

Notes on Good Practice for Research Organisations in the

Management of a Portfolio of Trials 3: Management of risk and recommendation for further work.

1. MANAGEMENT OF RISK

In considering what a research active organisation needs in place in order to encourage a culture in which clinical research activity has the opportunity to flourish, a good starting point is to consider the organisation's research strategy, structures and systems.

1.1 Organisation - R&D Strategy

A clear strategy for research and development which includes a continuous quality improvement plan which is based in research governance/GCP standards and is well supported by senior management, well resourced, communicated to staff and reviewed at appropriate intervals, is recommended.

For example, a strategy may aim

to produce high quality research activity to the benefit of patients and clinical practice, to strengthen alliances with universities/NHS/industry, to increase research capacity, to increase the involvement of patients in the research process, to optimise R&D income and to enhance the institution's reputation for research and development

Establishing such a framework for strategic direction will help to provide objectives and implementation plans for moving the organisation forward.

1.2 Organisation - R&D Structures

An effective quality and risk management system will depend to an extent on the appropriate research support and management structures within the organisation.

This may include a R&D Committee which has agreed terms of reference, multidisciplinary membership, and a reporting structure to the organisation's Executive. It may also link to a Joint NHS/University Committee.

In a NHS organisation, it will link to a research or clinical/research governance committee.

A defined committee structure will help to ensure that objectives, implementation plans and performance indicators are driven by the R&D strategy and implemented via the R&D office.

Support structures for researchers could include a central office, which will provide advice on the regulatory framework for research and may provide assistance in the preparation of submissions to the MHRA, Research Ethics Committee and the NHS Trust/University – for clinical trial approval.

Such a structure will help to ensure that the potential 'burden' of the regulatory procedures is reduced to the minimum for the researchers – thus encouraging them to partake in clinical research and reducing the risk that such activity will decline.

If the organisation alone does not have the capacity to provide or develop this level of support then, as part of its strategic development, it may consider contracting with another research active organisation that does have the capacity.

There are several examples of such arrangements in the NHS sector.

1.3 Organisation - R&D Systems

Systems for the effective and efficient management of quality and risk at organisation level will improve the quality of research, reduce risks and reassure partners in research - whether these partners are funders or research collaborators, including patient groups - and reassure participants in research.

Exemplars of such systems relevant to trial portfolio management, from various types of organisation who may be sponsors/co-sponsors for publicly funded trials, or funder/non-sponsors are summarised below.

1.3.1 The NHS Research Governance System

The NHS approach has been to develop a governance framework based on self-assessment, which is open to external audit, and action plans based on the degree of compliance.

Research and development is a core function of the NHS and it is government policy to encourage and facilitate both commercial and publicly funded research in health and social care.

The aim is to manage any significant risks and also to minimise bureaucratic processes and facilitate high quality research.

The NHS is expected to work with others to maintain research governance systems and procedures that are proportionate to the risk presented by particular studies.

An extract from the NHS Research Governance Framework which summarises the standards which will support a quality research culture, is included in *Appendix 1*.

Each NHS Trust is required to have a Research Governance Policy, and Procedures for the governance of research in the areas of science, ethics, information, employment, health and safety, finance and intellectual property.

The policy will also set out the organisation's plans for quality improvement in areas such as research agreements, research support arrangements, information systems and arrangements for the approval and monitoring of projects.

The NHS R&D Forum provides advice and exemplars of good practice produced by its [Research Governance Working Group](#).

Progress towards compliance with research governance indicators has historically been assessed via the DH R&D Annual Report.

NHS Trusts were required to develop Implementation Plans by July 2002, and full compliance with all indicators was expected by March 2004.

Following completion of this implementation phase, assessment of research governance standards has now become part of the performance management role of the Strategic Health Authority under the NHS Controls Assurance system.

Controls Assurance Process

The controls assurance process for research governance defines a number of standards, the majority of which are broadly similar to the indicators previously used by the DH.

Additional standards are included which relate to accountability through the organisation, including Trust Board involvement in managing research governance and independent assurance of governance systems.

Organisations are asked to estimate % compliance with the standards and to identify any outstanding actions through a self-assessment process.

