Academy of Medical Sciences review of regulation and governance of medical research: Call for evidence

Submitted by the Medical Research Council on behalf of Research Councils UK

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Background

Research Councils UK (RCUK) is a strategic partnership set up to champion the research, training and knowledge transfer supported by the seven UK Research Councils. RCUK was established in 2002 to enable the Councils to work together more effectively to enhance the overall impact and effectiveness of their research, training and innovation activities, contributing to the delivery of the Government’s objectives for science and innovation. Further details are available at www.rcuk.ac.uk

The seven UK Research Councils are the largest public funders of research in the UK, investing around £3 billion per annum in research, training and knowledge transfer across a broad spectrum of research areas.

Evidence is submitted by RCUK on behalf of Research Councils and represents their independent views. It does not include or necessarily reflect the views of the Science and Research Group in the Department for Business, Innovation, and Skills. This submission is made on behalf of the following Councils:

- Economic and Social Research Council (ESRC)
- Medical Research Council (MRC)

Summary of Key Points

- The Research Councils recognise the need for a certain level of regulation of medical research to ensure that participant safety and rights are being appropriately and transparently safeguarded. In addition, regulation should enable the public to have confidence in the conduct of medical research. However, we strongly support the position that there is a serious problem in the UK at present, due to difficulties imposed on medical research by the current regulatory approach.

- The central questions to be addressed are:
  - What level of regulation is required to achieve the aims above?
  - What is the necessary framework to provide this level? and
  - How should that framework be implemented in practice?

- As public sector funders, we have an imperative to ensure appropriate use of public monies for well-governed research while avoiding navigation of regulation causing undue delays or excessive use of resources. We recognise that the costs of regulation do not simply relate to extra administrative staff in offices - there are also considerable delays to high cost projects which translate into delays in providing patient benefit. There are also times when optimal research approaches are simply not pursued because the regulatory route to follow is so difficult.

- The existing legislative and regulatory framework is unarguably complex and multi-faceted and this reflects the diverse and evolving nature of medical research. As different issues have arisen over past decades so different pieces of legislation have been introduced to address them eg. organ retention and human tissue use; embryo and then admixed embryo
and stem cell research; genetic modification. In addition, EU Directives have had to be transposed into national legislation eg. clinical trials; human tissue and cells; and data protection.

- It could be argued that the legislative framework should be contained in a single statute. However, we are concerned that this would create the potential for expansion of the intention of existing statutes. There is a risk that this approach would be seen as an opportunity to legislate for regulation across the whole spectrum of medical research. The Research Councils do not view all medical research as requiring regulation and so would not support such an approach. However, there could be opportunity to reduce the scale of the pyramid of legislation and the scope of some of the statutes, for example, the Human Tissue Act 2006.

- In addition to consideration of restructuring the legislative framework it may be more worthwhile to concentrate resources and attention on reducing the difficulties encountered in implementing the current requirements; ensuring that unnecessary steps are not being added to agreed regulatory requirements and that appropriate guidance and training are supported. A key area is to ensure that discrepancies between central and local interpretation and implementation are removed.

- The Research Councils strongly support a risk-based approach to regulation and governance of medical research. This approach, more than any other, may provide the best return in reducing unnecessary steps in regulation.

- There have been significant improvements in consistency and coordination between regulators, as evidenced in initiatives like the Integrated Research Application System (IRAS), Stem Cell Tool Kit and UKCRC Regulatory and Governance Advice Service. Concerns remain, however, that there are steps in regulation that go beyond those required or intended in the underpinning legislation and statutory requirements.

- It is clear from the responses from researchers that significant inconsistencies remain in local interpretation of the myriad of requirements. This end-stage interpretation is often subjective and, for those with less expertise, daunting. This can lead to a risk-averse culture which is overly prescriptive owing to concerns, which may be disproportionate, about potential negative repercussions or sanctions if research is allowed. It appears that it is the cumulative effect of this risk-averse culture that causes most problems rather than any one single impediment.

**Full response to the call for evidence**

**Introduction**

1. RCUK welcomes the opportunity to contribute to the Academy of Medical Sciences review of the regulation and governance of medical research.

2. The Research Councils, specifically the MRC and ESRC, have a long-standing interest in the development and implementation of appropriate guidance and regulation of medical and social science research. The Councils work closely with researchers, both in the UK and globally, with
regulatory agencies, with UK Government Departments, other research funders and with the National Health Service.

3. The MRC is a major funder of medical research from basic exploratory through to experimental medicine and clinical trials. The MRC funds research that is regulated under all of the statutes considered by this AMS review. This includes research which involves large data collections; human tissue collection, storage and use; and early and late phase clinical trials. The MRC also supports a significant portfolio of research involving stem cells work, some involving human embryos. Many studies require access to patient populations and health records and research is also supported that involves children and adults without capacity to consent.

4. The ESRC funds an increasing amount of research in conjunction with the MRC and other biomedical and health research funders. The focus of the current review relates to aspects of the research undertaken by many of these researchers, most obviously through access to and interrogation of data about patients/participants, and how it is used and stored.

5. The ESRC has worked hard to ensure the link between medical and social science research is covered in its Framework for Research Ethics and it is at the intersection between medical and social research that ESRC would like to be involved in any review of governance.

6. Both Research Councils require that the research they support conforms to key ethical principles as outlined in respective policies and guidance. The areas of overlap between what has been considered as ‘social science’ and ‘medical science’, and the different expectations as to governance and ethics requirements, are recognised by both councils and are under further discussion.

7. This response has been compiled from evidence submitted from Research Council funded researchers, including grant-holders and research council units, institutes and centres. It is also based on discussions which took place at a UK workshop on regulation convened by the MRC and Wellcome Trust in 2008, and a recent consultation held with the Social Science Community on the review of the ESRC Framework for Research Ethics. Finally, it draws on information that the MRC Regulatory Support Centre has collected via their routine work with the research community and delivery of the UKCRC Regulatory and Governance Advice Service. A list of sources is available in Annex 1.

8. Quantitative data on the areas that the research community finds particularly challenging are found in Annexes 2 and 3.

9. In addition, it is likely that many individuals and organisations funded by the Research Councils will submit separate responses to the call for evidence. Collectively, we hope that this input will help to inform discussions to help ensure that medical and social science research is appropriately regulated and governed.

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1 ESRC Framework for Research Ethics: www.esrc.ac.uk/ethics
2 MRC publications: www.mrc.ac.uk/NewsPublications/Publications/Ethicsandguidance/index.htm
ESRC publications: www.esrc.ac.uk/ESRCInfoCentre/about/CI/CP/index.aspx
3 Annex 2: Analysis of the regulatory and governance needs of MRC researchers
4 Annex 3: UKCRC Regulatory and Governance Advice Service query metrics
10. This response comments on the regulation of medical and related social science research in general, supporting a risk-based approach to regulation and its interpretation; describes what works well; then focuses on the effect of the EU Clinical Trials Directive and its implementation in the UK; and the impact of regulation and processes that affect other such research, describing recommendations for the future where appropriate. [It does not include research involving animals which is outside the scope of this review, nor does it address more general issues of Good Research Conduct or Scientific Misconduct].

