Research Governance and Good Clinical Practice

Chris Rollinson
UK’s Governments commitment to R&D

Budget statement 2011

‘Health research has a key role in the National economy as well as improving health and care’
Guidance and discussion papers: Governance

Academy of Medical Sciences Report: A pathway for regulation and governance of health research (Jan 2011).

“Proportionate and symmetrical approach to regulation rather than a one size fits all”

Calls for improvements in GCP monitoring

Establishment of a Health Research Agency (HRA) to streamline and improve cost effectiveness.

(http://acmedsci.ac.uk/p47prid88.html)
Health Research Agency (HRA)

A new regulation and governance pathway

- Health Research Agency
  - Integrated Research Application System
  - Triage and single point of contact

- National Research Ethics Service
  - UK-wide single ethics opinion
  - Streamlined process for specialist approvals and licences

- National Research Governance Service
  - NHS R&D permissions
  - Undertake all study-wide governance checks
  - Co-ordinate local NHS feasibility assessments

- Medicines and Healthcare Regulatory Agency
  - Clinical Trial Authorisation

- Other approvals
  - Ministry of Justice and Ministry of Defence

Plymouth Hospitals NHS Trust
Significance of standards in research?

- Protection of research subjects
  - Risk reduction

- Quality Data
  - Without quality data we lose public trust and...

- Protection of the public
  - All changes made to health care procedures need to be evidence based to ensure the public is protected.

**Leads to excellent research, good science.**
Responsible Research Conduct

Research integrity:

• adherence to rules, regulations, guidelines, and commonly accepted professional codes or norms.”

• Research integrity is essential to ensure the reliability of research results and to preserve public support for research.
Incidence of Research Misconduct

- 1.5% falsification or plagiarism.
- 7.6% circumvented some requirements
- 12.5% overlooked flawed data
- 15.5% changed design, method or results

Medical Misconduct

305 new medical consultants:
- 55.7% observed misconduct
- 5.7% committed misconduct in the past
- 18% would commit in future
- 17% had research ethics training

Geggie, J Med Ethics (2001)
Millions of surgery patients at risk in drug research fraud scandal

By Heidi Blake 03 Mar 2011

Millions of NHS patients have been treated with controversial drugs on the basis of "fraudulent research" by one of the world's leading anaesthetists, The Daily Telegraph can disclose.

Joachim Boldt was a leading anaesthetist, internationally respected for his prolific research and renowned in medical circles for his charm and charisma.

Joachim Boldt is at the centre of a criminal investigation amid allegations that he may have forged up to 90 crucial studies on the treatment. He has been stripped of his professorship and sacked from a German hospital following allegations about his research into drugs known as colloids.

Experts described Mr Boldt's alleged forgeries as possibly the biggest medical research scandal since Andrew Wakefield was struck off last year for falsely claiming to have proved a link between the MMR vaccine and autism.

Guidelines for British anaesthetists regarding colloids – used to boost blood volume in patients undergoing surgery – are being revised after it emerged that four of the key studies on which they were based are to be formally retracted.
Some explanations

- Heightened pressure to publish
- Increased competition for research money
- Lack of strong surveillance mechanisms
- Limited infrastructure to support ethics codes
- Character issues / Personal problems
- Financial reward
- Cultural Differences
- Absence of education and training
Standards in Research have been around for sometime

1947 – Nuremberg Code
1964 – Declaration of Helsinki
1968 – Medicines Act
1974 – U.S. National Research Act
1978 – Belmont Report (US)
1995 – WHO-GCP guidelines
1996 – ICH GCP (MRC GCP)
2001 – EU Directives
2004 – CT regulation
2002/5 – Research Governance Frame Work
Background to Research Governance

What is Research Governance?

- “Research Governance is aimed at continuous improvement and the reduction of unacceptable variations in research practice across health and social care” (DoH, 2001)

- The framework is not law but must be adhered to for all research (CTIMPs and non-CTIMPs) carried out by the NHS in England.

- CTIMPs also governed by UK law overseen by the MHRA

- Remember research should be carried out to the highest standard whether governed by law or not
Differences between the devolved nations

- Clinical Trial Regulations SI 2004 1031)
  - Applicable to the whole of the UK

- Research Governance Framework
  - Each nation publishes its own

- Some regulations are different in the other nations, e.g.
  - Protection of Children Act
  - Mental Capacity Act
  - Welsh Language Act
Caldicott Guardian

Jan 2012 - PC hard drives belonging to Brighton and Sussex University Hospitals NHS Trust that contained significant amounts of person identifiable data being stolen and ending up on eBay.

The Trust has been asked to pay a fine of £375,000 for this breach of the Data Protection Act 1998.