The NHS organisation's R&D Group is responsible for approving the Controls Assurance Return, which may be ratified by the Clinical Governance Committee as well as the Trust Board.

The NHS Internal Audit system reviews all controls assurance standards to validate self-assessments, and research governance will now be included in the audit programme. Each standard is likely to be audited every 2-3 years.

Overall, the controls assurance process is likely to be a more rigorous assessment of research governance standards than the previous system, with greater involvement at senior level.

This reflects the primary purpose of the overall controls assurance process i.e. to provide the Board with a mechanism to review management arrangements in key areas.

In assessing compliance for the return, key actions will be identified.

An exemplar of a 'typical' controls assurance return is summarised with brief comments in *Appendix 2*.

In a risk assessment of the gaps in compliance, they were all considered to be low risk.

1.3.2 The University Sector

The Universities do not have a centrally specified system but an example of a self-assessment type approach is the one adopted by the University College London Hospitals NHS Trust following agreement with the University, which was launched last year.

The aim was to provide an opportunity to clarify research governance requirements and for principal investigators with ongoing projects to measure the progress of their research practice towards these standards.

The exercise had the support of both the UCLH Research Governance Committee and the Medical Director for Specialist Hospitals.

Building on this, the University sector members of the working group have devised a set of guidelines for the Implementation of the UK Regulations on Clinical Trials: This is put

forward as a draft for discussion and feedback, both on the approach and the content – see *Appendix 3*.

The premise is that if both the NHS and the Universities can work with a set of standards where compliance is assessed, non-compliance actioned and which is open to external audit, this may reduce the need for complex agreements between them as regular co-sponsors.

Other examples of University quality and risk assessment systems, from Oxford and from Imperial College, London, are summarised in *Appendix 4*.

Some common features which are being reviewed specifically in response to the European Directive and the UK regulations include provision of central support to help with the regulatory hurdles, formal sign-off of responsibilities, broader insurance cover, more formal training of investigators in GCP and consideration of what agreements are needed, particularly regarding the governance of multi-centre trials.

1.3.3 University/NHS Joint Management System

This system of joint management arrangements between a University and NHS Trust(s) is to be encouraged and will assist in the process of assimilating sponsor/co-sponsor relationships.

Clinical trials – Quality and Risk Management : Institute of Psychiatry and South London and Maudsley NHS Trust

All research taking place within the Institute of Psychiatry (IoP) and the South London and Maudsley NHS Trust (SLaM) is co-ordinated by the Joint R&D Office.

All research involving the NHS is scrutinised and controlled under the requirements of the Research Governance Framework for Health and Social Care.

The R&D Office employs a Research Governance Facilitator dedicated to ensuring that both organisations are fully compliant with the RGF.

The good practice approaches set out in this document have been extended to all research involving human participants, records or tissues. In the context of quality and risk management this includes:

- All research must be peer reviewed before it can start. All 'own account' research and research from commercial funders is subjected to peer review before consideration by the Local Research Ethics Committee.
- The Joint IoP/SLaM Research Ethics Committee reviews all research projects from IoP and SLaM employees.
- All research taking place within SLaM requires formal R&D approval before it can start
- All research taking place with SLaM is monitored for compliance with Research Governance requirements
- Our R&D tracking data system co-ordinates submissions from the ethics committee, R&D approval and Research Grants so that applications cannot 'fall between the cracks'

The Research Governance Facilitator is responsible for disseminating information to staff throughout IoP and SLaM about the requirements of the Research Governance Framework by giving talks, email information and guidance documentation.

The R&D Office produces several publications which provide information on good practice including a Research Handbook and leaflets on Research Governance, Consent, Data Protection and Health & Safety.

We expect to extend these approaches to take on the formal requirements of the EU Directive for Clinical Trials of Medicinal Products by extending, for example, the monitoring role, and extending the Research Governance talks to staff to include GCP training.

IoP / SLaM Joint Clinical Trials Co-ordinating Committee (reporting to both IoP Research Committee and SLaM R&D Steering Group).