Basis for regulation of medical research

11. The report from the MRC/Wellcome Trust workshop Regulation and biomedical research which took place in May 2008, concluded with the following points:

- Regulation of medical research is necessary – It is important to protect the public against the risks of untested medicines and other technologies, to provide appropriate checks on commercial motives and scientists’ interests, and to protect research participants and the researchers themselves.

- Regulation is complex – There are difficult balances between public benefit and participant, patient and consumer risk. There are several reasons for the complexity: the issues themselves, the language, the design and implementation.

- There is a lack of understanding of the risks involved – The current regulatory regime does not take account of the substantial difference between research that involves an intervention on an individual, and that which requires access to information from his or her tissue samples or information. (This issue is explored further in the next section.)

- Communication is vital – it is a way of addressing the interests of researchers, to prevent inhibition of research; and helps researchers understand that regulation of medical research is often a small part of a larger issue, e.g. Mental Capacity Act 2005, Human Fertilisation and Embryology Act 1990.

- At the root of regulation there must be trust – trust stems from transparency and communication and perception that the rules are realistic and related to the magnitude of risk. With more trust, there is more compliance.

Risk-based approach to regulation and governance

12. The Research Councils fully endorse the principle that protecting the safety and rights of study participants is paramount.

13. A risk-based approach to medical research regulation and governance, including inspection, is strongly supported, along with the need for a system that will deliver a real decrease in the administrative and resource burden for lower risk studies (see Examples 1a and 1b). This is in line with
the Government’s own advice. It must be recognised that some academic sector studies will be of high risk, but many are lower risk. Thus, a trial of a novel medicine used for the first time in man could be high risk; while those studies requiring access to medical information by research professionals with safeguards in place to protect against confidentiality breaches would be considered low risk. Equally, trials using a licensed treatment would normally be of lower risk than those using novel interventions.

14. The profile of risk posed by a particular study will also depend on an organisation’s ability to manage those risks. Individual organisations will have differing levels of expertise and competence for hosting or sponsoring studies across the spectrum of medical research. Mechanisms to assess risk should therefore take this into account, with those organisations that are highly competent research environments being recognised as lower risk.

15. The ESRC in its guidance to award holding institutions and award holders provides advice on how to approach risk while developing and conducting social science research.

16. In commenting on Clinical Trials of Investigational Medicinal Products (CTIMPs) the MRC Clinical Trials Unit (London) highlighted that:

‘a real appreciation of and agreement about different levels of risk is needed so that risk-adapted approaches to medicinal product labelling, safety reporting procedures and trial monitoring are facilitated, and public resources are not squandered.’

Example 1

Example 1a
The current system is having a profound effect on academic trials across Europe but particularly in the UK (Langstrom et al.). This is evident, for example, in radiopharmaceuticals that may have been in use in one EU member state and not in another, requiring full justification, in each State for a clinical trial and an Investigational Medicinal Product (IMP) process (e.g. Fluorocholine, C-11 choline, methionine, FLT etc). These types of studies involve a very low risk to the patient/volunteer involved in radiotracer studies. The radiotracer is normally in the microdose range when administered, particularly for PET tracers but also for nuclear medicine tracers. The whole raison d’être for tracers is that they do not perturb the system they are studying. The subjects are studied with 1 or 2 non-pharmacological doses delivered to patients with known disease under medical supervision in hospitals with a known quantifiable risk from the radiation dosimetry.

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The requirements of regulation mean that the development of molecular targeted therapies that are supported by biomarker studies involving radiotracers is being slowed down. There is a need for the processes involved to be commensurate with the risk involved in administering agents that have no pharmaceutical activity.

**Example 1b**

Much of the research at MRC Cognition and Brain Sciences Unit (Cambridge) is non-interventional, non-invasive research into human behaviour and the way that behaviour can change as a result of brain injury. Depending on who the research participants are and where the research is carried out, the governance demands vary, whilst the risks to participants remain at the same low level.

A study looking at “spatial neglect” syndrome in people who have suffered stroke examines patients’ and healthy participants’ abilities to respond to stimuli on a computer screen. The risks are minimal, i.e. that they are bored with the task; their time is wasted because the hypothesis being tested is wrong; or that despite strict management, data regarding their reaction times might leak out. If the research involves NHS patients and is carried out in a facility that is owned by the local university, the following are needed:

- NHS Research Ethics Committee approval - the process reviewing precise details of how, on whom (including how recruited) and where the study will be conducted;
- Tri-party agreements between the local NHS organisation, the MRC unit and the university;
- NHS R&D permission (from the local hospital and community NHS organisations for those patients discharged from hospital), with requirements that Good Clinical Practice (GCP) training has been undertaken by the researchers in the last two years (training which is not designed for this research but for clinical trials), CRB checks that are not older than six months, and that research passports and honorary research contracts are in place for some researchers;
- Patients who have spatial neglect syndrome must be identified by clinicians, with many demands on their time, as researchers are not permitted to review patient medical notes, even though safeguards are in place to protect against potential disclosures of information.
- If during the project methods are refined in light of emerging results, much of the above has to be revisited (via notification or amendment) because some specifics of the project change even though the principles and risks remain the same.

By way of contrast, if the exact same tests were to be performed on healthy participants in the MRC Research Unit, ethical approval from the University Research Ethics Committee (REC) would be required. This often takes less than a week, and is valid for 2-3 years with the caveat that only if the project is substantially changed should the committee need to be re-contacted. This level of governance is assessed by the university REC to be proportionate to the risks involved.
Which parts of the regulatory framework work well?

17. Within the current regulatory framework there are examples of regulation and regulatory bodies that work well.

18. The regulatory environment itself is necessarily complex as it is a response to EU Directives (e.g. Data Protection and Clinical Trials); particular concerns that have emerged in the UK (e.g. human tissue legislation); and advances in science and technology (e.g. Human Embryology and Fertilisation Act). The result is discrete areas of research that come under specific areas of regulation. It is notable that different areas of research have been considered to require regulation in different ways. Some require licences – e.g. premises storing human tissue and individual research projects involving embryonic cells or clinical trials. Others, such as data use, are subject to statutory requirements and oversight but not to specific licensing arrangements.

19. An overarching piece of legislation regulating all clinical research would be likely to be extremely complicated in order to include these various existing statutes, EU Directives, public opinion and scientific advances.

20. The passage in 2008 of the amendments to the Human Fertilisation and Embryology Act 1990 was a good example of communication and engagement between relevant stakeholders (public, researchers, government and regulators), resulting in constructive discussions and legislation to balance views across different sectors.

21. Over the last few years, there has been a noticeable increase in communication between regulatory and governance bodies with each other and the communities they oversee. Many are amenable to working in partnership to address concerns and solve problems, smoothing the path for investigators and reducing delays. Some, such as the Human Tissue Authority (HTA) are viewed as proportionate regulators, regulating according to risk. For the HTA, research is not generally viewed as a high-risk sector and is managed as such.

22. The Scottish Government (then Executive) addressed widespread public concerns about the retention of human organs from deceased children without consent by legislating for the research use of tissues from the deceased only. This was seen as a proportionate solution to the problem which did not require a new regulator or licensing system.