In light of this, please ensure that you take note of the following points:

 Data should never be stored on computer C: (Hard) drives – all information should be stored on the network, either the H: (Home) drive or the G: (Groups) drive.

 Person identifiable data should never be stored on personal PCs or laptops.

 Trust provided encrypted laptops are available for those working away from the Trust.

 Personal email accounts should never be used for the transmission of work related person identifiable data.

Further information and advice can be obtained from the Trust’s Information Governance Team.

Plymouth Hospitals NHS Trust
Five Statutory Instruments now form the U.K. Regulations which cover ctIMPS.

- Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 1031)
- Medicines for Human Use (Clinical Trials) Amendment Regulations (2006 (SI 1928)
- Medicines for Human Use (Clinical Trials) Amendment No. 2 Regulations 2006 (SI 2984)
- The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008 (SI 941)
- The Medicines for Human Use (Miscellaneous Amendments) Regulations 2009 (SI 1164)
- The Medicines for Human Use (Advanced Therapy Medicinal Products and Miscellaneous Amendments) Regulations 2010 (SI 1882)

You are open to criminal prosecution if you fail to follow these regulations when conducting ctIMP studies.
Changes – UK Legislation

MfHU(CT) 2010:1882

Advanced therapy products and miscellaneous amendments (tissue engineered products, gene/somatic/xenogenic cell therapy, genetically modified organisms for use in humans)

REC and MHRA approval required, must have documented traceability for product and patient, archive for 30 years; must produce only if holding GMP licence (systems for controlled handling, controlled storage, controlled distribution; details specified for packaging and contents of label)
HTA - Material Transfer Agreements

- Tissue / Body parts: Human Tissue Act requires MTA (Material Transfer Agreement) between supplying institution and receiving institution
  - If Sponsor or receiving tissue bank requires MTA – R&D signs off.
Public Registers

UK’s DoH recommends for ctIMPs:
- National Institute for Health Research (NIHR) Portfolio Database managed by UKCRN Coordinating Centre (http://www.crncc.nihr.ac.uk/index/clinical/portfolio_new.html)
- Current Controlled Trials Ltd (CCT) (www.controlledtrials.com/mrct)
- International Standard Randomized Controlled Trial Number www.isrctn.org (ICMJE accredited)

Further mentioned by DoH:
- World Health Organisation established an International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp)
- US National Institute of Health: (http://clinicaltrials.gov/) (ICMJE) (via organisation, PHNT R&D)

REC/NRES web database for all clinical research from autumn 2009 (www.nres.npsa.nhs.uk/researchsummaries)
# Research Passport/Letter of Access

<table>
<thead>
<tr>
<th>NHS employed (but not local Trust)</th>
<th>e-mail employing R&amp;D for “Confirmation of pre-engagement checks”</th>
<th>Letter of Access (LoA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-NHS with Honorary Clinical Contract (e.g. Honorary Consultant/Registrar/Clinical Fellow)</td>
<td>Primarily for treatment/diagnosis (NHS Trust conducts CRB, Occ. Health) - automatically includes research</td>
<td>“Confirmation of pre-engagement checks” and copy of Hon Clin. Contract and CV to R&amp;D for LoA in other NHS Trusts</td>
</tr>
<tr>
<td>Non-NHS</td>
<td>Research Passport Form, with CV to receiving NHS R&amp;D (copies CRB, Occ Health sheet not required)</td>
<td>“lower” level Letter of Access “higher” level Hon Research Contract - employer conducts CRB, Occ. Health</td>
</tr>
</tbody>
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Changes to Medical Devices Legislation

There are currently four sets of Medical Device Regulations implementing all of the Medical Devices Directives and amendments to date;

- SI 2002/618 (Consolidated legislation),
- SI 2003/1697 (Amendments to cover the re-classification of breast implants and additional requirements covering devices utilising materials from TSE susceptible animal species),
- SI 2007/400 (Amendment to cover the re-classification of total hip, knee and shoulder joints),


If you are doing a Devices study please ensure you liaise with your sponsor and Host organisation regarding study specific requirements.
Approval Process Update
Approvals required

- **Minimum required approvals:**
  1. Sponsorship
  2. Research Ethics Committee (NRES)
  3. Trust R&D / University RGO (Letter of Access/Hon Res. Contract)

- **Additional trial specific approvals:**
  - MHRA - Clinical Trial Authorisation for IMP and medical devices,
  - GTAC – Gene Therapy Advisory Committee,
  - IRMER – Ionising Radiation Medical Exposure Regulations,
  - ARSAC – Administration of Radioactive Substances Advisory Com.,
  - Ministry of Justice,
  - NIGB – National Information Governance Board for Health and Social Care Ethics and Confidentiality Committee (NIGHSC ECC) – former PIAG (projects using patient data without consent or identifying cohorts before consent)
IRAS - Integrated Research Application System

https://www.myresearchproject.org.uk/

- Web-based database which allows to submit information about research project to several regulatory/approval bodies (reducing duplication),
- Uses filters to ensure that the data collected collated is appropriate to the type of study, and permissions and approvals required,
- Helps to meet regulatory and governance requirements,
- Generic REC guidance http://www.nres.npsa.nhs.uk/
- https://www.myresearchproject.org.uk/elearning/
Study oversight & responsibilities
Roles and Responsibilities…

