Health Research Authority

Peer / Scientific review of research and the role of NRES Research Ethics Committees (RECs)

The Governance Arrangements for Research Ethics Committees (GAfREC 2011) now defines the RECs role;

'A REC need not reconsider the quality of the science, as this is the responsibility of the sponsor and will have been subject to review by one or more experts in the field (known as 'peer review'). The REC will be satisfied with credible assurances that the research has an identified sponsor and that it takes account of appropriate scientific peer review.'

This is interpreted to indicate there is no change in the REC's role under this redrafted guidance. We provide here a framework of questions (and considerations that would arise) RECs might ask when satisfying themselves of its adequacy, derived from this National Research Ethics Service (NRES) meeting.

The process of peer / scientific review

Question	Considerations
The REC and scientific review	
Is scientific review warranted and commensurate?	For studies with less than minimal risk, RECs may deem independent scientific review unnecessary and their decision can be based on the response within IRAS (see the example of Imperial College procedures presented at the NRES meeting)
Has the review been submitted to the REC?	The REC should be able to see the review if necessary.
How has the science been evaluated? (Categories from IRAS)	• Independent external review • Review within a company • Review within a multi-centre research group • Review within the Chief Investigator's institution or host organisation • Review within the research team • Review by educational supervisor • Other
The conduct of scientific review	
Is the REC reassured that the reviewers are sufficiently independent of the research with the appropriate expertise?	This might include: • Directly involved in the work or possibly working in the same department (although under guidance, some research could be reviewed by supervisors). • Personal (pecuniary or non-pecuniary) benefit, close friendship or family interest. • Close links with an institution seeking a grant • Working closely with the applicant(s) within the last four years.
The research team	
Does the review indicate that the team have the necessary skills and resources?	Has the researcher a record in the field and is s/he placed to deliver the work? If it is new work, can the applicants take the work forward?

The science of the project

Questions (the REC might raise)	Considerations
What is the research question? Has it been answered already? If so what is the justification for repeating a study?	There should be a clear definition of the question and evidence literature has been reviewed to establish what is known already. Repetition – per se - is not unethical but it requires justification
If it hasn't, can this project answer it?	The researcher should be able to explain how the method matches the question. *THIS IS A CHALLENGING AREA FOR RESEARCHERS*. A succinct answer requires time to prepare. RECs need summaries not details and are adept at recognizing lengthy jargon or obscure verbosity that hide a lack of understanding.
Is this the best approach?	Were other methods of answering the question considered, and why were they put to one side?
Is there a good medical, scientific or patient benefit rationale for the project? Is the question worth asking and answering?*	'Purpose wins over RECs'. They will allow greater burden, intervention and risk if persuaded of benefit. Has there been wide consultation, including patients?
Is there a methodical review of prior work? Have results of these been incorporated into the research design?	Good research practice dictates that research should build on prior research and current knowledge. The necessary detail and depth of this will depend on the study. Exploratory research with no risk to a subject may require lesser review than a clinical trial, in which best practice would be to provide a systematic review to protect patients and research participants. What is important is that the REC can see the method used and judge its adequacy. Does the review confirm the value of the research?
Does the study design expose participants to unacceptable risk?	This is a question both peer/ scientific review and RECs need to address.
What will happen to the results? Are there realistic approaches to the translation of research findings into improved practice?	Elaborate how the results will be available to participants, patient group, public and other researchers

*If the research is a therapeutic trial:

- Is there a real need for such a trial for this condition or group of patients?
- Is the most important question being addressed? Is it a question patients want answering?
- What impact are the results likely to have on clinical practice or understanding of the proposed intervention?
- Is there evidence of an appropriate degree of liaison with consumer groups?

On the 11 January 2011, the NRES held a meeting, attended by researchers and NRES Committee members to consider scientific review of research and the RECs duties under their governance arrangements (GAfREC) to satisfy themselves that this review has been methodical, robust and commensurate. Although in the interim GAfREC has been redrafted the principles, agreed by the Department of Health and NRES, are unchanged.

