found irregularities dating back to 2001 (prior even to Aptuit buying facility)
• CAPA – Training, Review and update of SOPs
• MHRA- ‘Independent action of individual employee’
Case 3: Consequences

• Dr Eaton- no longer a scientist

• Defence was – ‘pressure at the time and problems in personal life’

• Aptuit closed facility in 2011 for financial reasons

• Sheriffs statement

“I feel that my sentencing powers in this are wholly inadequate. You failed to test the drugs properly – you could have caused cancer patients unquestionable harm. Why someone who is as highly educated and as experienced as you would embark on such a course of conduct is inexplicable.”
Case 3; Dr Hugh McGoldrick (Downpatrick 2016)
Case 3: Summary

• GP acting as PI on a Sanofi insomnia trial 2007-2008
• Admitted conducting trial in **breach of protocol & deliberately breaching the conditions of GCP**
• first doctor in the UK to be convicted of deliberately falsifying data under the Medicines for Human Use (Clinical Trials) Regulations 2004.
• ineligibility of patients for the trial:
  • suffered from secondary insomnia;
  • prescribed medication which would have excluded them from the study;
  • the body mass index of one of the patients was too high
  • false information as to their sleeping patterns was knowingly submitted via the IVRS
Case 3: consequences

- Also charged with two counts of perverting course of justice with two arson attacks on surgery and 4 charges of false representation: *left on books not to be proceeded with after guilty plea to 2 charges*
- sentenced to **nine months imprisonment** suspended on appeal for two years and a **£10,000 fine** (*8 year delay in hearing case*)
- Mitigation was that he felt medication would be beneficial to his patients (not accepted by prosecution)
- **Agreed to repay monies received from sponsor at trial**
- GMC hearing 20th Feb 2017
- “Your only sorrow concerns the fact that you were caught.”
Isolated cases of Research Misconduct?
Medical Research Misconduct

• 36% of doctoral and post-doctoral students were aware of an instance of scientific misconduct;

• 15% were willing to do whatever was necessary to get a grant or publish a paper.¹

• survey of Biostatistician members of International Society for Clinical Biostatistics, revealed that 51% of respondents knew of fraudulent projects.²

• fabrication and falsification of data, deceptive reporting of results, suppression of data, and deceptive design or analysis has been observed in fairly similar numbers²

¹ Commission on Research Integrity. Integrity and misconduct in research CHSS, Washington (1996)

Other types of clinical trial fraud

• Forging
  • Invention of false or misleading data

• Cooking
  • Only analyse data that supports hypothesis

• Trimming
  • ‘Smoothing’ out data

• Misuse of statistics
  • Use of improper techniques

• Irresponsible authorship
  • Contribution to paper cannot be reasonably attributed to author
Other Cases

- Diederik Stapel, Psycologist, Tilburg University
- *Racial stereotyping, power of advertising, hypocrisy*
- Dozens papers retracted
- Doctoral students PhDs at risk
- Lord of the data’
- “I have failed as a scientist and researcher, I feel ashamed for it and have great regret.”
Review of 650 FDA inspections 98-2013

- 57 OFFICIAL ACTION INDICATED (OAI) trials:
  - 22 had falsified information
  - 14 trials had researchers who failed to report adverse events
  - 42 trials had violations of the trial’s protocols
  - 35 trials had record-keeping errors
  - 30 trials had researchers who failed to protect patient safety or acquire informed consent
- 78 papers reviewed (3 mentioned the violations)
- In USA – GSK fined $242m for failure to report safety data on Avandia.
- No sponsor convictions in UK

1. Seife. JAMA Internal Medicine Feb 2015
2. 2. US Dept of Justice, Office of Public Affairs, July 2012
Consequences of clinical trial fraud

- Damage to personal and professional reputation
- Damage to Institutional reputation
- Erosion of scientific trust
- Financial costs
  - returned fees/grants, delays in review, cost of investigations, reanalyse of data etc
- Time spent validating data increases and reduces time on building new knowledge
- Dangerous for patients- data used may lead to unsafe medications being licenced
- Denying patients access to potentially useful treatments
Reasons for Research Fraud?

• Greed
• Competition
• Highly pressurised research environment
  • Financial
  • Professional
  • From sponsors to complete study timelines
• Arrogance/ Stupidity
Lessons we can learn/ Prevention

• Research Governance required
• Clear peer review of activity- team work,
• Mechanisms in place to investigate any allegation of fraud
• Whistleblowing culture to be encouraged
  • (In USA 10—15% federal grant may be returned to whistle-blower)
• Regular review of data and suspicious data investigated: data sharing
• Monitoring reports acted on by Sponsors
• Understand that mistakes can happen; - open policy to ‘own up’
Summary

• Clinical trial fraud – more prevalent than thought - but still rare
• Literature is littered with examples - despite most cases dealt with ‘in-house’
• Examples often ‘lone workers’ or so exalted their work cannot be challenged
• Seriously undermines integrity of clinical research as a whole
• Onus on all staff to raise any suspicions with line manager or superior

• Are lessons being learnt?
• What’s the next ‘scandal’?
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