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Research Ethics Committees – the role of the statistician

John Kirkpatrick, Member of the Cambridge South Research Ethics Committee
PPD Inc

The role of the National Research Ethics Service (NRES)

Protecting the rights, safety, dignity and well-being of research participants and facilitating ethical research…

NRES - England

- 68 RECs
- 5 REC Centres – Bristol, Jarrow, London, Manchester, Nottingham
- Operations Team
- Volunteer Service – 1000 volunteer members
- National Research Ethics Advisors Panel

Research Ethics Committees (RECs)

- Appointed by an NHS Appointing Authority
- Meet monthly
- Up to 18 Members appointed to a Committee (optimum 15)
- Some expert (for example - doctors / nurses / pharmacist) some lay (for example - non medical people / people who work outside of healthcare and research). All volunteers and un-paid.
- One third of the membership must be lay (and half of this must be lay plus)
- Minimum of 7 members at a meeting (at least one lay member)

How I joined a REC

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- NRES (now HRA) website is intended for users, not joiners
  - Information not easy to find
- Application process straightforward
  - Form
  - Referees
  - Face-to-face interview
- Choice of RECs on acceptance

My choice of REC

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- About a dozen RECs were interested
  - Widely spread geographically
    - London to Leeds
  - Wide variation in meeting times and durations
    - Morning , afternoon, evening, all day
  - I chose Cambridge
    - Geography
    - Time of day
    - Uninformed (but justified) suspicion that applications would be interesting

REC membership: the employer's view

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- I joined the REC as a freelance
- A year later, I started at PPD
  - Continued membership was important to me
  - I expected some resistance
- PPD actually very supportive
  - Good company PR
  - Practical benefits

What the employer gains

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- Good corporate citizenship
- Internal feedback
  - Unofficial advice
  - Training and awareness
- Specific clients
  - Authoritative view can short-circuit discussion
- Personal
  - Not “just a statistician”

What does a REC review?

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- The Governance Arrangements for Research Ethics Committees (GAfREC) sets out the remit for the types of studies which require approval from an NHS REC:

- Research in the NHS
  - Patients
  - Staff
  - Facilities
- Research involving healthy volunteers – Phase 1 studies
- Research involving the use and storage of human tissue
- Research involving adults who are unable to consent
- Research involving prisoners
- January 2015 – Social Care research

Who are the researchers?

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- MSc and PhD students
- Clinicians and surgeons
- Pharma and biopharma
- National health initiatives
  - 100,000 Genomes Project
- Academic researchers
  - Water fluoridation

Review should be appropriate to the purpose of the research

And facilities available to the researchers and risk to participants

“(almost) all research is ethical if consent is informed”

Decisions available to the Committee

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(All NHS healthcare related research and all clinical trials MUST have a favourable ethical opinion before they start)

Favourable Ethical Opinion (5%)

Favourable with conditions (20.4%)

Provisional Ethical Opinion – further information needed (69%)

Unfavourable Ethical Opinion (option to appeal decision)

(5.6%)

*Based on 2013 – 2014 data

What makes a bad application?

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- Problems are rarely just statistical
- Almost all “bad” applications have issues in more than one area
  - Degree and speed of agreement still surprises me
- Statistical methodology is rarely a deciding factor
  - For me, z-test vs t-test vs rank sum test is not an ethical issue

When things (might) go wrong

Some examples where statistics has played a part in the decision

The over-enthusiastic researcher (1)

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- Coronary artery plaque ablation
- Device delivers pulsed current to plaque via catheter
- Optimum settings unknown, even though device is in regular use
  - Implies small differences
- 2x2 factorial
  - Shape of pulse
  - Strength of pulse

The over-enthusiastic researcher (2)

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- Low-risk addition to required surgery
- “About 30 subjects per year come through my clinic”
- One year to complete surgical registration
- Device manufacturer is already running a 160 subject study to same design

The potentially biased sponsor

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- Prophylactic treatment to reduce post-surgical bleeding events
- Both current and proposed prophylactics are also associated with bleeding events
  - But much less frequently than surgery alone
- Primary analysis based on mITT
  - mITT: patients who undergo surgery

The honest sponsor

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- CTIMP for regulatory submission
- Power >99% for primary endpoint
- “we know we’re over powered, but we need the exposure for the safety database”

- Is this ethically different to two separate, appropriately powered studies?

The student in need of advice

- Pilot study for variation of surgical technique
- Pre- and post-operative assessment
  - 22 subjects *per group* gives 90% power for stated reference effect and SD
  - Two sample t-test
- Why not paired t-test?
- With 90% power, why is it a pilot?

Statistical ethics: 1

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- Equipoise
  - Freedman: genuine lack of knowledge about which treatment is better
    - Almost all confirmatory (Ph III) CTIMPs are unethical
    - Most Ph II CTIMPs are unethical
  - Miller: ethics of research and ethics of treatment are different
    - Consider societal good

Statistical ethics: 2

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- Adaptive design introduces ethical issues
  - Play the winner randomisation
  - Arm dropping
  - Group sequential (superiority) design
- All imply greater chance of benefit from late entry
- How to explain concepts in PIS?

Statistical ethics: 3

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- Are some designs just too bad to use?
  - 3 plus 3?
    - Inherent design assumptions unknown to investigators
    - Poor design characteristics
      - Mitigating risk increases chance of incorrect answer
      - Inherent risk of overdose
      - Little information about doses of future interest

NRES/RSS workshop: main issues

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- Credit for academic statisticians
- Statistical referees used without knowledge