Ethical & other approvals for studies involving human participants

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Research jargon


- **IRAS Integrated Research Application System**, on-line application system for approvals for UK research in health & social care [https://www.myresearchproject.org.uk/](https://www.myresearchproject.org.uk/)

- **Chief Investigator (CI)**: has overall responsibility for the study

- **Principal Investigator (PI)** - responsible for specific site(s) in a multi-site study - CI/PI may be same person in small study

- **Student research up to doctoral level**: Supervisor is CI

- **PhD studies**, student is CI, supervisor, the PI

- **BREC (Biomedical Research Ethics Committee)**
Session Outline

- Why research governance is important
- Guiding principles

Coffee (Literature review students leave)

- Defining research, audit, evaluation etc

**Exercise: Research, audit or evaluation**

- When NHS/BREC ethical approval required
- NHS Ethical &Trust approval process
- BREC application process
What’s this got to do with me?

From a University/NHS perspective, those conducting studies involving human participants, including their data, tissues etc, should understand their responsibilities:

- Research
- Audit & Evaluations
- Dissertations/professional projects
- Other: e.g. those transcribing audio tapes, manuscripts
What’s this got to do with me?

- Relevant to everyone undertaking studies relating to health/social care setting
- Whether research setting involves the NHS or private patients
- Even though you routinely undertake such studies in your clinical role
Why? Liability and Sponsorship

- Important to distinguish between sponsorship for research, audits, evaluations etc undertaken in a clinical context and those undertaken as education projects.

- Warwick University, as sponsor, is responsible for all research, audit, evaluation conducted by staff and for student studies.

- Indemnity covers negligent harm – and non-negligent harm if required.

- Studies overseas may require:
  - co-sponsorship – to spread the risk
  - local ethical approval
  - additional insurance or those deemed high risk.
Why Research Governance is important

*Response to major cruelties/blunders in research history:*

- Herophilos of Chalcedon (ca. 300 BC), known as “father of scientific anatomy” reputed to have vivisected at least 600 prisoners
- Medical experiments WW2: Germany, Japan, China – Helsinki agreement
- Porton Down, Alder Hey, TeGenero TGN1412 drugs trial
Examples of poor research
Chemical Defence Experimental Establishment Porton Down

- 1999 Police inquiry launched into the death in 1953 of airman Ronald Maddison, age 20
  - allegations that servicemen tricked into taking part in lethal tests with nerve gas not a cure for the common cold.
- 200mg of Sarin, a deadly nerve agent, was dripped on to the arm of his uniform to test its protective properties

2001 Government launched independent medical investigation biological and chemical trials at Porton Down

2004, Coroner’s Inquest into Maddison’s death ruled he was “unlawfully killed” at the hands of the state - Scientists 'knew nerve gas risks'
Alder Hey 2001

Pathologist Dick van Velzen ordered the "unethical and illegal stripping of every organ from every child who had had a post-mortem"

• 2000 dirty containers stored in basement, organs poorly preserved - inadequate levels of formalin

• One specimen was of the severed head of an 11-year-old child.

• Parts taken included brains, eyes from foetuses, 1,500 stillborn foetuses, number of entire children's limbs and bodies.

One mother has had three funerals for baby James following the gradual return of her tiny son's bodily organs.

• Nearly half 188 eyes taken from foetuses never used for research

• Investigations into the root cause of cot death not advanced "one iota" by this organ stripping

• No parental knowledge or consent
Tegenero TGN1412 drugs trial 2006

• 6 volunteers fell violently ill with multiple-organ failure within minutes of being injected with a new autoimmune drug.

• Participants survived, but two suffered serious long-term disabilities.

• Tegenero offered £5,000/victim in return for accepting a no-fault agreement rejected (common US payout of £532k).

• Tegenero under insured for the TGN1412 drug trial, unable to meet compensation claims.