Terms of Reference

1. To develop a clinical trials* strategy for IoP /SLaM considering the approach to acceptance of trials by IoP / SLaM and proactivity with commercial funders
2. To keep under review and monitor the clinical trials* portfolio of IoP/SLaM
3. To ensure that all clinical trials have an identified sponsor and that documentation is in place confirming that the sponsoring organisation is aware of its responsibilities.
4. To consider new clinical trials in terms of recruitment feasibility, risk and reputation (ratification of decisions by a subgroup).
5. To keep abreast of clinical trials legislation relating to medicinal products and ensure that IoP / SLaM are compliant
6. To advise IoP / SLaM on other external issues impacting on clinical trials management and corporate risk/reputation

1.3.4 The Funder/Sponsor - NCCHTA

The NHS R&D Health Technology Assessment (HTA) programme is a needs-led research commissioning programme.

The National Coordinating Centre for HTA (NCCHTA) provides the scientific and administrative support for the programme. At any one time NCCHTA is responsible for managing a diverse portfolio of around 90 live research projects.

These are a mixture of primary and secondary research, taking from 12 to 60 months to complete and with funding ranging from £50,000 to over £1m.

The NCCHTA monitoring team has developed a series of policies and procedures designed to monitor the ongoing performance of projects and to facilitate their timely and cost-effective completion to inform the NHS.

As the Department of Health's agent, the NCCHTA has been asked to provide the means for DH to take on sponsorship of trials commissioned through the HTA programme.

The monitoring team consists of part time academic and clinical staff and administrators at various levels of seniority.

The team receives projects commissioned via the HTA Commissioning Board and tracks them through their contract signing to start-up and for the duration of their active research to the completion of their draft final report.

The draft final report, if accepted for publication, is published in the HTA Monograph Series.

The monitoring team also play the lead role in the discharge of the HTA programme's responsibilities, as sponsor on behalf of the Department of Health (DH), under the requirements of Research Governance.

The activities of the monitoring team are to:

- Provide a point of contact between the HTA programme and the project teams.
- Provide general and specific information to, and support for, the projects.
- Provide guidance on the establishment of a Trials Steering Committee and a Data Monitoring and Ethics Committee (if required) for primary research projects.
- Obtain and publish key project information for general consumption.
- Input and maintain project information on the HTA Management Information Database (Access database).
- Arrange, organise and administer a schedule of welcome meetings and monitoring visits.
- Monitor progress via six monthly and ad hoc progress reports.
- Advise the DH regarding regular project payments and specially withheld payments.
- Process time and/or financial extension requests from the projects.
- Monitor and pursue the progress of project draft final reports.
- Monitor and record project outputs, such as conference papers and papers accepted for publication in peer reviewed journals.
- Provide the link between the HTA programme and the UK Trial Managers Network.

A standard monitoring approach is used for all research projects, with opportunity for more intensive monitoring, such as requiring monthly recruitment figures, if the monitoring team is concerned the project is at risk.

A number of tools/resources have been developed to assist with the active monitoring of projects. These include:

- A bespoke Access database, used in conjunction with paper files.
- Standardised communications such as letters, progress reports, welcome meeting and monitoring visit documentation, and request forms for additional time and/or money.
- Detailed procedures available via NCCHTA's Intranet.

The monitoring process is instrumental in the early identification of problems that potentially risk the delivery of the agreed project outputs, within an acceptable timeframe and budget.

A fine balance is maintained between formal framework procedures and ad hoc processes, to permit projects to optimise their expertise and innovation and for NCCHTA to work in partnership with researchers.

1.3.5 The Funder - MRC

Principles

As a funder of clinical trials research, the Council needs to be assured that the individuals and employing institutions who conduct MRC-funded research involving human participants adhere to guidelines that safeguard the study participants and ensure that the trial data are of high quality.

This needs to be done without destroying the essential element of trust backed by formal controls and without unnecessary (and stifling) bureaucracy.

MRC aims to ensure its controls are proportionate to the risks to research participants, the progress of the research and, consequentially, to MRC reputation and funding.