**PI & other Researchers**
- Submit proposals for ethical review
- Conduct research according to agreed protocol & in accordance with legal requirements
- Ensure participant welfare
- Record keeping
- Adverse Event reporting
- Dissemination of results

**Sponsor**
- Assure of scientific quality of proposed research
- Ensure ethics approval obtained
- Ensure arrangements in place for management & monitoring of research

**Employing Organisation**
- Promote quality research culture
- Ensure researchers understand & discharge their responsibilities
- Ensure independent scientific review
- Ensure research is properly managed & monitored

**Care Organisation**
- Authorises all research involving their patients, staff or facilities
- Ensure research meets standards of RGF
- Ensure ethics committee approval obtained
- Duty of Care to participants
Do you understand?

- Substantial / Minor Amendments
- Protocol Deviations / Violations
- Serious Breach
- Urgent Safety Measures
Consent Refresher
Who can consent a subject?

- Nurses and allied health professionals may be granted the right to take consent for a specific trial, provided they are appropriately trained.

- Consent may be delegated to an appropriately trained sub-investigator (must be documented).

- The Investigator retains overall responsibility.
When should a subject be consented?

- Prior to participation in a trial
- Before ANY trial procedure - including the taking of blood to screen patients if it is not part of normal clinical practice or a questionnaire to access health etc
- Specific exceptions may be allowed in emergency situations
How should someone be consented?

- The Patient Information sheet and the consent form must have been approved by the Ethics Committee.
- The process must have been approved by the Ethics Committee (e-mail, telephone).
- There should be no coercion to enter the trial.
- Non-technical language must be used.
- The information must be presented to the subject in the most appropriate way.
- The subject must have “ample” time to consider their decision.
- Document consent in the medical notes.
How should a consent form be completed?

- Subject must sign & date the form (also preferably print their own name as well!)
- Original patient consent form - site file
- Copies of patient information leaflet and & consent form - Patient notes and to the patient
- The consent form & patient information leaflet should always be kept together
Guidance and discussion papers: Consent

- Adults lacking capacity to consent (Oct 2010)
  - An online tool kit on research involving adults lacking capacity to consent for themselves
    https://connect.le.ac.uk/alctoolkit/

- Time to Consent (Sept 2010)
  http://www.nres.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=76306&type=full&servicetype=Attachment

- GMC Good Practice in Research and Consent to Research (Apr 2010)
  http://www.gmc-uk.org/research_guidance_FINAL.pdf_31379258.pdf
Update on Safety and Pharmacovigilance
Safety Reporting

Can we identify an event? (AE)

Is it serious? (AE/SAE)

What is the cause? (AR/SAR)

Was it expected? (SUSAR)

This is the process we need to record
Expected ADR

For CTIMPs detailed in:

- **Investigator’s Brochure (IB):** pre-clinical information, all data available (also from other research projects on the relevant IMP), scientific analyses; risk assessment PK and PD data and expected side-effects

- **Summary of Product Characteristics (SmPC):** IB becomes SmPC after marketing licence
SAE – Serious Adverse Event

- Resulting in death
- Life threatening
- Requiring in-patient hospitalisation or prolongation of hospitalisation
- Resulting in persistent or significant disability/incapacity
- Resulting in congenital anomaly/birth defect
SAE and the strategic protocol

Is the patient cohort likely to have hospitalisation/ prolonged hospitalisation/ death?

- In agreement with Sponsor / REC / MHRA a protocol can allow to expedite only those SAE that are related to the study intervention

- However, all AE must be assessed by a medic on their relatedness in CRF
## Adverse Event Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>AE</td>
<td><strong>Adverse Event</strong></td>
</tr>
<tr>
<td></td>
<td>Not always causally related</td>
</tr>
<tr>
<td>AR/ADE</td>
<td><strong>Adverse Reaction/Adverse Device Effect</strong></td>
</tr>
<tr>
<td></td>
<td>Causally related. Subset of AE</td>
</tr>
<tr>
<td>SAE</td>
<td><strong>Serious Adverse Event</strong></td>
</tr>
<tr>
<td></td>
<td>Not always causally related</td>
</tr>
<tr>
<td>SAR/SARADE</td>
<td><strong>Serious Adverse Reaction/ Serious Adverse Device Effect</strong></td>
</tr>
<tr>
<td></td>
<td>Causally related. Subset of AE</td>
</tr>
<tr>
<td>SUSAR/USADE</td>
<td><strong>Suspected Unexpected Serious Adverse Reaction; Unanticipated Serious Adverse Device Effect</strong></td>
</tr>
<tr>
<td></td>
<td>Causally related. Not previously documented in literature.</td>
</tr>
</tbody>
</table>
SUSAR or ‘only’ SAE?

