Medical Research Council position statement on research regulation and ethics

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Introduction

1. Some recent events have raised concerns within the medical research community about the level of regulation This paper summarises the Medical Research Council's (MRC) views about the need for regulation, and the balance that needs to be struck between this and the importance of not impeding vital medical research to improve individual and public health.

2. The mission of the MRC is to encourage and support high-quality research with the aim of improving human health. The MRC is a national organisation funded by the UK taxpayer. It promotes research into all areas of medical and related science.

3. The MRC aims to set standards of good practice in all aspects of medical research, including ethics, patient safety, and the use of animals, personal information and human tissue in medical research. We produce a variety of publications[1] defining and explaining good practice in these and other areas, for use by scientists and other

interest groups. Our work to develop and promote good practice encompasses informing and responding to new Government initiatives, developing ethical guidance for researchers conducting science in emerging areas such as stem cell research, and keeping in touch with public opinion about ethical issues in medical research. The MRC also produces guidance on good research practice generally[2], and has a published policy on scientific misconduct[3].

4. The MRC recognises that there is a need for formal regulation in certain areas of science, in particular those known to be of concern to the general public (or which may become of concern to the public). However, recent events that have raised concerns about the level of regulation have included:

- Incorporation of the EU clinical trials directive into UK law.
- Passage of the Human Tissue Bill, now Act (2004).
- Concerns over the increasing requirements of Research Ethics Committees (RECs), in part arising from complexities of some new legislation.
- The great variation in implementation of regulations in RECs, Universities, NHS Trusts and R&D departments and others.

These developments have prompted the MRC to review its position on this topic, including establishing a new Subcommittee of Council, the "Committee on the ethics of research involving human participants or tissues and personal information".

5. First we set out some ethical principles in relation to human and animal studies.

General ethical principles - humans

6. The MRC is committed to the highest ethical standards in medical research. It was the first research organisation to publish (in the early 1960s) ethical guidelines concerning investigations on human participants[4]. These pre-dated the first version of the Declaration of Helsinki (1964). The fundamental principles underpinning research on human beings and information relating to them have been elaborated and refined in various national and international guidelines[5]:

- Participants' interests must prevail over those of science and society, where there is conflict
- The research must have potential to generate scientific understanding that may be a basis for improvements in human health and well-being.
- There must be an acceptable balance of risk and benefit for participants.
- Researchers can only proceed if they have obtained voluntary informed consent from the participant to participate in research. Special safeguards apply when this is not possible.
- An appropriate independent research ethics committee must review and approve the research proposal. If the research is to be conducted outside the UK,

appropriate ethical approval from within the other country must be sought in addition.

- Researchers collaborating with other countries must take account of all the circumstances pertaining to the country in which the research is to be carried out and must satisfy themselves that standards there are consistent with the principles underlying the standards in the UK. [Guidance on this is available from MRC[1]; and more detailed discussion has been provided by the Nuffield Council on Bioethics (6)].

General ethical principles - animals

7. The ethical principles underpinning research involving animals applied by the MRC[7] follow from the Animals (Scientific Procedures) Act, 1986:

   - The MRC supports only scientific studies that are well designed and likely to provide new information on important questions relevant to human health.

   - All experimental programmes supported by MRC must avoid using animals wherever possible. The researcher must give sound scientific reasons for their use, and explain why there are no realistic alternatives.

   - Animal experiments must use the simplest possible, or least sentient, species of animal.

   - The MRC expects researchers who use animals to consider the ethical issues associated with: keeping animals in captivity; killing animals; causing animals distress or pain.

   - Experiments should use the smallest number of animals that can clearly answer the question posed, and take every practical step to avoid distress or suffering.

   - All staff involved in animal research, and in the breeding, housing and care of animals, must be properly trained and supervised.

   - By law, all research must be scrutinised by a local ethical review process and by the Home Office Inspectorate before work begins. In addition, the MRC's scientific committees have a responsibility to scrutinise scientific plans for animal experiments to ensure they are worthy of support.