23. The advice and guidance provided by organisations such as the HTA and the National Research Ethics Service (NRES) is clear and helpful. Researchers have commented that the MHRA provides good advice orally in which complex intricacies of individual projects are discussed and addressed. This type of discursive support has been seen to make a very positive difference to those working in research that falls at the boundaries or overlaps of regulation or in newly regulated fields.

24. The process of submitting applications for the required research approvals has improved with the advent of the Integrated System for Streamlining Research Approvals (IRAS). IRAS means that information need only be inputted once into a single dataset and the forms for all applicable ethics,

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9 Human Tissue (Scotland) Act 2006
NHS and regulatory bodies are automatically populated. This effectively reduces the administrative burden of form-filling and the need for submission of duplicate copies. The system is said to be user-friendly for those to whom it is familiar (repeat users), and the guidance leads to pragmatic solutions to users’ problems.

25. The coordinated approach to the management and organisation of NHS Research Ethics Committees (RECs) brought about by NRES, has improved the operation of RECs and, as far as possible within the current system, has standardised the ethics review of research proposals. A single opinion from one REC that is valid across the UK for multi-centre studies is a significant step in reducing multiplicative applications. This is an aspect that researchers wish to see paralleled in NHS R&D and which it is hoped that the Coordinated System for NHS Permissions (CSP) will address.

26. Despite these changes and positive interactions, the majority of feedback received by the UK Research Councils from researchers remains negative about the impact of regulation on research. The remainder of this report sets out examples of these concerns, and where possible offers constructive recommendations for the future.

**Impediments to UK medical research**

**Regulation of Clinical Trials of Investigational Medicinal Products**

27. These trials are regulated by the EU Clinical Trials Directive (CTD), which is implemented in the UK by the Clinical Trials Regulations and regulated by the Medicines and Healthcare products Regulatory Agency (MHRA). The MRC broadly supports the key aims of the EU CTD to:

- Increase the protection of health and safety of trial participants
- Increase the ethical soundness of clinical trials
- Increase the reliability and robustness of data generated in clinical trials
- Simplify and harmonise the administrative provisions governing clinical trials in order to allow for cost efficient research
- Achieve the above while promoting high-quality research in the EU and the competitiveness of the European pharmaceutical industry

28. However, the last two purposes have not been realised by the current CTD and its implementation. In response to the Public Consultation on the Assessment of the Functioning of the Clinical Trials Directive, the MRC encouraged the European Commission to consider:

- developing a framework of risk-commensurate assessments;
- easing multinational sponsorship by encouraging co-sponsorship;
- clarifying the scope and intent of the Directive; and
- improving the consistency of application of the Directive without moving to single European Authority opinions.

**Increased administration and cost as a result of EU CTD**

29. The implementation of the CTD has significantly increased the administration costs and time involved in gaining approval for multicentre clinical trials; this is often due to regulatory authorities in different member states differing in their assessment of what constitutes a clinical
trial. This has significant financial effect on the ability to conduct 
international trials that are led from the UK.

30. As an example, the increased administration duties that have arisen from 
the implementation of the current Directive have led to the MRC Clinical 
Trials Unit doubling the number of trial management staff (from 22 in 
2004 to 44 in 2010), even though the number of trials being co-ordinated 
has not changed significantly over the past six years. Furthermore, as 
academic trials are largely supported by grant funding of a specified 
duration, time delays in starting trials can lead to problems of continued 
funding, as grant support may run out before the trial is completed; this 
can lead to further administrative costs and delays for the investigators 
and increased costs for the funder. It may also put the trial at risk of not 
being completed.

Inconsistent classifications of Clinical Trials of Investigational Medicinal 
Products (CTIMPs)

31. Inconsistent classification of studies by the MHRA based on subjective 
decisions made about study design and IMP, is a main concern. Examples 
2, 3 and 4 illustrate this point.

Example 2
A UK-based research group had previously performed five studies exploring 
the effects of various licensed agents in healthy volunteers which had 
previously all been classed as not a CTIMP and thus out side of the remit of 
the Clinical Trials Directive. They submitted a similar protocol (to assess the 
effects of a different licensed chemical) with the same outcome measures to 
the MHRA for confirmation, but the protocol was judged by the MHRA to be a 
CTIMP. According to the researchers, this protocol differed in no substantial 
way from the previous or subsequent protocols, which were judged not be 
CTIMPs. The researchers considered that the proposed study had no direct 
clinical implications and that the results would not change the known efficacy 
or safety assessments of the chemical. This type of issue inevitably leads to 
delays in starting research and in this particular case a student’s first eight 
months of funding were spent dealing with the issues related to this decision 
before the researchers reluctantly decided to discontinue the study.

Example 3
Within UK academia, there is confusion as to whether a compound used in 
specific circumstances is classified as an IMP or not. This situation appears to 
have arisen, in part, because most academics do not have sufficient access to 
the type of specialist regulatory support provided in the industry sector, and is 
also due to differing interpretation by the MHRA. A researcher reported that 
his group were advised that the use of a specific PET tracer compound came 
derunder the governance of a 'Specials Licence' for one application (because it 
was a proof of principle or a mechanistic study). However, in another, very 
similar proposal dealing with a different disease process it was classed as an 
IMP. The general confusion over these issues and the time and resources 
required to resolve them have meant that PET research groups in the UK 
often proceed on the assumption that they need to meet full CTIMP standards 
for every compound.
Example 4
The MRC Clinical Trials Unit conducts multinational clinical trials comparing treatment policies in HIV infection in which the protocol allows investigators to select the particular drugs used from licensed drugs within a specified class. These have been subject to differing assessments by competent authorities in individual countries, with some classifying these as clinical trials within the scope of the Directive, and others as a study that is outwith the scope. This has led to considerable confusion and difficulties for the authorisation and conduct of such multinational trials.

32. The creation of the concept of “non-IMPs (NIMPS)” is a good example of ‘regulatory creep’. These are medicinal products that are specified in a clinical trial protocol but which are not the products being tested. There is considerable confusion about the classification of IMPs and NIMPS. Although not included in either the Clinical Trials Directive or the UK implementing regulations, the Commission Guidance on NIMPs requires that “a sponsor should implement a system allowing traceability of medicinal products which allow adequate reconstruction of NIMP movements...”.

33. Recommendation: Where the NIMP is a marketed product that is being used as in normal clinical care, the Research Councils would suggest that the normal pharmacy standards for drug handling dispensing and recording should suffice.

Amendments in CTIMPs

34. It is generally agreed that the current situation to manage clinical trial amendments is overly burdensome and may give rise to risks of insufficient patient protection due to inconsistency in implementation and also to increased administrative costs owing to over reporting.

35. Recommendation: Greater clarity regarding ‘substantial amendments’ is required, and the definition should be reviewed to ensure that it is fit-for-purpose without being disproportionate. There is a risk that researchers may not amend protocols to achieve optimal trials, owing to the excessive bureaucracy this entails. The consistent interpretation of what is considered a ‘substantial amendment’ is crucial as differences in interpretation result in increased administration. For example, in the UK (but not necessarily in other member states), adding an extra study site is interpreted as a substantial amendment, necessitating ethical review, and regulatory authorisation. If several such ‘substantial amendments’ occur in large multicentre trials, this generates a large administrative burden and is resource-intensive.