• May 2006, MHRA suspended all approvals for first-in-human trials of immune-system-targeted biological trials pending investigation.
Guiding principles: Helsinki
Ethical and legal regulations

- Research involving humans governed by national/international ethical/legal frameworks
- Specific UK regulatory frameworks for conduct of research e.g. HTA, MHRA, GTAC (gene therapy)

Key ethical principles underpinning the regulatory frameworks:
- Protection from harm.
- Informed consent
- Promoting benefit
- Justice
Protection from harm

CI’s responsibility to: protect life, health, privacy, dignity of the human subject & balance risks/benefits and ensure:

- degree of risk to be taken never exceeds the humanitarian importance of the research problem
- proper preparations made and adequate facilities provided to protect participants against even remote possibility of injury, disability, or death
- Reject or terminate studies at any stage, if continuation is likely to result in death/disabling injury
Protection from harm

*Ethics Committees also consider:*

- potential harm in studies using focus groups, questionnaires, interviews, on-line data collection
- possible harm to researchers/transcribers
- whether study is conducted/supervised by qualified people
- whether appropriate arrangements are in place to ensure confidentiality, anonymity, secure storage of data
Protection from harm – in practice

TeGenero design – inquiry questioned why:

• drug tested on healthy volunteers not patients – (drug intended for patients with compromised not healthy immune systems)

• new drug previously untested on humans was administered simultaneously to all volunteers?

• administered gradually, with no test dose?

• Conducted when earlier trials on animals had 17 adverse incidents?
Informed consent

Requirements for a valid consent:
- Information (beginning from recruitment advert)
- Voluntariness
- Capacity

Possible difficulties when seeking consent:
- Information affects participant behaviour, cultural, language difficulties associated with ethnic minorities
- Patients lacking capacity (e.g. children, people with dementia, emergency situations)
- Participants capacity to consent can fluctuate e.g. in critical care context

Ending experiments:
- Participants must be told that they are at liberty to leave the study - without fear of retribution
Informed consent – in practice

Porton Down/TeGenero

Information – quality, risks?
- Healthy volunteers accepted fee for participating in trials they thought safe. Would they have done so had they known of the possible risks?

Voluntariness? Unable to leave study - too ill or dead

Well-being, dignity, consent
- Alder Hey – blatant disregard for dignity and right of parents and children/their organs, lack of information, consent etc – for no useful purpose
Promoting benefit

Studies should:

- yield fruitful results for the good of society, and future patients, unprocurable by other methods or means – Alder Hey?

Investigations into the root cause of cot death had not been advanced "one iota" by this organ stripping

- be designed/based on results of previous knowledge so anticipated results will justify the performance of the study – Tegenero trial
Justice - core value underpinning equity

- Studies ensure the benefits and burdens of research be distributed fairly among all groups and classes in society, taking into account age, gender, economic status, culture and ethnic considerations.

- Control groups - is it ethical to test interventions against a placebo control when effective intervention is in use elsewhere e.g. HIV studies in 3rd world countries

- Is it ethical to exclude ethnic minorities? in the UK 60% of ethnic minorities speak several languages, including English so why exclude them on the basis of language?

- Scarce resources make translating everything into several languages impractical and unnecessary

- May have to consider other ways of gaining consent…… no point in sending information sheets to people who cannot read or write
Justice

Is withholding of treatment ever justified?

- Tuskegee Syphilis Study: effects of untreated syphilis on living subjects. None told they were infected with syphilis. Either not treated or treated at a level that was judged to be insufficient to cure the disease.

- Is it ethical to use NHS resources for those who participate in a trial but not to other patients (exclusion of certain groups, exploitation, BUPA etc)

- Will the research participants/population themselves benefit from the findings?
Summary

- Although working within the Governance Framework determined by the Department of Health, Research Ethics Committees (RECs) are convened to provide independent advice to participants, researchers, funders, sponsors, employers, care organisations and professionals on the extent to which proposals for research studies comply with recognised ethical standards.

- Ethical Committees are responsible for acting primarily in the interest of potential research participants and concerned communities, but should also take into account the interests, needs and safety of researchers who are trying to undertake research of good quality.

- However, the goals of research and researchers, while important, should always be secondary to the dignity, rights, safety, and well-being of the research participants.

- Important to demonstrate to Ethics Committees in applications that you have given these matters consideration and tried to address them in your study.
Thank you and goodbye to those undertaking literature or systemic reviews!
Part 2: Types of ethical approval
Research, Audit or Service Evaluation?

