Sensible guidelines for clinical trials

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University of Edinburgh
Outline

• Impact of regulation on clinical research
• The Sensible Guidelines group
• Quality assurance
  – Which types of error matter?
  – Detecting fraud
• Steps to making trials succeed
  – Design
  – Marketing

• Doubling in costs of running non-commercial cancer trials and 6-12 month delays to starting

• Major concerns about correct interpretation due to lack of central guidance, lack of clarity regarding interpretation of guidance notes, and increased documentation

• Clinical trial units unable or unwilling to start in non-UK centres due to different interpretations in different European countries
Over-regulation of clinical research: a threat to public health?

• Regulation of clinical research is now extraordinarily bureaucratic, expensive and confusing – and is getting worse
• This will delay and sometimes even stop research, except where supported by industry which has the resources to comply with the regulations,
• This will inevitably lead to an over-concentration on new drugs
• Losing the clinical research base in the UK will damage present and future patients, and compromise the public health
Number of working days taken to approve research governance applications for 57 hospitals within 50 NHS trusts (4 trials: CLOTS, GALA, IST-3, HELPS)

Over-regulation of research – an ethical problem?

• 'From a perusal of the innumerable guidelines on medical research you could be forgiven for thinking that medical research, like smoking, must be bad for your health

• ‘...in a liberal society, since it cannot be altogether banned, strict regulation is needed to minimize the harm that research can do.'
Sensible Guidelines Group

- Worry that implementation of more legislation to *improve* clinical research has *reduced* our ability to undertake high quality clinical trials
- The ‘Sensible Guidelines Group’, led by Salim Yusuf, therefore met in Washington in 2007 to:
  - bring together trialists, regulators and industry
  - define the key problems,
  - assemble *empirical evidence of barriers* and *evidence-based solutions*
Washington meeting main themes

- Specific barriers to independent studies
- Impact of privacy laws on trial conduct
- Identifying and reporting adverse events
- Data quality assurance
- Monitoring methods
- Do we need to adjudicate events?
- Economics of trials
- Challenges of trials in vulnerable populations

Full articles published in Clinical Trials 2008; 5
Quality Assurance – why?

- The purpose of quality assurance is not to ensure that the data are 100% error-free.
- Its purpose is to ensure that the clinical trial results are reliable, i.e.
  - observed treatment effects are real
  - the estimate of magnitude is unbiased
A taxonomy of errors

Random errors*

- Measurement errors (eg due to assay precision or frequency of visits)
- Errors due to sloppiness (eg transcription errors)
- Many types of fraud (most cases of data fabrication)

Systematic errors

- Design flaws (eg exclusion of patients with incomplete treatment or unequal schedule of visits)
- Some types of fraud (most cases of data falsification)

* Random with respect to treatment assignment
Do data errors matter?

• Random errors do not matter much
• Systematic errors do matter but are largely preventable through proper trial design
A randomized trial of anti-VEGF therapy for age-related macular degeneration

Patients with exudative AMD

Stratify by
- Centre
- Lesion subtype
- Prior therapy

Intra-ocular injections

Sham
0.3 mg
1 mg
3 mg

Trial primary outcome: visual acuity over time (assessed through vision chart)

Visual acuity = number of letters read correctly
Changes in visual acuity from baseline to 1 year by treatment arm

<table>
<thead>
<tr>
<th>Visit time</th>
<th>VAS change</th>
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<tbody>
<tr>
<td>Week 0</td>
<td>-17</td>
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<tr>
<td>Week 6</td>
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<tr>
<td>Week 12</td>
<td>-15</td>
</tr>
<tr>
<td>Week 18</td>
<td>-14</td>
</tr>
<tr>
<td>Week 24</td>
<td>-13</td>
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<td>Week 30</td>
<td>-12</td>
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<tr>
<td>Week 36</td>
<td>-11</td>
</tr>
<tr>
<td>Week 42</td>
<td>-10</td>
</tr>
<tr>
<td>Week 48</td>
<td>-9</td>
</tr>
<tr>
<td>Week 54</td>
<td>-8</td>
</tr>
</tbody>
</table>

0.3 mg vs sham $P = 0.0001$
1 mg vs sham $P = 0.0003$
3 mg vs sham $P = 0.03$
Impact of adding random errors to visual acuity

• Let $\sigma^2$ be the within-patient variance of visual acuity over time
• Add random error $\sim \mathcal{N}(0, \sigma^2)$ to given proportion of patients selected at random
• Simulate 1,000 trials with added random errors
• Calculate 1,000 t-test P-values
• Report the median (and quartiles) of the distribution of these P-values
Median simulated t-test P-values with increasing proportion of patients with error

Proportion of patients with random error

P-Value (Log scale)