Safety reporting in international CTIMPs

36. Recommendation: A consistent and clearer approach to suspected unexpected serious adverse reaction (SUSAR) reporting across countries needs to be developed and adopted to counter concerns that current practice in relation to serious adverse events (SAE) and SUSARs leads to serious cost burdens without significant patient benefit. Developing a
system that would allow a sponsor to submit a single SUSAR report to one central place, and for that report to be automatically accessible to all relevant regulators would greatly reduce the administrative burden for multinational studies, and improve patient protection by reducing duplicate records.

**MHRA Inspection**

37. In 2009, as part of the Government’s Better Regulation initiative to reduce the regulatory burden, the MHRA launched a risk-based approach to inspections. The objective was to enable inspectorate resources to be concentrated in those areas that maximise protection of public health while reducing the overall administrative and economic burden to stakeholders, and was welcomed by the research community. However, rather than focussing on the risks of the research that organisations are undertaking, the risk assessment for the Good Clinical Practice inspections is concerned with the potential for regulatory non-compliance.

38. To assess the risk, all organisations involved in clinical trials are asked to complete a compliance report annually, including detailed questions about numbers of participants by phase, status and patient group. As the same information is requested from all organisations, whether a sponsor, clinical trials unit, collaborator or clinical site, and failure to return the questionnaire automatically gives that organisation a high-risk status, for multi-centre, non-commercial collaborations, a vast amount of duplicate data is being collected. So instead of reducing the regulatory burden, it has increased.

39. A huge amount of time is spent in preparation for an MHRA inspection both centrally in Universities and NHS organisations and for each trial. For example, for six weeks in the lead up to an MHRA inspection, one trial used at least 50% of its MRC-funded staff time preparing for the inspection rather than recruiting more patients. Edinburgh University had contracted a private company to train and advise the researchers on how to get through the inspection, and the MHRA charged the university approximately £20k for inspection. In addition there was continual and lengthy work with MHRA afterwards to get everything perfect.

40. **Recommendation**: The solution could be random spot checks so that researchers were ‘inspection ready’ all the time, but in a lighter touch way.

**Pharmacy issues**

41. The requirements for IMP handling and documentation cause serious difficulties for pragmatic trials comparing different treatment regimens. Trials that compare the effectiveness of different standard treatments are of no greater risk to the patients than normal routine care. There is therefore no evident need for additional information on temperature control, different handling requirements, documentation of dispensing or special labelling other than that which would be the norm in high quality clinical care. However, such information has been reported to be required by the regulatory authority inspectors.

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10 MRC/Wellcome Trust workshop: Regulation and biomedical research, 13-14 May 2008. Full Report
42. Some elements of the Medicines for Human Use (Clinical Trials) Regulations 2004 appear contradictory and the lack of clarity can add significant burdens to the approvals for clinical trials.

**Example 5**

The MRC Clinical Trials Unit (CTU) has experienced apparent disparity between the division of the MHRA approving the trial (the CTU) and the GCP inspectorate team, which creates confusion and difficulties with site pharmacies.

Advice obtained from MHRA during the approval process on the regulatory requirements for pharmacy records clearly stated that the sponsor could introduce specific modalities related to the handling of IMPs as long as the pharmacists and investigator procedures and records allowed adequate reconstruction of IMP movements and administration and included, as a minimum, a procedure to record which patients received which IMPs during the trial with an evaluation of the compliance.

Regulation 13 of the Regulations 2004 stipulates that no person shall supply an IMP without the necessary requirements, licensing authority approval, product manufactured in accordance to the Manufacturing Authorisation and the product has been checked and certified by a qualified person. However, the mechanisms for assuring compliance with these requirements are business decisions for the sponsor according to Regulation 3 which allows the sponsor to delegate any or all of their functions.

Despite MRC CTU procedures being set out to comply with these requirements pharmacists at sites have refused to participate in studies unless they received Qualified Person (QP) release with each drug order because during inspection of similar studies the lack of QP release documentation in the pharmacy was identified as a finding.

In a large multinational study in which the MRC CTU receives and monitors the QP release documentation, this creates a large amount of unnecessary paper work, with associated costs in terms of staff and resource to manage this.

43. Site pharmacies charge the sponsor for the research costs, including relabelling of drugs, which can be considerable. When that relabelling is purely to meet the regulatory requirements and does not provide any additional safeguards for the patient, such as in a treatment or prescribing strategy trial, this is a waste of public funds. One site pharmacy MRC CTU work with has recently started to charge £500 if any trial run by CTU is inspected by the MHRA in the course of a routine GCP inspection.

**Barriers to trials in more than one member state**

44. Large-scale non-commercial trials are commonly the result of international collaborations between several organisations, often with more than one funding body. For a non-commercial sponsor in one member state, often a university or hospital in the UK, to take on all the responsibilities and
liability of sponsorship in other member states is a real barrier to such trials.

45. The definition of a sponsor given in the Directive would seem to allow for the division of responsibilities, and the regulations that transposed the Directive into UK law allow two or more bodies either to take joint responsibility, or to allocate responsibilities of the sponsor between them. Absolute clarity and formal agreements that specify how the responsibilities are divided between sponsors are essential, but we believe that it would be of benefit to patients and the public to allow such arrangements to be made.

**Approvals processes for various types of study**

**Research approvals using IRAS**

46. Those new to IRAS report that it can be difficult to navigate and find guidance. This is evidenced in Annex 2 where a large proportion of MRC researchers that responded to a regulatory and governance needs analysis survey cited it as an area that they needed help with.

47. Although IRAS is supposed to omit non-applicable sections of the form according to how users complete the filter, this does not always seem to make sense. Users report that when describing studies other than clinical trials there seem to be many questions where “non-applicable’ needs to be written in the progress and end of study reports.

**NHS R&D permission**

48. Obtaining NHS R&D permissions creates a great burden to many types of study, owing to many factors including:

- alleged local over-interpretation of requirements;
- inconsistencies between NHS organisations;
- differing implementation of honorary research contracts and the Research Passport - in particular in relation to research involving children;
- requirements to attend non-relevant training (eg. in GCP which is designed for drug trials for researchers not undertaking such research);
- in England with additional requirements from Comprehensive Local Research Networks (CLRNs), the CSP process and NIHR portfolio adoption.

**Example 6**

In a project which had REC approvals to establish a research tissue bank involving multiple tissue collection centres, there was an explicit statement in the REC approval letter that no NHS R&D approvals or site-specific assessment were required under the research governance framework since tissue collection centres were not deemed research sites. The majority of the R&D departments of the recruitment centres still insisted that their clinicians make formal applications through the site-specific assessment process.
Example 7
CSP appears to have not yet achieved its goal of standardising and streamlining NHS permission for research sites. In a multi-centre trial comparing two types of emergency interventions for ruptured aortic aneurysm, it reportedly took eight months for CSP to approve the trial. Delays in approval varied from site to site with major factors being:

- iterations between local site NHS R&D and CLRNs;
- some sites required Ionising Radiation Medical Exposure Regulations (IRMER) clearance, and others did not;
- the contracting process between the trial sponsor and the NHS sites;
- the requirement for multiple signatures, documents and agreements from emergency medicine, radiology, surgery and critical care.