Not all projects involving the NHS are research. Audits or service evaluation are NOT classified as research by the NHS so would not require ethical review by an NHS REC. However ……

Audit or service evaluations - health topics

- Need approval from the Biomedical Research Ethics Committee (BREC)

- Need to demonstrate to BREC that the study has been registered with NHS Trusts in which they are being conducted (but NHS ethical approval not required)

- Non-NHS researchers may still require an honorary contract with the Trusts involved + clinical researchers without substantive contracts

Some projects may have elements of all three – need to agree primary intent ……..
# Audit, Service Evaluation or Research?

## Comparison

<table>
<thead>
<tr>
<th>In Research</th>
<th>In Audit &amp; Service Evaluation</th>
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<tr>
<td><strong>INTENT</strong> – primary aim to derive <em>new knowledge</em>, discovering the right thing to do</td>
<td><strong>INTENT</strong> – aims to measure or compare <em>existing</em> level of care, to ensure service/treatment is right</td>
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<td><strong>TREATMENT</strong> – <em>unlike</em> audit and service evaluation may test a new practice, therapy/drug which may lead to change in clinical practice</td>
<td><strong>TREATMENT</strong> – only use a treatment (intervention) arising from evidence based <em>clinical judgement &amp; necessity</em></td>
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<td><strong>ALLOCATION</strong> – <em>only</em> research allocates treatment by a protocol</td>
<td><strong>ALLOCATION</strong> – of treatment is decision of clinician/patient</td>
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<td><strong>RANDOMISATION</strong> – only used in research</td>
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- **Comparison**
- **Randomisation** – only used in research
- **Treatment** – only use a treatment (intervention) arising from evidence based clinical judgement & necessity
- **Allocation** – of treatment is decision of clinician/patient
- **Audit** & service evaluation
- **Research**
- **New knowledge**
- **Existing level of care**
- **Primary aim**
- **Research Randomisation**
Audit, Service Evaluation or Research?

Research
- creates new knowledge about whether new treatments work and whether certain treatments work better than others. It tests, hypothesises and should help determine what is best practice.

Clinical audit/evaluation: *predetermined standards*
- seeks to establish whether we are doing what we should be doing. Are we following guidelines, applying best practice?

Similarities:
- involve answering a specific question relating to quality of care
- may be carried out either prospectively or retrospectively
- may involve careful sampling, questionnaire design & analysis
Still confused?

Studies may contain elements of audit, evaluation & research

Focus on three key questions:
1. Is the purpose of the proposed study to try to improve the quality of patient care in the local setting?
2. Will study involving measuring practice against standards?
3. Does project involve anything being done to patients/participants which would not have otherwise been part of their normal routine care?

Generally speaking:
- Yes to 1\textsuperscript{st} two questions and No to 3\textsuperscript{rd} question, probably audit
- If answer to 3\textsuperscript{rd} question is Yes, probably research
CASE STUDY EXERCISE

- Research?
- Audit?
- Evaluation?
What approvals does my study require?

- Literature/systematic Review of published data: •Supervisor/Course Director •No other approvals required
- Secondary analysis of unpublished data: •BREC Expedited Review
- Research NOT involving NHS: •BREC Full Review
- Audit/Evaluation, Service Development incl. those involving NHS: •BREC Expedited Review •NHS involvement discuss with audit dept/service manager(s)
- Research involving NHS patients/data/Staff/resources etc: •NHS Ethical Approval •NHS Trust R&D Approval •Honorary contract/CRB checks
Approvals necessary for research (not audit or evaluation) involving human participants

**Ethical Approval is not required for:**
- Studies using published sources of information e.g. literature reviews, systematic reviews: books, journal articles, public domain web-sites (not intranets) but

**Ethical Approval is required for:**
- Studies involving human participants, their data, blood, organs, tissues etc
- Which REC? Two possible options ..........................
Approvals for research involving NHS

NHS Ethical Approval required
Note: studies that combine NHS elements & non-NHS should still be submitted to NRES

PLUS

Trust R&D Approval

from each Trust involved in the research

• CRB checks
• Occupational Health checks
• Honorary contracts/letters of access
Process for research in the NHS

- On-line registration/application
- Filtering form for study
- Template for consent documentation
  - https://www.myresearchproject.org.uk/Forms/MainFormList.aspx

Ethics Approval Part A & B
- Design, aims & objectives of study, methodology, researcher qualifications

Self-populates Parts C&D
NHS Trust specific site information

• NOTE:
  • More Trusts involved = more complexity, more delays
  • CRB/Honorary contracts for non-NHS researchers
  • Research passport scheme
CASE STUDIES (2)

What kind of ethical approval is required?