3mg 1mg 0.3mg
Conclusion

Adding random error has little overall impact on overall study conclusions
Reduce data collection to reduce error: CRFs and operations manuals for AbESTT-2 and IST-3

Errors in a few non-essential items among a great mass of variables (many of which will never be analysed) don’t matter. However, errors in the few key outcome variables must be avoided at all costs -> restrict data collection to essential items only
Systematic errors: errors avoidable by design (and analysis), e.g. by

- No post-randomization exclusions
- No “per-treatment received” analyses
- Identical follow-up schedules
- Blinding to avoid outcome assessment bias
- Minimise outcome data collection to
  - maximise response rates
  - maximise data completeness for key items
Prevalence of fraud?
(Fraud = “intention-to-cheat”)

- Industry (Hoechst, 1990-1994)
  1 case of fraud in 243 (0.43%) randomly selected centres
- FDA (1985-1988)
  1% of 570 routine audits led to a for-cause investigation
- CALGB (1982-1992)
  2 cases of fraud in 691 (0.29%) on-site audits
- SWOG (1983-1990)
  no case (0%) of fraud in 1,751 patients

→ fraud is probably rare (but possible underestimation ?)

Buyse et al, Statistics in Med 1999;18:3435
Statistical approaches to monitoring/looking for data fabrication

- Humans are poor random number generators → test randomness (e.g. Benford’s law)

- Plausible multivariate data are hard to fabricate → test correlation structure

- Clinical trial data are highly structured → compare expected vs observed

- Clinical trial data are rich in meaning → test plausibility (e.g. dates)

- Fraud or gross errors usually occur at one centre → compare centres

Most frauds have little impact on trial results because:

- they introduce random but not systematic errors (i.e. noise but no bias) in the analyses

- they affect secondary variables (e.g. eligibility criteria)

- their magnitude is too small to have an influence (one site and/or few patients)

Altman, Practical Statistics for Medical Research 1991
Peto et al, Controlled Clin Trials 1997;18:1
Baigent. Clinical Trials 2008; 5: 49–55
Marketing the IST-3 trial

- Trial of a thrombolytic (‘clot busting’) drug for patients with acute stroke
- Brand value: independent, investigator led, high quality science, peer reviewed and funded by MRC, well designed logo
- Product and market planning: Simple processes: web randomisation, short CRF, central follow-up
- Making the sale: Engaging champions (national coordinators), ‘Stand’ at conferences
- Maintaining engagement: frequent positive reinforcement; ensuring positive ‘moments of truth’
A large randomised controlled trial of thrombolysis with intravenous recombinant tissue plasminogen activator (rt-PA) for acute ischaemic stroke within 6 hours

world's largest thrombolysis for stroke trial with over 1500 patients - Congratulations to

Randomise a Patient

Improve your acute stroke imaging interpretative skills!

See - BASP CT Training Series

ACCESS Study - The Acute Cerebral CT Evaluation Study

**NEW! Implications of ECASS-3 results for IST-3

October IST-3 Newsletter
MRC IST-3: negative impact of regulation -> delayed recovery after extra funding + marketing drive

- EU trials directive
- New R&D approval
Closing thoughts

• The greatest risks to trials are not fraud, but:
  – That they won’t happen at all, or
  – They will be too small and not answer questions reliably

• There is flexibility in regulations – use it!
• Don’t over-interpret guidance
• Keep trial design and processes simple
• Collect less data = better data quality
• Need to adopt a marketing approach to all aspects of, and all stages of, a trial
Acknowledgements

Professor Marc Buyse
International Drug Development Institute,
Louvain-la-Neuve, Belgium
A problem with regulators

- Understands the importance of large scale trials
- Supportive of investigator led trials
- Considers FDA guidance to be flexible….but his staff (in common with regulators worldwide) go by the letter of the law (as they see it).

Dr Robert Temple,
Head of Cardiovascular,
FDA
If there is to be monitoring, how to do it; practical examples
ICH GCP: guidance on monitoring

“... extent and nature of monitoring should be based on considerations such as the objectives, purpose, design, complexity, blinding, size and endpoints of the trial. In general there is a need for on-site monitoring before, during and after the trial; however ... central monitoring ... can assure appropriate conduct of the trial in accordance with GCP”

ICH GCP 5.18.3
Range of options for on-site monitoring

- Routine visits to all sites
- Visits to random selection of sites
- Targeted visits to less experienced sites, or those for which central monitoring suggests possible problems
Central monitoring by coordinating centre

Record checks for:

- Patient eligibility (eg, pathology report to substantiate diagnosis)
- Patient existence (eg, ONS flagging or imaging investigation)
- Outcome (eg, ONS flagging for death; investigation results)

Statistical checks for:

- Missing or invalid data (eg, range checks)
- Calendar checks (eg, dates of recruitment)
- Unusual patterns (eg, digit preference, rounding or unusual frequency distribution)
- Reporting rates (eg, frequency of adverse events or missing data)
- Repeated measures (eg, variability and within-individual changes)

MRC/DH joint project (www.cl-toolkit.ac.uk)
COMMIT: Effect on death/re-MI/stroke of adding clopidogrel during heart attack (45,000 patients)

Placebo + ASA: 2310 with event (10.1%)
Clopidogrel + ASA: 2121 with event (9.2%)

9% (SE3) relative risk reduction (2P=0.002)
COMMIT (clopidogrel in acute MI): lack of value of on-site data audits

- Site visits to highest recruiting 300 of 1250 hospitals (representing 66% of randomised patients) plus 44 randomly selected hospitals

- Coordinating centre selected 10 patients (50% with relevant events) at each hospital for note review

- No material discrepancies between hospital notes and study records for patient characteristics or study outcomes (e.g. death always correctly reported and 98% of reported reinfarction/stroke confirmed)
Prevention of misconduct by better trial design (rather than by more policing)

- *Relax eligibility criteria:* Excessively restrictive entry criteria may lead to entry data being altered
- *Assess compliance crudely:* Detailed pill counts may be unnecessary (& random sampling better)
- *Limit data collected:* Important adverse events may be under-reported if data collection is excessive
- *Accept missing values:* Undue pressure for complete data may lead to values being invented (e.g. ENOS trial website)

More cost-effective design allows much larger numbers to be randomised, yielding smaller random errors
On-site monitoring and the ‘monitoring industry’

"(...) the trial management procedures ensuring validity and reliability of the results are vastly more important than absence of clerical errors. Yet, it is clerical inconsistencies referred to as ’errors’ that are chased by the growing GCP-departments."

Grimes et al, Lancet 2005;366:172
Acknowledgements

Professor Marc Buyse
International Drug Development Institute,
Louvain-la-Neuve, Belgium
Regulatory burden and its impact on trial quality
Proliferation of laws and “guidelines” may make trial results LESS reliable (and so harm, not help, patients)

Clinical trial conduct:
- ICH Guideline for GCP
- EU Clinical Trials Directive
- NHS Research Governance

Data access/confidentiality:
- 1998 Data Protection Act
- GMC guidance on confidentiality
- Health & Social Care Act/PIAG

Ethics & consent:
- Helsinki Declaration
Declaration of Helsinki 2000: obstacle to research in developing countries

“The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods....... At the conclusion of the study, every patient entered into the study should be assured of access to the best proved prophylactic, diagnostic and therapeutic methods identified by the study.”
Doing research to find more efficient methods for trials: are site visits useful?
A phase IV randomized trial of adjuvant treatment for breast cancer

Patients with node-positive resected breast cancer

Stratify by
- Centre
- Patient’s age
- Number of positive nodes

6 x FEC *

4 x FEC → 4 x T **

* 5FU, Epirubicin, Cyclophosphamide
** Taxol
A randomised study of the impact of on-site monitoring

Centres accruing patients in trial AERO B2000

Stratify by
- Type (Academic vs Private)
- Location (Paris vs Province)

Group A (site visits)
Group B (no visits)

Liénard et al, Clinical Trials 2006;3:1-7
## Impact of initiation visits on patient accrual

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<th>B (no visits) 67 centres</th>
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<tr>
<td>0</td>
<td>33 (48%)</td>
<td>33 (49%)</td>
</tr>
<tr>
<td>1-2</td>
<td>8 (12%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>3-5</td>
<td>12 (18%)</td>
<td>11 (16%)</td>
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<td>6 +</td>
<td>15 (22%)</td>
<td>16 (24%)</td>
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No difference
## Impact of initiation visits on quality of data submitted

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<th>A (site visits) 444 pages</th>
<th>B (no visits) 571 pages</th>
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<tr>
<td>0</td>
<td>102 (23%)</td>
<td>91 (16%)</td>
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<tr>
<td>1-2</td>
<td>195 (44%)</td>
<td>314 (55%)</td>
</tr>
<tr>
<td>3-5</td>
<td>120 (27%)</td>
<td>132 (23%)</td>
</tr>
<tr>
<td>6 +</td>
<td>27 (6%)</td>
<td>34 (6%)</td>
</tr>
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No difference
Progress in clinical trials

1950-1990: False POSITIVES increasingly well controlled by randomisation

1990-2000: False NEGATIVES increasingly well controlled by “mega-trials” and “meta-analyses”

2000 & beyond: Increasing regulation (without appropriate interpretation) may prevent many important public health questions from being answered reliably
Visit the sensible guidelines website

- Downloadable powerpoint presentations
- Main theme documents
- Background papers and references
- Discussion boards
- Please comment on draft position paper (for *JAMA* or *Lancet*) and papers on main themes for *Clinical Trials*

http://www.rumix.org/phri/
Acknowledgements

Salim Yusuf
Rory Collins
Marc Buyse
&
Google images

Who provided most of the material for this talk!
Many regulatory requirements are not supported by evidence that they improve the quality of research. We need to assemble evidence about which aspects of trial conduct and management improve quality, improve efficiency, and reduce cost.