It was the view of the research team that: ‘unless matters can be improved rapidly, it will become very difficult to assess new technologies in a timely manner through clinical trials’.

Example 8
This example illustrates delays caused by CSP and Research Passport in a multi-centre acupuncture trial in oncology patients that did not use any IMPs. The experiences of the research team listed below are concerned with the CSP process for approving seven sites and issuing independent members of the research team with honorary contracts, using Research Passports to apply for these:

- CSP quality assurance (QA) process took four times as long as it should.
- Repetition of checks eg. two sites in an acupuncture trial underwent QA checks for one CLRN that had already issued a central quality assured approval.
- Access problems to documents on a centralised database leading to independent review.
- As a result of Principal Investigator changes between IRAS submission and SSI submission, the site was unable to process the SSI as it had no Standard Operating Procedures (SOPs) relating to this eventuality. Despite assurances from the CLRN that it could be handled in the usual way, a minor amendment had to be submitted to local site R&D as this was the only way the local site would allow the approval process to continue.
- Research passport and honorary research contracts – Following sign-off by the local R&D Office, passports were presented to six sites: one site issued letters of access without delay; one site was unfamiliar with the process but with the researchers’ help issued contracts without delay; two sites required further occupational health (OH) questionnaires, one of which required an OH interview; one site was so unfamiliar with the process they thought they already had the contracts (the R&D staff required basic training); and one site decided the passport had not been completed correctly, despite communication with the lead R&D. This site said they would not accept the passports so the process was abandoned and honorary contracts were applied for directly with that Trust.
49. The coordination of R&D permissions has considerable potential to simplify the process and reduce the time taken to obtain permissions. In practice, this does not appear to have been achieved uniformly and the increased confusion and complexity attached to navigating through this process is reported to have actually increased the time taken to get full approvals for some studies. The requirement that the CSP process cannot be started until the study has been adopted into the NIHR portfolio has resulted in an increased timescale for approvals. Many R&D offices that researchers contact appear unclear about the new processes. Some Trust R&D departments will not start any of the local approval processes until “global” approval has been given, and with a 60-day time period for local approval this adds delay rather than streamlining the process.

50. Researchers conducting trials adopted onto the NIHR Portfolio during 2007 and 2008 have reported that they are disadvantaged by not having access to CSP which makes it difficult to recruit additional sites.

51. CSP is confined to England and so studies in which the Chief Investigator is in one of the devolved administrations are very cumbersome to organise, providing a disincentive to UK-wide collaborative research.

52. A survey\footnote{Thompson, AGH and France, EF. One stop or full stop? The continuing challenges for researchers despite the new streamlined NHS research governance process. \textit{BMC Health Services Research} 2010; 10:124.} investigating the use, preferences and need for information by people making choices or decisions about health care has highlighted how the differences in structure and governance processes between the constituent nations of the UK has added complexity to cross-border studies. In particular it demonstrated how the new system of streamlining NHS permissions was not consistent across the UK, and was unlikely to be so unless changes were made to the implementation and management of governance processes.

\textbf{Research Ethics Committee (REC) approvals}

53. As above, there have been considerable improvements in the REC service reflecting changes implemented by NRES. However, there do appear to be issues remaining relating to inconsistencies within the REC community and a lack of transparency of decision-making.

\begin{example}
MRC researchers had a proposal for an epidemiological survey turned down by a REC because the committee did not view that the “science for the study was robust enough”. The study was part of an international multicentre investigation, and the design had been subject to peer review by the MRC, and by funders in other countries. The outcome of the formal appeal was that the researchers were allowed to take the proposal to a different committee, where it was approved. Another example of scientific peer review being conducted by a REC, in breach of NRES operating procedures, is available in the case study in Annex 4.
\end{example}
Example 10
A group of researchers conducting a wave of a cohort study submitted a substantial amendment to a REC to add an additional component. The amendment was rejected on the grounds that more information was required and submission of a new application was needed. It took over six weeks for the researcher to find out from a committee member the information that was needed and only through direct contact, for which the researchers were mildly reprimanded. A full application was submitted and the committee asked for protocol changes to modify the scientific methods, which were already in place and being used based on approval from the same committee in the full ethics application at the outset. Preparation of a full ethics committee application on the new system, the ensuing NHS R&D permission and iterations with these bodies delayed the start of the work by many months, by which time a number of the cohort participants were no longer eligible for the study as their age by then exceeded the target age range.

Example 11
An area where difficulties may arise for RECs is dealing with large surveys. Organisations that carry out field work such as NatCen tend to have specialists in dealing with RECs. Others attempt to find an approach which is flexible enough to support longitudinal or survey research which makes use of medical information or patient groups but is not strictly ‘medical’ research.

No doubt new issues will arise when linking field data to medical records is better. This will place different demands on the way research is governed and regulated and the role of RECs.

The longest-standing record linkage study in the UK is the ONS Longitudinal Study (LS), which links census data to vital events for one percent of the population of England and Wales. It has been used to address a wide range of research questions including studies of social mobility, ageing and migration. Studies that make the fullest use of LS data are those that link social, occupational and demographic information at successive censuses to data on vital events. Examples include studies of mortality, cancer incidence and survival, and fertility patterns. As with the Nordic register studies, this linkage has no explicit ‘consent’. Completion of the UK Census is obligatory and the Census did not have explicit consent to perform such linkage. As a result, use of the study is much more restricted than, for example, the Health Surveys for England, the British Household Panel Survey, the Millennium Birth Cohort Study and others. This heavily restricts what use may be made of the data. This does somewhat contrast with Nordic register data, which is quite widely used despite extensive, and expensive procedures for ethical approval. This may change when the ONS LS of England and Wales is also linked to hospital discharge data (as is already the case in Scotland).

54. Other examples relate to the length of time a positive opinion can take. In particular for students or short-term projects where resources are very limited, there are a number of instances where approval took so long that the students in question had no time left to conduct the research.
55. **Recommendations:** The submission process for low risk studies is currently equal to that for other more high-risk studies. The move that NRES is piloting to review proposals on a risk proportionate basis is encouraging, as long as the application process reflects the reduced risk of the project not just the actual review. A complementary approach would be for Research Ethics Committees more obviously to take into account the likely risks of research and provide wider approval for a particular programme of research that broadly used similar low risk methods, rather than being project focussed. In addition, to aid transparency in decision-making, minutes of REC meetings should be published.

Consent for access to health information

56. The legislative framework for access to health information relates to the common law of confidentiality, the NHS Act 2006 and the Data Protection Act 1998. The issues are complex and interpretation varies\(^\text{12}\). The conservative interpretation of this framework is that only immediate members of the clinical care team are permitted to access patient notes. Within this interpretation, researchers who are not members of the clinical care team would not have legitimate access to patient records without consent. Other pragmatic and more facilitatory approaches permit researchers to access medical notes without consent as long as appropriate safeguards are in place to protect against disclosure breaches, such as honorary NHS contracts and NHS R&D and REC approvals, providing that patients are informed that this may happen. Interpretation of the Data Protection Act is often cited as a reason to deny access to health information for research purposes without consent, or to not allow opt-out mechanisms for consent in various studies. Similarly interpretation of the NHS Act, which allows for confidentiality laws to be set aside in certain circumstances, varies.