Summary of conclusions

- Poor science should and must trouble RECs. It is evident that it does.
- RECs have an important role but given the recent rapid expansion in published information, RECs cannot be expected to have the expertise to necessarily conduct the review.
- Many applications coming to RECs will have been through rigorous scientific review to secure funding or sponsorship. The REC should take fair account of these and recognise that the reviewers will have considerable expertise and the funding body will have given considerable thought to the application. If review has been undertaken, RECs should be able to see it and very clear arguments need to be presented if a scientific review is withheld after such a request.
- The NRES has a Memorandum of Understanding (MoU) in place which enables RECs to refer to the MHRA for issues relating to the safety of drugs in CTIMP applications.
- There was support for the draft framework of questions that the REC might ask of the process of scientific review (see below). It would also be a useful proforma for sponsors, scientific reviewers and researchers and incorporated into IRAS question A54.
- There was full endorsement of the need for commensuracy / proportionality. Any scientific review should not hinder or undermine ethical research and it was even more important to ensure regulation did not turn good science into bad science.
- Systematic review of existing research evidence is an important part of scientific review and it should meet published standards (e.g. PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses). A clinical trial without a systematic review requires explanation. For other, less intrusive or risky research, a record of prior work and how this new project fits in would suffice.
- If RECs disagree with the scientific review they should be able to deliver their opinion but in the case of clinical trials must also inform NRES that a possible unfavourable opinion is based on the scientific standard of the project as this will need to be discussed with MHRA.
- There is a need to evaluate any processes established.
- In this area, early discussion with the medicines regulators would be helpful. NRES should use the Academy of Medical Sciences recommendations to promote this and the teaching of research ethics

- The concept of accredited, trained, scientific reviewers was discussed as a future initiative.

The purpose of the scientific review: what is its added value or is it a purposeless hurdle?

Scientific review should provide judgement on:

- The value or harm (to ALL parties) if the research is blocked.
- The value or harm (to ALL parties) if the research goes ahead.

It can do this by providing:

- Detailed knowledge of the subject area (disease etc.), accommodating the controversies, difficulties and uncertainties and taking account of the research that has already been undertaken:
    - Is there evidence of one or more review(s) of prior research?
    - Has the question been answered already?
    - Is there a need for this research?
    - Will it add to current knowledge and treatment?
    - Will patients or communities benefit?
    - Will the proposal answer the question it sets itself, and is this a relevant question?
- An assessment of the feasibility of the project (given the proposed personnel and resources) by someone in the field.
    - Is it likely that this research team will be able to successfully conduct and conclude the project?
    - Is there similar or complementary research underway elsewhere?
- An understanding of what is normal care and how research will impact on this (if at all).
    - Is research in this area needed?
    - What is the context of this work and how will it affect care?
- an assessment of the risks from someone with knowledge of the field.
    - Does it withhold proven therapy, or is it researching treatment that prior research has demonstrated is inferior?
    - Does it expose participants to risk?

Professor Savulescu outlined the contention that, given the current explosion in knowledge and information, no REC can have the expertise to undertake scientific review of all research proposals it sees, so processes must adapt. Independent scientific review can meet the needs of ethical review and the REC's role is then to conduct a secondary review commenting primarily on its CONDUCT. This raised the

question 'what is the appropriate expertise on a REC' and what is the exact nature of the expert's role?

Scientific review matters

There are strong arguments that scientific review of research proposals matters. Patient and public safety depend on it.

Chalmers and others have demonstrated this has consequences for RECs. Savulescu et al presented evidence 15 years ago that unnecessary and dangerous research seems to obtain REC approval (Savulescu J, Chalmers I, Blunt J. Are RECs behaving unethically? Some suggestions for improving performance and accountability. British Medical Journal 1996;313:1390). They suggest that:

'Performance and accountability of RECs would be improved if they required those proposing research to present systematic reviews of relevant previous research in support of their applications'.

Savulescu wrote later of two deaths in research approved by IRBs (Institutional Review Boards). In one, a comprehensive review of the literature would have highlighted the danger of the research; in the other scientific review might have indicated that the therapy (from which the subject died) was not appropriate (Savulescu J. Two deaths and two lessons, Journal of Medical Ethics 2002; 28: 1).

The importance of this has been re-emphasised by the study at the Royal Free Hospital London investigating a possible link between the Measles, Mumps and Rubella vaccine and autism. Harris asked why those responsible for research regulation seemed to permit invasive, painful procedures on a group of children with autism when it was well recognised that these were beyond routine clinical care and not in the child's best interests (Harris E. MMR after Wakefield, British Medical Journal 2010, c2829). He argued that appropriate independent scientific review would have at least been more likely to question the proposed work.

(and we're not there yet)

Clarke et al (2010) (Clinical trials should begin and end with systematic reviews. Lancet, 376, 20) would argue it has been broken for 15 years at least. A more recent paper (A systematic examination of the citation of prior research in reports of randomised trials Robinson and Goodman, Annals of Internal Medicine 2011;154:50-55) indicates that in reports of RCTs published over 4 decades, less than 25% of preceding trials were cited.

Science does trouble ethics committees, which see 'Bad science as bad ethics'

Poor science troubles RECs. Researchers from the University of Leicester, funded by NRES, found that, in a sample of 141 generic letters, scientific issues were raised as causing concern in 104 (74%). Moreover, there was tentative evidence to suggest that projects considered to have scientific flaws are more prone to unfavourable opinions. Those areas that raised concern included sampling, rationale for methods, problems with the research question, instruments or measures, approach to analysis and bias.

http://www.clinicaldiscovery.com/readArticle.aspx?articleId=98

But how do Research Ethics Committees meet their responsibilities?