   - The MRC actively supports the development and dissemination of techniques that reduce, refine, or replace animal experiments.

   - Researchers collaborating with laboratories in other countries must ensure that standards there are consistent with standards in the UK.

   In 2004, the MRC reviewed it practices and guidance concerning the use of primates in research, and published guidance on breeding[1] and on accommodation and care[1], in addition to introducing some further safeguards though the peer review process.

The nature of research

8. Medical research is aimed at improving human health. Everything else being equal, the quicker the research is done, the more quickly benefits will accrue. In addition, there is competition in research, so it is in the interests of researchers to progress quickly and to be the first to make discoveries. Research funded by the MRC and most other funders is rigorously peer-reviewed in order to ensure that it is of high quality. Peer review, together with systematic reviews in certain areas, also helps to avoid unnecessary duplication. Research – seeking the unknown – is exciting. Research by its nature is unpredictable; indeed many important findings were not those that were being sought at the time. Examples include the discovery of monoclonal antibodies and smoking being a cause of lung cancer. Opportunities may arise that need to be taken quickly, or be lost. These features present challenges to researchers. While researchers want to progress their work quickly, they are of course members of a wider society and need to take account of the views of society in deciding what they do and how they go about it; this may have the effect of slowing their work down.

9. Participation by human volunteers or patients in research may take a number of forms with different levels of invasiveness. Also, it may be added to routine medical treatment or be a study independent of any treatment. For example, participation may involve analysis of data from a patient's medical notes, being observed, responding to surveys, undergoing non-invasive imaging, providing blood or tissue samples (for example for genetic or biological tests), or inclusion in trials of drugs or other treatments.

The need for regulation

10. Regulation not only protects participants in research (human and animal), but it also protects researchers. It sets out clearly what is acceptable and what is not, and therefore provides a framework within which researchers work. Any regulatory system needs to be appropriate to the level of risk to the participants and the researchers. Research involving access to a patient's medical notes, for example, should require fewer constraints than research involving administering a new drug. In research involving access to data, to the patient confidentiality may be more important than consent (and the bureaucracy and possible intrusion that goes with it). With certain exceptions, people can give consent for themselves, but animals cannot, so regulation for research involving animals has to be different to that for humans. The MRC expects the researchers it supports to be familiar with the regulations relevant to their areas of research. Some of this regulation will be contained in statute, but statute can be a blunt instrument in guiding human behaviour and is often hard to understand for non-lawyers. There is therefore need for additional guidance in some areas to help researchers understand the law and to enable them to put their daily work into the appropriate legal context. Also, research funders and employers have responsibility to ensure that their work meets societal standards, and that, within the powers that they have, the people they support or employ abide by the law. In addition, effective regulation helps to ensure that the reputation of funding bodies and employing organisations is not damaged by misjudged or unethical experimental work.

Sources of regulation

11. The regulation applying to biomedical research derives from a variety of sources;

    - Statute – Acts of Parliament (primary legislation, could include directly applicable EU law) may prohibit certain activities or may require certain conditions to be met before activities can take place.

- Common Law – principles contained within the common law (case law) may impose requirements on the conduct of research, the common law duty of care, for example.

- Secondary legislation – rules made under statutory authority and approved by Parliament, including provisions implementing obligations arising from EU Directives.

- "Administrative" rules, including self-regulation. Rules and guidance may come from Government Departments, professional bodies, employers or funders. Such rules may not have the formal effect of law but may impose real obligations on researchers.