- Discrepancy in SAE assessment between Chief Investigator and Principal Investigator or Sponsor

  - always reported on the higher level (e.g. as SUSAR not just SAE)

  - Add comments for MHRA if Sponsor disagrees with CI/PI on assessment of relatedness
# CTIMP Safety Reporting

| SUSAR | On becoming aware of - Report to Sponsor **immediately**  
If **fatal** or life-threatening, Sponsor reports to competent authorities (MHRA in UK) and main REC within **7 days**, follow-up report within further 8 days.  
All **non**-fatal/life-threatening - Sponsor report to competent authorities (MHRA in UK) and main REC within **15 days** |
|-------|---|
| SAE | On becoming aware of - Report to Sponsor **immediately**  
Report in timely manner to the host organisation, main REC (only where death has occurred), CI, Data Safety Monitoring Board etc.  
Provide follow-up information to sponsor within 5 days. |
| All SAE | PI submit to CI regularly.  
CI submits to safety report **annually** to main REC, MHRA and Sponsor (R&D if required)  
CI / Sponsor analyses for **final report** to REC, MHRA and Sponsor, (R&D if required) |
Non-IMP SAEs

- Report to Sponsor *immediately you are aware* using SAE report form.
- Assess for relatedness (known side effect) and whether expected?
- Sponsor must report all unexpected and possibly related SAE’s to REC within 15 days of the initial report.
Every year (within 60 days from MHRA CT authorisation date):

- CI sends Development Safety Update Reports (DSUR) *(replaced the Annual Safety Report on 1st Sept 2011)* directly to MHRA / REC and cc R&D if sponsor (NOTE: this is different from Annual Progress Report which is required by REC annually and should be copied to R&D; separate template on HRA [NRES website])

- The sponsor updates Investigator Brochure or completes file note that no new information to be included (determines classification of future SUSARs). CI should check this occurs.
Archiving
How long do you archive?

- For CTIMPs legislation is a minimum of 5 years
- PHNT policy 5 years minimum for all studies – check your local policy
- Each Trust should have nominated archivist
Monitoring / Audit

- What’s the difference?
- What Is Monitored / Audited?
Inspections & Common Inspection Findings
Changes to procedures

MHRA Inspection process

Risk base Inspections- dependent on organisation risk status.

MHRA categorise CTIMPs into high, medium and low according to risk.
MHRA UK-wide Inspection Findings

- Delay in adding *new safety info* to SmPC & IB.
- Medical oversight (lack of *documentation* on decision to *include* participant in medical notes / ISF, no *dated signatures*) problem can be the design of CRF
- Lack of evidence that protocol *amendment* was *implemented* following approval (print / document correspondence with date)
- Lack of *file notes*
- Lack of *sponsor notification* (sponsor assessment / response) for protocol/GCP deviations/serious breach classification
- Delegation log not completed
- Delays in completing *final study reports*
MHRA UK-wide Inspection Findings

- Contracts/agreements missing or missing sections
- Insurance
- **Out-of-hour cover**
- Statistical analyses, **SOPs for Statistical Calculations**
- **Written** agreements about storage and archiving (document assessment of storage area for ISF)
- **Delegation of duties logs**
- **Calibration** of equipment before use
- **Temperature** monitoring for IMP (ambient temperature)
- Correct **labelling** of lab samples
- Import of IMP without authorisation – Switzerland **not** part of EEA
Miscellaneous


- EMA also given guidance on missing data in confirmatory clinical trials.

- Trial Master File Reference Model (June 2010)
  http://www.tmfreferencemodel.com/tmf/

- CT results for IMP to be broken down by race, gender, age of participants. This is a DSUR requirement.

- Not sufficient number of CTIMPs for elderly population, even though growing market (changed metabolism, multiple chronic conditions, polypharmacy)

- Approval for Multinational Studies within the EEA – new process called Voluntary Harmonisation Procedure (VHP), will hopefully reduce time for approvals (must be at least 3 MS).
Summary

- Always follow the study protocol, if you deviate from the protocol ensure the reason for non-compliance is documented and the sponsor informed.
- Ensure all data is recorded accurately
- If in doubt or need advice ask R&D
There is too much documentation in research these days!

Paul Ehrlich in his study, some things never change 😊