Sponsorship

All new grant and fellowship applications to MRC to fund clinical trials subject to the Directive should include details of arrangements made by the Research Organisation for sponsorship as defined in the EU Clinical Trials Directive.

Standards

The MRC requires that the MRC Good Clinical Practice Guidelines are implemented as appropriate in all MRC-funded clinical trials; many of the principles of GCP also apply to other research involving human participants (such as the requirement for proper consent, ethical review and strong data management).

MRC's guidelines are based on and are consistent with the 13 principles laid down in the ICH-GCP agreement, 1996.

Systems of achieving high standards

Before awarding a grant to support a trial, the MRC will ensure through peer-review that:

- The research addresses the most appropriate question
- The proposed research strategy and methods are optimal
- The research is deliverable
- Due consideration has been given to ethical and safety issues, and that in terms of objectives and design the research can meet statutory and MRC good practice requirements
- Appropriate arrangements for the day-to-day management and independent supervision of the study have been proposed.

The Host Institution is required to accept the [Terms and Conditions for MRC Grants and Fellowships](#) and in doing so has a responsibility for ensuring that the trial is run to high standards.

A statement acknowledging receipt of these guidelines and accepting the responsibilities laid out in them is signed by a representative of the Host Institution and by the Principal Investigator before funds are made available.

MRC-funded trials are required to have expert advice that is entirely independent of the Principal Investigators and the Host Institution.

This normally takes the form of a Trial Steering Committee, to provide overall supervision of the trial, and a Data and Ethics Monitoring Committee to monitor un-blinded data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue.

The TSC and DMEC are key parts of the quality and risk management system of a clinical trial. They are there to inform the decision-making by the trialists, sponsor and MRC as funder.

Once a trial is underway the MRC monitors its risks, in particular progress of the trial, through consideration of annual reports. MRC may either audit or request an audit of individual trials.

1.3.6 The Funder/Sponsor - MRC

Principles

In addition to its role as research funder, the MRC may accept some or all of the sponsorship responsibilities under the EUCTD for trials initiated and managed by MRC Units (i.e. where MRC is both the funder and employer), where the Unit is best placed to exercise those responsibilities.

It is not appropriate for the MRC to take responsibility for aspects of the trial that are outside its control.

Responsibilities are best allocated in a way that reflects who is best placed to exercise those responsibilities.

Conditions for MRC accepting a sponsorship role

MRC will accept some or all of the sponsorship responsibilities under the following conditions:

- Another organisation is not best placed to undertake the sponsor's duties
- AND one or more of the MRC employees acts as Principal Investigator(s) and accept responsibilities for the design and/or conduct of the trial
- AND the research proposal has been peer reviewed and approved for funding by MRC or by a funder with equivalent assessment standards
- AND the MRC Unit is able to exercise the sponsor's duties.

MRC may exceptionally agree to co-sponsor trials under other circumstances, subject to appropriate agreements and controls.

However, the Council will not accept liability for responsibilities that properly belong elsewhere.

Sponsorship delegation

Where MRC is best placed to exercise some or all sponsorship responsibilities, these are undertaken at the level of the MRC Unit undertaking the study.

MRC Unit Directors have delegated authority to accept sponsorship responsibilities on the Council's behalf and are required to have appropriate research governance systems in place.

MRC Unit Actions

Where the individual Unit is best placed to take on a sponsorship role, it is required to assess, adopting a trial-by-trial approach, how responsibilities will be allocated to participating organisations and relevant stakeholders.

Agreements are required with partner organisations, for smaller studies these may be documented at the protocol level, or, for larger more complex trials, additional agreements, over and above the protocol, may be needed.

Each Unit has the authority to decide how this is best achieved.

Directors of MRC Units must ensure that their local systems identify the authorisation and sponsorship details of new trials involving Unit staff (including visitors under Unit supervision).

These should be documented such that the council can be given sponsorship information promptly on request.

Assurances to Council

The MRC's controls assurance procedures, quinquennial reviews and dip-stick audits provide assurances to Council, along with informal visits by head office staff.

MRC head office will work with its Units to develop systems appropriate to the missions and competencies of the Units.