12. In the early 19th century, reliance was placed simply on the good faith of those conducting medical research. However, it became clear that a few researchers were breaching the trust of the people they purported to serve, and this resulted in legislation in the 19th century, including the Anatomy Act (1832) and the Cruelty to Animals Act (1876). Since then, the volume of legislation has grown enormously in reflection of a change in social attitudes. There is now a large number of statutes and pieces of secondary legislation which cover the conduct of medical research; the most important of which include:

    - Animals (Scientific Procedures) Act (1986)

    - Human Fertilisation and Embryology Act (1990)

    - Radioactive Substances Act (1993)

    - Data Protection Act (1998)

    - Genetically Modified Organisms (Contained Use) Regulations (2000)

    - Health and Social Care Act (2001)

    - Control of Substances Hazardous to Health Regulations (2002)

    - UK Medicines for Human Use (Clinical Trials) Regulations (2004)

    - Human Tissue Act (2004)

    - Mental Capacity Act (2005)

    Furthermore, different Acts cover different parts of the United Kingdom (and different parts of the UK may interpret EU legislation differently). The likelihood of this occurring has increased with devolution. For example, most of the Human Tissue Act does not apply in Scotland. It is thus important that researchers are aware of the law where they work. This can present problems for researchers who move within the UK and also for cross-border collaborations.

13. Whatever the regulatory scheme, however, trust must remain an important element. Most human behaviour and activity still relies on trust; indeed it can be no other way:

"Each of us and every profession and every institution needs trust. We need it because we have to be able to rely on others acting as they say they will, and because we need others to accept that we will act as we say we will." – Baroness O'Neill[8].

14. No regulatory system can work without relying on trust, but some systems unfortunately operate to undermine trust – they appear to assume that people cannot be trusted. It is therefore essential to encourage regulatory schemes which are designed to support trust, not to replace it.

15. Responsibility for adherence to legislation and guidelines lies with a variety of people or bodies. These include primarily the individuals concerned and their managers, but also their employers (often a university), the funders of their research, the research sponsors (as defined in the NHS Research Governance Framework), regulators (such as the Health and Safety Executive), and ultimately the criminal justice system. (For MRC research staff, MRC is the employer, but may also be the funder and/or the sponsor). The effectiveness of these systems depends on clear governance arrangements.

Striking the right balance

16. Put simply, regulation is brought in with the good intention of defining standards, putting in place governance arrangements to ensure that they are adhered to, and providing some form of audit or reporting mechanism to ensure that the governance arrangements actually work. A stated aim is often to improve or retain public confidence. In practice, regulation requires additional bureaucracy and costs, both in terms of money and time. Thus the intention of regulation to ensure high ethical standards may have the perverse effect of creating so many barriers that ethical research may be discouraged, even to the point where it may not take place, and this itself may be unethical. The barriers to participation by individuals may lead to poor research as those who participate may be systematically different from those who do not and thus lead to biased results. There is no easy solution to finding the right balance, for example because:

- aspects of the process are not easily controlled (eg EU legislation);
- the balance may be very different for apparently quite similar situations, so it is difficult to generalise;
- the balance will change with time, public attitudes and events outside the researcher's control.

17. Advances in science and the increasing interest of the public in how developments may affect them mean that there is a tendency for more regulation, rather than less. Furthermore, such regulation arises from a variety of sources and normally adds to what is already there; there is no systematic approach to regulation as a whole, and little attempt at impact assessment, other than through consultation which is normally done case-by-case.

18. An example of the complex process involved in research involving people concerns multi-centre trials. A description of this is at the annex.

Particular challenges

19. Scientific challenges include:

- Human embryonic stem cells (9); advances in reproductive technologies[10].

  These are fast-moving fields which raise various ethical concerns and are subject to legislation that needs to be reviewed regularly.

- Social science research

  Social science research within the field of health and medicine may not be formally subject to approval by NHS Research Ethics Committees, though many RECs do agree to comment and indeed approve such research proposals. Social science research that recruits patients or staff (including GPs and pharmacists) through NHS channels and/or uses NHS premises does require formal REC (and Research Governance) approval. Some social science involves vulnerable groups, for example drug users, prostitutes and/or minors, and this can present particular challenges. Many Universities have established their own research ethics committees to consider research proposals, including those within social science that have a health or social care focus. To date there has been no formal national framework or 'best practice' within which they might operate. However, the ESRC (in conjunction with funding agencies on the Strategic Forum for the Social Sciences) has recently prepared a Research Ethics Framework[11] that aims to meet this need, and which should, in some cases, provide an alternative to LREC scrutiny.