57. In many NHS organisations, members of busy clinical teams are relied upon to identify patients who have specific conditions, as researchers are not permitted to review patient medical notes even though safeguards are in place to protect against potential disclosures of information. Where these resources are simply not available or adequate, researchers can apply for NIGB approval for permission to screen medical notes without consent, in order to identify potential participants to be approached for consent for individual studies; or extract anonymous data for epidemiological research. To many, these systems appear to be disproportionate to the risks posed by the research.

58. **Recommendation:** Patients entering hospital or attending GP practices could be asked at that point for consent for their data to be reviewed by trusted research organisations, and used in an anonymous form in the research, or with the possibility that they could subsequently be approached to participate in specific research studies. Patients would be given reassurances of the standards that apply to those organisations and researchers in terms of confidentiality and use of that data.

National Information Governance Board (NIGB)

59. A case study\textsuperscript{13} presented in 2008 in Journal of Medical Ethics described eight months for permission to access basic identifiable information on individuals in GP surgeries, and a decision to access clinical information without consent took 18 months. Although this case predates NIGB citing the Patient Information Advisory Group (PIAG) as the approving body, this is an area which researchers have had continued problems with. The MRC also has longstanding concerns about the legal framework for access to health information without individual consent and the interpretation of the relevant statutes.

Example 12
A government committee approached researchers requesting an updated analysis of cohort studies that were conducted 20 or more years ago. The additional data required were an updated list of deaths and cancer registrations. The REC fully supported the proposal; however, the Ethics and Confidentiality Committee of NIGB did not advise that a section 251 exemption (which recommends that use without consent is lawful) could be applied. The cohort participants had been identified from existing registers and no contact had ever been made with them. NIGB initially stated that consent should be obtained; this was later modified to an opt-out procedure. However, the cohorts were small and particular types of cancer were of interest; therefore one person opting out could introduce bias and compromise the scientific validity of the study. As a result the study has not proceeded.

60. The lack of statutory legislation in Scotland creates problems, as the system relies on researchers to go to every relevant NHS organisation’s Caldicott Guardian and an NHS REC in order to obtain approval to use identifiable data without consent. A single more joined-up approval mechanism to obtain this would be preferable.

61. The concerns of the public about security of personal and sensitive data must be recognised by all dealing with such information. However, it must also be recognised that many medical research datasets only include anonymised data and so risks to confidentiality are minimal. In addition, researchers have a good record in not allowing inappropriate breaches of such security.

Access to Office of National Statistics (ONS) data

62. The process of obtaining health status information has undergone significant change recently due to the Statistics and Registration Services Act 2007. ONS has been reorganised and requests now pass to the new NHS Information Centre, with NIGB approving requests for ONS data. Access to ONS data is therefore more complex and exact processes are still being defined. During this period of reorganisation, researchers with existing approvals are experiencing significant delay in obtaining

information. One research project sponsored by the MRC has received no mortality data since 2008 despite having existing approvals from the ONS.

Information from other government departments

63. Obtaining information from child benefit records in a nutritional survey of 4-18 month olds, at the request of the Food Standards Agency, has been problematic and lengthy. Correspondence to identify the process to get approval to obtain the information took between July 2009 and February 2010.

Other regulation and regulatory bodies

Human Tissue Act 2004 and Human Tissue (Scotland) Act 2006

64. The requirements of the human tissue legislation do allow provision for medical research; however, in certain instances, requirements may have been over interpreted, as can be seen in restriction of research access to tissue samples held in NHS pathology archives. There are concerns regarding difficulties in engaging NHS pathologists in research and so NCRI set up a Task Force to explore the issues and identify areas where action can be targeted to best effect\(^{14}\).

65. In specific research areas, human tissue legislation and regulation has hampered research, eg. In the study of non-accidental injury in babies, since retention of the tissue for research often requires consent from the person suspected of assault. This problem has been highlighted on several occasions, including in a letter to the BMJ\(^{15}\).

Human Tissue Authority (HTA)

66. As described in the previous section, the Human Tissue Authority regulates in a risk-proportionate way, and comments regarding their activities in the research sector are very positive. There are a couple of concerns regarding a lack of clarity in the precise role of Health and Safety Executive Inspectorate and that of the HTA Inspectorate; and high staff turnover within the HTA and lack of continuity when dealing with specific issues.

67. The lack of an equivalent to the HTA in Scotland makes it difficult for researchers in tissue banks from either the living or the deceased to demonstrate compliance with HTA standards (even if this is the case in practice), which might have an adverse effect in the case of bids for competitive funding, since there is no effective standard against which these banks can demonstrate quality and good practice. The Chief Scientist Office move to accredit NHS tissue banks in line with HTA standards will address this to a certain extent, but they will have no jurisdiction in non-NHS banks.

\(^{14}\) Fostering the role of pathology in research, NCRI, 2009

Mental Capacity Act 2005

68. With regards to medical research in emergency situations there is a need to define a consistent approach to be used across the UK. The issue of consent has been dealt with in England and Wales through the provisions of the Mental Capacity Act 2005. This Act does not apply in Scotland, where there can be considerable difficulties conducting clinical research in emergency situations, as the Adults with Incapacity (Scotland) Act 2000 does not address this circumstance.

69. In a recent consultation on the ESRC Framework for Research Ethics, several respondents highlighted the difficulties that social scientists may face when working under the requirements of Mental Capacity Act. The Mental Capacity Act is a complex area for social science research as it is regulated by a medical model in areas including mental health and children within the boundaries of the NHS. There is a significant amount of ESRC funded research that falls within this category and feedback to ESRC’s consultation noted concerns regarding restrictions placed on research that falls within the remit of this Act.

Is it research or clinical practice?

70. Often clinician researchers are forced to categorise their activities as either research or clinical practice when distinctions may be blurred. The tendency, where permitted to do so by NHS R&D and CLRN staff, may be to categorise as clinical practice to avoid the disproportionate administrative burden of classing as research.

Example 13
A person with a cluster of rare cancers seeks advice from a health professional about possible diagnosis. A research laboratory is working on a gene that may cause a similar phenotype. No NHS service is yet available as the gene being researched has only recently been thought to link to the cancer. The patient understands this and consent for the DNA to be sent to the research team. The Principal Investigator has REC approval to do the research. To obtain full NHS R&D approval from each of the potential sites that a patient could be identified in is prohibitively time consuming, as this is a rare occurrence. Researchers therefore either a) send the samples as part of clinical practice therefore bypassing the research governance procedures, or b) do not send the samples therefore depriving applicable patients for a potential diagnosis. Such examples occur on numerous occasions in many different settings and amount to a significant amount of research activity.

Conclusion

71. There is a need to move towards trust- and risk- based models. Instead of the current situation whereby research governance often appears to be a set of procedures to highlight all conceivable risks, with researchers required to document how each of these risks is dealt with and minimised; governance should be operated on the basis of the principle that researchers in reputable organisations can be trusted to operate in an ethical way and are answerable to their employer and/or the regulator if they do not. The level of external regulation in addition to this ‘self-
regulation’ should be proportionate to the risks of the individual research project in that particular environment.