To achieve this goal, MRC is establishing a project to assist Units in building locally relevant and sustainable systems that support researchers, and that allow Units and other organisations to implement good practice standards, and give assurances to Council that proper systems are in place.

Warranties, Indemnities and Insurance

- Government policy requires that MRC does not use indemnities to define boundaries between its liability and that of other public bodies. Instead it concentrates on ensuring roles and responsibilities are well defined.
- As a public sector organisation, MRC acts as its own insurer. Partner organisations will need to determine whether they need to make provision for insurance (including non-negligent harm) in managing their risks.
- In the event of any claim, all organisations should be consulted for management of the claim.

1.3.7 NHS Collaborator Organisation

As a guide to NHS organisations who are considering taking part in a trial but are not taking on the role of sponsor or co-sponsor, the view of the working group is that they would not need to implement more than what is currently agreed to be good practice.

The following is a suggested checklist:

Ethics: The REC approval should provide reassurance regarding insurance issues since this is now an aspect which RECs have to consider. If the trial is sponsored by a company, or, in some cases, uses drugs supplied free of charge by a company, an ABPI indemnity will still be issued.

Staff Competency and Training: Have staff received GCP training and if not, is the sponsor able to provide it, or is advice available from a support organisation such as a local Research Development and Support Unit or the NHS R&D Forum

Adverse Events: All events must be defined in the study protocol (adverse/ serious adverse event/ reaction, suspected unexpected serious adverse reactions - SUSARS) and reporting lines for each type of event must be clear and understood. All SUSARs need to be reported by the PI to the Trust, the Sponsor and the Research Ethics Committee.

Research Governance: Controls assurance self-assessment is completed and up-to-date.

Agreements: An agreement or exchange of letters, which spells out clearly the responsibilities and requirements of both the Trust and the sponsor/co-sponsors.

1.4 Agreements

Two types of agreement have been discussed:

1.4.1 Framework Agreements – Regular Collaborators

DH research governance policy is to encourage framework agreements among organisations that collaborate regularly.

Such agreements provide an opportunity to specify the normal allocation of responsibility for systems to comply with general legal requirements across a portfolio of trials.

For example, for networks of NHS collaborating sites, a framework agreement could specify how the sites will act jointly through the network to comply with GCP.

For large trials, a framework agreement could specify that a named lead organisation will normally take on the sponsor's functions on behalf of a network.

A framework agreement could remove the need for elaborate contracts for particular trials. It may then be sufficient to rely on the wording of honorary contracts, local standard operating procedures, and the terms of NHS permission for a trial.

The framework agreement could specify that these documents will set out what is agreed for individual trials or types of trial.

1.4.2 Multi-centre Trials - Occasional Collaborators

An exchange is needed between the trial management organisation and trial sites in multi-centre trials.

This could be an exchange of letter spelling out the commitments of each type of organisation.

For example, the trial site letter could acknowledge the site's responsibilities described in the protocol, and the host organisation letter would cover assurances to do with ethical approval and peer review and practical issues such as financial, staffing/contact details, and monitoring arrangements.

The letter of permission from the trial site could also be explicit about the liabilities it accepts under NHS Indemnity policy when it gives permission and issues honorary contracts.

Further details of the normal allocation of liabilities in clinical trials can be found in the joint statement by Universities UK and the Department of Health.

1.5 Peer Review, Patient Consent

Aspects of good practice in these areas will all help to reduce risk for organisations and should be addressed in the organisation's policy and procedures for research governance.

For peer review, the issue is to consider what is appropriate for the different types of trial in a portfolio.

For commercially funded medicinal trials the company will have organised peer review but it may be appropriate to ask for recorded details of this process.

For publicly funded trials where there is no external funder, there needs to be independent review and a judgement taken whether it is necessary for this to be independent of the research group or independent of the organisation.

Apart from clinical review, scientific review is often advisable using the free resources offered in most areas of the country by Research Development and Support Groups or Units who have access to statisticians, economists, public health, nursing and AHP professional researchers.

It is the job of the Research Ethics Committee to review the arrangements for the patient consent process in clinical research.