- Large population/genetic cohorts, such as Biobank[12].

  With advances in information technology, there will be greater opportunities to link people's genetic and health data to other information about them. This has great potential for medical research, for example in unravelling the genetic and environmental causes of diseases, but people are naturally concerned about the extent of linkages and confidentiality. [However, to date the MRC is unaware of any legal claim for breach of confidentiality in observational epidemiology in the UK].

- Neuroethics

  Neuroethics is the consideration of good and bad consequences in medical practice and biological research as it relates to the brain. It encompasses both understanding and altering the brain. Examples include the ethical issues that can arise from i) the growing predictive power of brain imaging, genetic or other tests, and their potential uses in educational decisions, employment, or legal decisions on culpability; and ii) screening for wanted/unwanted traits in the normal range (e.g. IQ, behavioural traits). The ethics of such issues are little different from those surrounding research on other parts of the body, but the research findings might lead the public to seek additional regulation.

- Inter-disciplinary research

  The growing amount of interdisciplinary research across the medical/natural/social sciences raises issues about the determination of risk

across these disciplines and how this is to be properly assessed and managed with due regard to both the research subject and the researcher. This calls for a more nuanced form of regulation.

20. Other challenges include:

- Media balance

  The media frequently adopt the practice of finding an opposing view to challenge scientific orthodoxy. While on many occasions this is justified, it can have the effect of giving spurious credibility to findings for which the scientific evidence is weak. In the area of health research, this can be very damaging: it can encourage false beliefs in the population about what may be good (or bad) for people's health, and imply levels of risk for which there is no evidence. This can lead to public and political pressure for regulation where the scientific evidence of need is weak. This risk can be avoided with adequate balanced information.

- "Dual use"

  "Dual use" is where research findings may be used for harmful (in addition to beneficial) purposes. The MRC believes that knowledge itself is a public good, but recognises that knowledge may be put to bad as well as good use. An example is research into the structure of micro-organisms where the findings may lead to new treatments, or could be used to develop particularly virulent strains for terrorist use. There is a risk that Government and the public, in recognising this, press for over-regulation of the research itself. This would have the effect of stifling research that may have very beneficial outcomes. [The MRC is preparing a Position Statement on Bioterrorism and Biomedical Research[13]].

What will the MRC do?

21. The MRC will continue to:

- Engage in dialogue with the public about the research it undertakes in order to understand the public's concerns and to explain the rationale for the research it supports. Possible methods include through the MRC's Advisory Group on Public Involvement, and though the use of opinion surveys.

- Keep in touch with active researchers in order to understand the issues that concern them.

- Maintain awareness of developments in broader aspects of regulation, including law, political science and accounting.

- Maintain the highest standards of peer review so that the research it supports is excellent and so that the findings may be relied upon.

- Through the UK Clinical Research Collaboration and by other means, engage with Government and other regulators over existing and proposed regulation to ensure that important medical research is not impeded by excessive regulation. [This will involve: i) reviewing and removing bureaucratic procedures that are counterproductive in that they may generate not only unnecessary burdens (in

terms of time and costs) but also work against the interests of those they are supposed to protect; and ii) setting proposals for new regulation in the context of existing regulation, taking account of the likely level of risk to the participants].

- Keep its guidance up to date so that researchers have access to clear information about regulation and ethics; and thereby to maintain high standards in the conduct of research and the trust of the public.

References

1. The MRC's publications on ethics and best practice and on clinical trials are at: www.mrc.ac.uk/index/publications/publications-ethics_and_best_practice.htm

2. Good Research Practice. London. Medical Research Council, 2000*

3. MRC policy and procedure for inquiring into allegations of scientific misconduct. London. Medical Research Council, 1997*

4. Responsibility in investigations on human subjects. Annual Report of the Medical Research Council, 1962-63 (Cmnd. 2382).