72. There is little confidence in the community that the current regulatory and governance arrangements truly safeguard research participants’ interests. The converse may indeed be the case as research activity and resultant health benefits are compromised as a result of current requirements.

73. The Academy review is welcomed as an opportunity to reconsider research regulation and to assess options to make it fairer, more proportionate, streamlined and transparent.

74. Closer alignment between clinical activities and research, rather than rigid demarcation between the two, should be encouraged to create a clinical environment that fosters research activity.

75. Whilst not all of these examples are 'show-stoppers', the cumulative effect is that despite all the efforts that have gone into trying to streamline and improve the environment, it is still very difficult and time-consuming (and hence expensive) to get all of the necessary approvals to conduct UK-wide multi-centre clinical studies. From the researchers’ perspective it appears that more harmonisation between approvals processes, particularly at local level, would make the greatest difference in reducing this difficulty.
Annex 1

Sources of evidence for the RCUK response

1. MRC/Wellcome Trust workshop: Regulation and biomedical research, 13-14 May 2008. The full report is available from the MRC website:
   
   www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC005613

2. European Commission Public consultation: Assessment of the functioning of the Clinical Trials Directive 2001/20/EC
   http://ec.europa.eu/enterprise/sectors/pharmaceuticals/human-use/clinical-trials/

3. Analysis of the regulatory and governance needs of MRC researchers
   MRC Regulatory Support Centre Highlights 2009-2010, hard copy available from RScinfo@hrsu.mrc.ac.uk.

4. UKCRC Regulatory and Governance Advice Service:
   www.ukcrc-rgadvice.org

5. MRC funded researchers, including submissions from the following MRC research Units, Centres and initiatives:
   
   - MRC UK Brain Banks Network
   - MRC Clinical Trials Unit
   - MRC Centre for Brain Ageing and Vitality
   - MRC Cognition and Brain Sciences Unit
   - MRC Epidemiology Unit (Annex 5)
   - MRC Epidemiology Resource Centre
   - MRC Human Immunology Unit
   - MRC Human Nutrition Research Unit
   - MRC Institute of Hearing Research
   - MRC National Institute for Medical Research
   - MRC Social and Public Health Sciences Unit

Associated researchers from the following organisations:

- University of Bristol
- University of Southampton School of Medicine
- University of Sussex
- Imperial College London
- University of Edinburgh
- University of Stirling
Annex 2

Analysis of the regulatory and governance needs of MRC researchers

In 2009, the MRC conducted a survey of MRC researchers to understand more about their regulatory and governance needs. 142 people responded from MRC Units and Centres. The following figure highlights the regulatory and governance issues that respondents would like further support with.
Annex 3

UKCRC Regulatory and Governance Advice Service query metrics

The UKCRC Regulatory and Governance Advice Service received 1025 queries from 580 enquirers (NHS and University R&D staff and MRC researchers) between May 2006 and March 2010. The following table illustrates the regulatory and governance issues these queries related to.

<table>
<thead>
<tr>
<th>Research Governance</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>RG - NHS R&amp;D management issues &amp; HRCs</td>
<td>480</td>
</tr>
<tr>
<td>RG - General Study Management</td>
<td>165</td>
</tr>
<tr>
<td>RG - Insurance &amp; Indemnity</td>
<td>24</td>
</tr>
<tr>
<td>RG - Agreements / Contracts</td>
<td>23</td>
</tr>
<tr>
<td>RG - Framework(s) and guidance / principles</td>
<td>20</td>
</tr>
<tr>
<td>RG - Sponsorship</td>
<td>17</td>
</tr>
<tr>
<td>RG - Archiving / Record Retention</td>
<td>10</td>
</tr>
<tr>
<td>RG - Is this research? (audit / service / evaluation)</td>
<td>9</td>
</tr>
<tr>
<td>RG - Good Clinical Practice</td>
<td>5</td>
</tr>
<tr>
<td>RG - Risk Assessment, Audit &amp; Monitoring</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CTIMP - Trial Management (including protocol / intellectual property / financial agreements)</td>
<td>328</td>
</tr>
<tr>
<td>CTIMP - Agreements / Contracts</td>
<td>46</td>
</tr>
<tr>
<td>CTIMP - Investigational Medicinal Product(s)</td>
<td>38</td>
</tr>
<tr>
<td>CTIMP - Pharmacovigilance</td>
<td>32</td>
</tr>
<tr>
<td>CTIMP - Good Clinical Practice</td>
<td>29</td>
</tr>
<tr>
<td>CTIMP - CTA applications and related issues</td>
<td>28</td>
</tr>
<tr>
<td>CTIMP - Legislation / Regulation(s) / Guidance / Principles</td>
<td>26</td>
</tr>
<tr>
<td>CTIMP - General Approval Issues</td>
<td>18</td>
</tr>
<tr>
<td>CTIMP - Insurance &amp; Indemnity</td>
<td>18</td>
</tr>
<tr>
<td>CTIMP - Archiving / Record Retention</td>
<td>16</td>
</tr>
<tr>
<td>CTIMP - Sponsorship / Legal Representative in the UK</td>
<td>15</td>
</tr>
<tr>
<td>CTIMP - Definition of a Clinical Trial</td>
<td>11</td>
</tr>
<tr>
<td>CT - Data Protection / Confidentiality / Access to Data (&amp; PIAG)</td>
<td>8</td>
</tr>
<tr>
<td>CTIMP - Trial Monitoring</td>
<td>7</td>
</tr>
<tr>
<td>CTIMP - Trial Registration</td>
<td>4</td>
</tr>
<tr>
<td>CTIMP - Laboratories</td>
<td>4</td>
</tr>
<tr>
<td>CTIMP - Training</td>
<td>3</td>
</tr>
<tr>
<td>CTIMP - Investigator’s Brochure / SmPc</td>
<td>2</td>
</tr>
<tr>
<td>CTIMP - REC issues, involving prisoners</td>
<td>1</td>
</tr>
</tbody>
</table>

Total regulatory and governance issues: 1025

Total enquirers: 580

Enquirers breakdown:
- NHS: 40%
- University R&D staff: 28%
- MRC researchers: 32%
<table>
<thead>
<tr>
<th>Topic</th>
<th>Queries</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Tissue Act/Human Tissue (Scotland) Act</td>
<td>125</td>
<td>10%</td>
</tr>
<tr>
<td>Data Protection / Confidentiality / Access to Data (&amp; PIAG/NIGB)</td>
<td>74</td>
<td>6%</td>
</tr>
<tr>
<td>Other</td>
<td>73</td>
<td>6%</td>
</tr>
<tr>
<td>Consent Issues</td>
<td>35</td>
<td>3%</td>
</tr>
<tr>
<td>Medical Device Research</td>
<td>33</td>
<td>3%</td>
</tr>
<tr>
<td>Ethical issues*</td>
<td>21</td>
<td>2%</td>
</tr>
<tr>
<td>Adults without capacity / with incapacity</td>
<td>18</td>
<td>1%</td>
</tr>
<tr>
<td>Children in Research</td>
<td>7</td>
<td>1%</td>
</tr>
<tr>
<td>Stem Cell Research</td>
<td>7</td>
<td>1%</td>
</tr>
<tr>
<td>Human Fertilisation &amp; Embryology Research</td>
<td>3</td>
<td>0%</td>
</tr>
</tbody>
</table>

NB The number of topics is greater than the total number of queries received, because one query can relate to more than one topic. 35 queries were not categorised.