Staff in regulatory bodies should be better trained and process subject to quality control. We need to be ‘unbelievers in the regulations’.
The top five recommendations to strengthen IDCT in Europe as ranked by the consensus conference were as follows:

1. To improve the education, training and career structure and opportunities for scientists involved in patient-oriented clinical research.
2. To increase levels of funding for IDCT.
3. To adopt a ‘risk-based’ approach to the regulation of IDCT.
4. To streamline procedures for obtaining authorisation for IDCT.
5. To ensure that IDCT are carried out with an appropriate number of patients to produce statistically reliable results so that the trials are ‘correctly powered’.
Impact of initiation visits on volume of data submitted

<table>
<thead>
<tr>
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<th>A (site visits) 302 patients</th>
<th>B (no visits) 271 patients</th>
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<tr>
<td>0</td>
<td>162 (54%)</td>
<td>114 (42%)</td>
</tr>
<tr>
<td>1-2</td>
<td>51 (17%)</td>
<td>44 (16%)</td>
</tr>
<tr>
<td>3-5</td>
<td>77 (25%)</td>
<td>96 (36%)</td>
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<tr>
<td>6 +</td>
<td>12 (4%)</td>
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**Identifying and reporting adverse events**

| Category General | Started by zanderj1 | Comments 2 | Last comment by peter.held | Last Active 1 day ago |

**HSP/BIMO Workshop: Protecting Human Subjects Involved in Clinical Investigations**

| Category General | Started by phri | Comments 1 | Last comment by phri        | Last Active Mar 13th 2007 |

**Talks and Presentations**

| Category General | Started by sandra.nevills | Comments 3 | Last comment by sandra.nevills | Last Active Feb 6th 2007 |

**European Legislation and guidelines**

| Category General | Started by Brian.Davis | Comments 1 | Last comment by Vladimir.Gacic | Last Active Feb 3rd 2007 |

**Research questions on trial processes**

| Category General | Started by peter.sandercock | Comments 1 | Last comment by peter.sandercock | Last Active Jan 29th 2007 |
**COMMIT: Example of central checks indicating problem at only one of 1250 participating hospitals**

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<tr>
<th></th>
<th>Hospital (n=93)</th>
<th>All hospitals</th>
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<tr>
<td>Patients/month</td>
<td>2.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Female</td>
<td>39.8%</td>
<td>27.6% *</td>
</tr>
<tr>
<td>ST↓ only</td>
<td>1.1%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Fibrinolytic &lt;12 h</td>
<td>73.3%</td>
<td>65.3%</td>
</tr>
<tr>
<td>Pain onset</td>
<td></td>
<td></td>
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<tr>
<td>&lt;6 h</td>
<td>33.3%</td>
<td>33.6%</td>
</tr>
<tr>
<td>6-12 h</td>
<td>59.1%</td>
<td>30.2% *</td>
</tr>
<tr>
<td>&gt;12 h</td>
<td>7.5%</td>
<td>36.2%</td>
</tr>
<tr>
<td>MI confirmed</td>
<td>100.0%</td>
<td>96.0% *</td>
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<tr>
<td>Antiplatelet stopped</td>
<td>0%</td>
<td>7.3% *</td>
</tr>
<tr>
<td>All i.v. BB given</td>
<td>98.9%</td>
<td>93.2% *</td>
</tr>
<tr>
<td>Oral BB stopped</td>
<td>0%</td>
<td>11.1% *</td>
</tr>
<tr>
<td>Possible side-effects</td>
<td>0.4%</td>
<td>3.5% *</td>
</tr>
<tr>
<td>Major adverse events</td>
<td>0.1%</td>
<td>3.3% *</td>
</tr>
<tr>
<td>Death</td>
<td>0%</td>
<td>8.0% *</td>
</tr>
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(NB: More than 4 significant differences led to on-site auditing of all patients)
Marketing clinical trials
MRC review: Potential for EU Clinical Trials Directive (2001) to be a major obstacle to important trials

- Increased bureaucracy due to requirement for single sponsor (possibly the funding source)
- Burdensome drug authorisation and supply (GMP & labelling) processes
- Threat to trials of emergency treatments for patients unable to give consent
- Rigid approach to pharmacovigilance and site monitoring (through over-interpretation)
- Substantial increases in costs could result in fewer important trials being conducted