- NHS
- BREC

Who else should be informed?

Any other issues?
Sponsorship, Insurance, Liability

Formal sponsorship declaration required:

- For NHS studies
- When funder requests
- For overseas studies

**NOTE:** Indemnity/sponsorship issues must be resolved through the Departmental/Faculty RSS Officer *before submitting applications* to BREC

- BREC is not qualified to resolve indemnity and sponsorship issues but may advise applicants on issues of concern
APPLICATIONS TO BREC

1. Research studies not involving the NHS

2. Non-Research studies e.g. audits, evaluations, service developments (incl those conducted in NHS)
   - Process similar for all studies but different application forms
   - Study documentation must accompany all applications regardless of type of study
BREC PROCESS – non-research studies

Submit application

Sent to two BREC reviewers

Chair makes decision based on reviewer comments

Applicants advised by email and letter usually within 3 working weeks of submission

For conditional approvals, applicants resubmit revised application

Chair makes decision usually within 1 working week

Applicants advised by email and letter usually within 1 working day of Chair’s decision
BREC PROCESS – research studies

Submit application 3 weeks before BREC Meeting

Sent to two BREC reviewers

Applicants attend BREC meeting to discuss study with BREC panel

Applicants advised by email and letter usually within 1 working weeks of BREC Meeting

For conditional approvals, applicants resubmit revised application

Chair makes decision usually within 1 working week

Applicants advised by email and letter usually within 1 working day of Chair’s decision
When informed consent is not required

- Research studies that DO NOT involve human participants

- Audit and evaluation of patient records where the applicant has clinical responsibility for the patient, and access to their records automatically in their clinical capacity
When informed consent **is** required

- Research involving human participants

- Audits and evaluations of patients records being undertaken by a clinician who does not have clinical responsibility for the patients (even if they are in the same Trust/Hospital) are required to obtain informed consent.

- Applicants planning to publish the results of audits, evaluations or similar studies involving patients are also advised to obtain informed consent as academic journals are increasingly making this a requirement of publication.
Supplementary documentation

1. Project protocol including a brief summary of the project (in lay terms), including the scientific benefit
2. Summary CV for other investigator(s) including student applications
3. Summary C.V. for supervisor (PhD Students only)
4. Copy of Course Director’s approval (for taught postgraduate students only)
5. Letters of invitation to participants and/or appropriate others * if appropriate
6. Project participant information sheet(s) (PIS) * if appropriate
7. Project participant consent form(s) * if appropriate
8. Interview schedules or topic guides for participants
9. Questionnaire(s)
10. Copies of advertisement material for project participants, e.g. posters, newspaper adverts, website. For video or audio cassettes, please also provide the printed script.
11. Verification of study registration from the organisation where it is being conducted e.g. NHS Trust Audit Department
Common mistakes that delay approval

- Study design unclear/unlikely to achieve stated objectives

- Means of accessing participants unclear

- Steps to ensure confidentiality, anonymity, secure storage of data not specified
  - see University Data Protection Policy
  - Encryption advice

- Poor grammar and spelling particularly in Participant Information Sheets/Consent forms that materially affects the meaning of the text.
Common mistakes that delay approval

- Information in protocol or IRAS form not consistent with information in other documents

- No informed consent documentation (when appropriate)
  Students using hotmail instead of Warwick email account

- Missing information and/or documents

- Failure to register study with appropriate NHS Trust(s) (obtain prior to BREC submission)

- Failure to correspond with BREC using warwick email account.
Summary

- Don’t be tempted to split your study up – describe your study in full and then submit it to the appropriate REC.

- Plan ahead: completing documentation properly takes time. Attention to detail may avoid amendments/delays.

- Pay attention to grammar and spelling - though not ethical issues BREC will ask for amendments where such errors affect understanding e.g. in Participant Information Sheet.

- Read BREC guidance and submit applications in the format with all the relevant documentation – to avoid delays.
If in doubt .......

- Email me with any queries
- Krysia.saul@warwick.ac.uk
- Thank you for listening