5. See eg MRC Ethics Guide: "Medical research involving children", Medical Research Council, 2004, for references*

6. Nuffield Council on Bioethics. The ethics of research related to healthcare in developing countries, 2002; and Follow-up discussion paper, 2005 http://www.nuffieldbioethics.org/go/ourwork/developingcountries/page_246.html

7. These principles are adapted from MRC's ethics guidance "Responsibility in the Use of Animals in Medical Research", 1993*

8. O'Neill O: A Question of Trust. The BBC Reith Lectures, 2002. Cambridge University Press

9. MRC Code of practice for the use of human stem cell lines (DRAFT), March 2004* www.mrc.ac.uk/pdf-stem_cell_lines_code_draft.pdf

10. Assisted reproduction: a safe sound future. London. Medical Research Council, 2004*

11. Economic and Social Research Council, Research Ethics Framework, to be published on www.esrc.ac.uk

12. See: www.ukbiobank.ac.uk/ethics/efg.php

13. MRC Position Statement on Bioterrorism and Biomedical Research, 2005 (to be published)*

* These documents are available on the MRC website (www.mrc.ac.uk)

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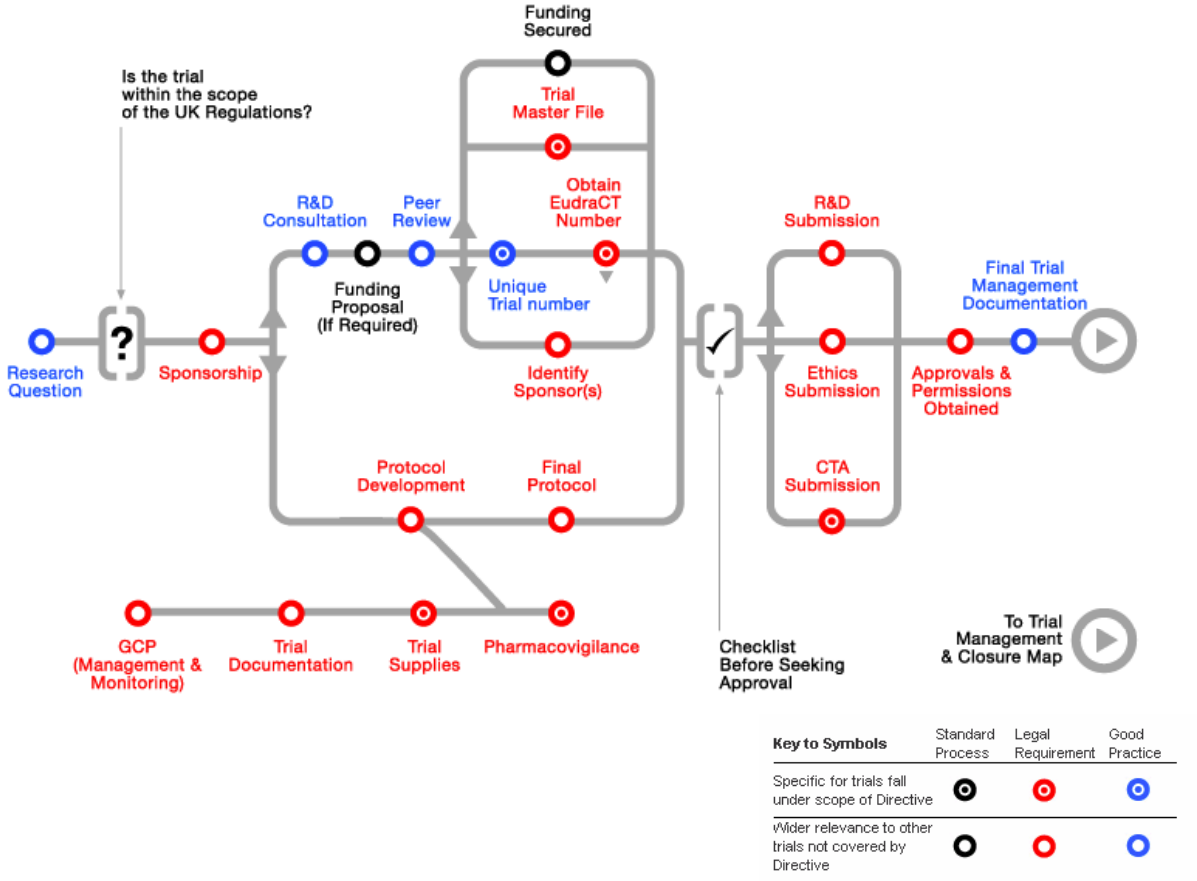
An example: What a researcher needs to do to set up a multi-centre clinical trial.