*Queries relating to NHS RECs were redirected to the NRES queries line and are not categorised here.
Annex 4

Case study from the MRC Institute of Hearing Research, Nottingham

The concept of ethical review is viewed as excellent and RECs should play an important role in proving guidance to scientists and the community. However, this requires that they be willing to be guided by their standards of practice and, above all, it requires that the level of review be proportionate to the project. If not, as in this case, the process is highly inefficient and stressful with little benefit either to the research or to the wider community.

An MRC researcher recently completed an application for ethical approval to develop a much-needed evidence-based questionnaire to screen for auditory processing disorder (APD). The whole process, from first application to final approval, took 6 months to complete. The study was low risk, involving parents filling in a series of questionnaires: the questionnaire under development, a family history questionnaire and four other questionnaires which are widely used in research and clinical practice.

There is a clear need for the proposed questionnaire, since tests for APD are not sensitive to the disorder and a commonly used, currently available questionnaire is poorly designed and has never been standardised. In the design of our prototype questionnaire, we consulted closely with all stakeholders, including clinicians and parents. Part of this process included a series of one-on-many and one-on-one focus group sessions with parents of affected children. Parents were very happy to donate their time to helping us in the development of the questionnaire. Many of them are very aware of the problems of assessment for APD and of obtaining appropriate help for their children.

RECs are expected to abide by the Standard Operating Procedures (SOP), but in this instance this did not happen. It is believed that the REC deviated from the SOPs in their handling of this application, which state amongst other things that:

1. 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.
2. REC review should be proportionate to the scale and complexity of the research project.
3. REC review must be competent, timely and authoritative....RECs may make a request for additional information once only.

1. **Scientific review**
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.

The first application to the REC was rejected outright on scientific grounds. Prior to submission, this project was reviewed by two independent experts in the field as well as the senior consultant scientist who is also an expert. All comments by the scientists involved in the review of the project were addressed prior to submission and the sponsor (MRC) was satisfied that the research was appropriately designed to achieve the stated research goals.

In addition to inappropriate review, some of the stated reasons for outright rejection were inaccurate. The REC statistician claimed that we could not incorporate a measure of test-retest reliability. This claim was overstated. Test-retest was planned and presented in the initial protocol, what was lacking were
precise statements of when we would collect this extra data. All of this could have been easily addressed in a request for more information. It was not fair grounds for outright rejection.

2. **REC review is proportionate to the scale and complexity of the research project.** This was an applied qualitative study which if successful would provide immediate improvements in the provision of clinical services to children suspected of APD. As noted, the risk was low relative to the benefit. A great deal of work went into both the initial and subsequent submissions to the REC. The project was extensively reviewed both internally and externally by experts in the field and comments raised by all reviewers were addressed prior to initial and subsequent application submission. Despite this the project underwent a lengthy review by the REC which, in our opinion, was wholly disproportionate to the risk involved in the study.

3. **Competent, timely and authoritative review** This is critical to the process but did not happen in a number of instances in this application process. The clearest example of this was with regard the issue of participant confidentiality. It was correctly highlighted that this represented the single biggest risk in this study and provided procedures to ensure confidentiality was protected at all times. The REC criticised us for not also providing procedures for when confidentiality would be broken. The request was completely inappropriate to the application. The study is based on self-report data which is posted to the research team and analysed at the group level. Clinical groups are recruited based on a previous diagnosis of disorder. The team would be unlikely to identify children at risk and in need of help. The REC was advised of this but research team was required to address the request. The REC itself gave conflicting advice on this point. The problems of breaking confidentiality were raised again in the review of the second application to the REC, and it was pointed out (correctly in the researchers’ opinion) that these procedures were inappropriate for the study.

RECs may make a request for additional information once only. The research team responded to all requests by the REC as fully as possible in the submission. The REC were again unable to provide a favourable opinion and responded with a series of requests for clarification, as well as some new requests – some of which were acknowledged as being new and some of which were slipped in along with requests for further clarification of sample estimates.

Timely review – After the review for the second application, the research team were advised to submit responses to the committee by email as well as in paper format to speed the process of review up. They waited 23 days from point of validation of the submission to receipt of the response by the REC.

**Bureaucratic delays** Further to the issue of timely review. As noted it took 6 months for the research team to obtain approval for the study. It is worth noting that of those six months from first submission, the applications were in the researchers’ hands a total of 6 weeks. The remainder of the time was taken up with various stages of validation and review.

The governance arrangements for Research Ethics Committees (2009)\(^\text{16}\) are quite clear that research is a core part of the NHS and other care services (see 1.2.1). They are also quite clear that any research undertaken should be worthwhile and safe (1.2.2) and they recognise that facilitation of ethical research is best served by co-operation and communication between all who share responsibility for the research (see 3.2.7).

Response from the MRC Epidemiology Unit, Cambridge

- Significant progress in the last year to streamline regulatory and governance requirements through introduction of IRAS, CSP and implementation of the model Clinical Trials Agreements welcomed. However, CLRNs could do more to educate researchers to the benefit of the CSP.

- Much of the recent legislation will ensure data is better protected and security issues and risks are identified much earlier.

- Regulatory support services have been very helpful, supplying information and advice swiftly.

- Concern remains that research governance guidelines promote unnecessary bureaucracy, slowing the conduct of research.

- Changes to the various regulatory frameworks have happened only relatively recently and therefore Research Councils must appreciate the time it will take for there to be a unified and consistent approach to the level and content of regulation required. For example, efforts to access data on participants who had moved to other regions of the UK led to inconsistency on the part of PCTs as some verbally confirmed that it was valid to approach the GP surgery directly, whilst others insisted on the completion of an ethics SSI form which then had to undergo local review despite MREC approval. In this instance there seemed to be an over-interpretation of NHS R&D requirements at the level of the PCT.

- To assist the dissemination of information from regulatory bodies it is essential that there is a structured communication strategy for cascading information to the relevant stakeholders. Seems that it is not solely the regulation itself that hinders but the communication of how to implement which can affect the guidance given to researchers.

- There may also be an argument for greater inclusion of stakeholders in the risk-based approach to regulation to aid understanding around the level of governance that is required. For example, IRAS and NHS-IS requiring CLSP’s (Corporate Level Security Policy) to be attached to applications. A considerable amount of time elapsed before this document became available suggesting that there was no lead notification at a corporate level. The announcement of and time at which new legislation becomes compulsory appears to be identical, appearing to give little thought with regards to practicality of implementation at the organisational level.

- Increased external audit welcomed however implications of this on research delivery need to be factored in to the planning and infrastructure of research organisations.

- There remains misinterpretation of what is a research cost and what is a service support cost. However, it is hoped that the new ReSet (DoH) guidance will clarify the issue. Further complication arises when trying to apply / access support funding for research crossing organisational boundaries (PCT, NHS Trust, CLRN, and PCRN) which can lead to an impact on research delivery. A clear process is needed, visible to all.