RECs should be able to receive the results of prior scientific review. The Research Governance Framework makes it clear that the sponsor is responsible for ensuring the quality of the science. Paragraphs 2.3.1 and 2.3.2 state that:

'It is essential that existing sources of evidence, especially systematic reviews, are considered carefully prior to undertaking research. Research which duplicates other work unnecessarily or which is not of sufficient quality to contribute something useful to existing knowledge is in itself unethical'.

All proposals for health and social care research must be subjected to review by scientists in the relevant fields able to offer independent advice on its quality. Arrangements for peer review must be commensurate with the scale of the research.

GAfREC (2001) defines the RECs role:

9.9 *'Thus, protocols submitted for ethical review should already have had prior critique by experts in the relevant research methodology, who should also comment on the need for the research. It is not the task of a REC to undertake additional scientific review, nor is it constituted to do so, but it should satisfy itself that the review already undertaken is adequate for the nature of the proposal under consideration.'*

NRES reviewed data on its Research Ethics Database (RED) to find out whether RECs used this review. Between the 1 July 2009 and 1 July 2010, RECs in the UK reviewed 8061 applications. Of these only 335 (4%) submissions seemed to include independent scientific review. Looking at medicinal trials only, the picture was little different. 1024 were reviewed, and only 25 included scientific review (2.5%). To explore this, one coordinator reviewed applications to his REC over 3 months in 2010 and the picture was only slightly better. A larger fraction of applications came with independent scientific review but these were still only a minority (5 of 25 applications). Within the application form, 19 had undergone internal review, 4 within a pharmaceutical company and 1 by the National Institute of Health Research. One applicant provided no comment. This picture has been confirmed by a recent analysis of paperwork submitted to two other RECs. Only seven of 27 (25%) applications had attached independent scientific review.

It seems therefore that NRES RECs recognise the importance of 'good science', and that 'Bad science is bad ethics'. In the majority of cases, however, they draw their own conclusions from the application form and/or the protocol, rather than from independent scientific review.

Commensurate review

RECs review a huge variety of research. What therefore is commensurate scientific review? One example is below:

Imperial College Peer review service

An example of classifying research to provide 'commensurate' peer review.

Level 1a No peer review required - *Studies that involve minimal risk*

Examples of projects or procedures in this category:

- Short questionnaire studies for use among hospital staff or GPs.
- Questionnaires asking patients about the quality of hospital services.
- Use of data from medical notes by clinician looking after patient.

Examples of projects or procedures not included in this category:

- Acquisition of new personal or laboratory data about patients.
- Lengthy questionnaires that represent a significant burden to the patient (e.g. taking more than 10 minutes for a patient, or 20 minutes for a healthy volunteer).
- Questionnaires involving sensitive topics (e.g. depression, sexual orientation).

(Level 1b No peer review required - *Studies that have been peer reviewed by major grant-giving bodies*)

Level 2 Review by project supervisor - *Student projects that involve either no patient/participant involvement or only minor involvement.*

Examples of projects or procedures in this category:

- Data handling studies.
- Administration of questionnaires.
- History taking.
- Non-intimate examination techniques, e.g. blood pressure measurement.
- Spirometry.
- Urinalysis.

Examples of projects or procedures not included in this category:

- Physiological experiments on fellow students involving an element of risk e.g. hypoxia.
- Administration of drug or device to participants.

Level 3 Review by departmental colleague - *Low-risk projects with minimal patient involvement*

Examples of projects in this category:

- Histological studies on existing/historical specimens.
- Projects using existing stored data.
- Administration of questionnaires.

Examples of projects not included in this category:

- Histological studies on newly acquired specimens.
- New acquisition of personal data.

Level 4 Review by individual within Hammersmith Hospital or Imperial College - *Projects with minor patient or participant risk*

Examples of projects or procedures in this category:

- Physical examination.
- Taking of up to two blood samples of no more than 10mls each.
- Taking of extra biopsies during biopsy procedure that is part of normal care.
- Minor lengthening of procedures (up to 5 minutes or 10%).
- New acquisition of personal data.
- Pilot studies of drugs or devices within their licensed use.

Examples of projects or procedures not included in this category:

- Intimate physical examination, unless it is part of normal patient care.
- Use of radiation.
- Randomized trials of drugs or devices within their licensed use.
- Withdrawal of existing/standard therapy.

Level 5 Review by individual outside HHT or IC - *Projects with greater than minor risk to participants*

Examples of projects or procedures in this category:

- Phase I, II and III drug or device trials.
- Randomized trials of drugs or devices within their licensed use.
- Intimate physical examination, unless it is part of normal patient care.
- Use of radiation.