The following route map has been taken from the Clinical Trials Toolkit, which was developed to help triallists and research managers navigate the regulatory requirements.



The first step after identifying the research question to be investigated is to ascertain whether the trial is within the scope of the EU Clinical Trials Directive. MHRA (the Medicines and Healthcare products Regulatory Agency) have released an algorithm for researchers to clarify this. MHRA will also advise on an individual trial basis.

Sponsorship

Sponsorship is a legal requirement under the Directive. For all other trials that utilise NHS resources, Sponsorship is also required under the Health Departments' Research Governance Frameworks. The responsibilities of the Sponsor include:

- Obtaining relevant authorisations to conduct the study
- Ensuring Good Clinical Practice management systems are in place
- Recording and reporting safety data (pharmacovigilance).

When setting up a new trial it can take a number of months to negotiate and clarify which parties will accept responsibility for these aspects of the trial. This process is particularly drawn out for international trials. In this respect, sponsorship discussions begin before funding is secured.

Obtaining Funding

The large funders of trials have a number of steps for applicants to go through before funding can be allocated, including peer review. Funding proposals contain lots of information on why the trial is necessary and how it will be conducted, and as such take time to develop, especially considering most chief investigators have clinical commitments. Depending on the type of trial, and if a pilot study is required, obtaining funding can take anything from several months to several years.

Protocol Development

Before relevant authorisations can be granted a formal trial protocol is required. It contains more in depth information than the funding proposal, including the arrangements for:

- Management and monitoring of the study
- Trial supplies
- Safety recording and reporting

It must also contain information on the investigational medicine (if applicable) and contain all Trial Documentation (e.g. patient information sheets and questionnaires).

Recruiting Centres

In order to conduct a multi-centre trial other centres need to be recruited. This is a lengthy process, and it is common for additional centres to be added after the trial has started.

Obtaining a EudraCT number

All trials that are within the Directive's scope must be registered on a European database. The database issues each trial with a unique number, this is required before authorisation to conduct the study can be obtained.

Seeking Approvals and Permissions

A trial cannot begin until all the relevant approvals and permission have been obtained.

- Clinical Trial Authorisation
    - If the trial falls under the scope of the EU Directive, it is a legal requirement to obtain a CTA from MHRA, and any competent authority in other member states if it is an international trial. MHRA must make a decision with in 60 days of receiving an application.
- Research Ethics Committee Positive Opinion
    - It is a legal requirement to obtain Research Ethics Committee approval before a trial can commence. Local committee approval is required for each individual trial centre. Ethics committees must give an opinion in 60 days of receipt of an application.
- NHS Trust approval
    - This is site specific, approvals are required from all local Trusts. There is no time limit for NHS Trusts to give approval for research studies.

Notification of all centres

Once the relevant approvals and permissions have been obtained. The Chief Investigator must inform all trial centres if they have/have not received ethical approval to conduct the study in that locale. Each centre must conduct the study in accordance with the protocol and so staff training is necessary.

The Trial Can Begin

Once funding has been secured, all the relevant approvals are in place, all documentation has been finalised, and all participating centres have the information they need and know that recruitment can start, the trial can begin. The whole process can take many years to complete.

(January 2005)