However, for research involving patients incapable of giving consent for themselves, NHS organisations need to have local operating procedures that comply with Part 4 of Schedule 1 of the Regulations – ie. establish a list of people in the organisation able and willing to act as patient representatives.

Further guidance on this is due from the DH soon.

1.6 Communications and Training

This is a vital aspect of the organisation's review because it is ill-understood hazards and unmanaged risks that have the potential to cause harm.

It is recognised by the DH, the MRC and the NHS R&D Forum that further work needs to be done to provide guidance on the best approach to GCP training, with a variety of sources which might be recommended, ranging from on-line courses which may be particularly suitable for principal investigators, through to a combination of external and internally provided lectures/exercises/workshops for research staff such as clinical research assistants/research nurses.

Good standards of communication in the conduct of trials, however, can be planned into the [Trial Management Systems Document](#).

They start with establishing a project team with documented communication responsibilities for each member – with each other, with other hospital/practice staff and with the participants of the research.

They extend also to consideration of external communications - with referring physicians and the general public – or other stakeholders – utilising trial launch events, newsletters and websites.

Some examples of what can go wrong and how the communication of defined responsibilities could avoid harm.

Managed risk	Unmanaged risk
<p>Urgent safety measures contain harm following an adverse reaction in a person who consented knowing the possible adverse reaction was recorded in the protocol.</p>	<p>Person dies because no-one noticed a well-known adverse reaction. It was not mentioned in the protocol or identified in patient information material.</p>
<p>A clinician employed by a NHS body initiates a trial. She secures funding from a charity that has no capacity for independent scientific review. The NHS body arranges for independent review, accepts responsibility for the protocol, and agrees to be sponsor.</p>	<p>A clinical academic on an honorary contract wants to initiate a trial. She secures funding from a charity that has no capacity for independent scientific review. No-one else is prepared to accept responsibility for the protocol or the management of the trial. After months of fruitless argument, she:</p> <ul style="list-style-type: none"> a. drops her research interest OR b. secures a job in the USA OR c. begins a press campaign with the charity's help OR d. starts her study anyway without permission. <p>(Do you want to phone a friend?)</p>

Managed risk	Unmanaged risk
<p>A research nurse starts fabricating data in a commercial trial. She is detected after three months by routine statistical analysis, and disciplined. Additional recruitment makes up for the fabricated data. The trial successfully completes the evidence required for a marketing authorisation. The sponsor issues a press notice holding up the NHS body as an exemplar of good practice in handling misconduct.</p>	<p>There are allegations of misconduct against an investigator who is heavily involved in commercial trials. There is no formal investigation. His head of department takes early retirement and the investigator is asked to leave. He then secures promotion at a series of clinical trial centres. Ten years later, a pharmaceutical company discovers extensive fabrication in one of his trials. On re-examination, major flaws are found in dozens of studies. Several products are withdrawn.</p>

2. RECOMMENDATIONS FOR ADDITIONAL WORK

These have been identified by members of the Working Group, from the results of the MRC survey on preparedness for the EUCTD and from consultation through circulation of these notes in draft.

With regard to this consultation, thanks are due to the members of the NHS R&D Forum Working Group on Research Governance, to the Secretaries of UK Universities Medical Schools and other individuals recommended by members of the Group.

Four main areas of additional work and discussion have emerged: agreements between organisations, the provision of GCP training, the nature of support provided to researchers and the streamlining of the regulatory environment.

Several aspects of these have resource implications.

2.1 Sharing of Responsibilities: Agreements

This has been an area of considerable discussion between the individuals and organisations who have taken part in the project.

It is agreed that more work needs to be done on:

- developing framework agreements between organisations who collaborate regularly and who will often be co-sponsors of a trial; it is hoped that Framework agreements will remove the need for elaborate contracts for individual trials
- multi-centre trial arrangements, between the trial management organisation, who will be a sponsor or co-sponsor, and the trial sites; the preferred model is a minimal approach, perhaps with an exchange of letters containing two-way basic requirements

The overall message however is that clinical trials should be regarded as part of the normal business of the NHS and that it is in the interest of all parties to avoid a proliferation of agreements and contracts which would have both significant resource implications and most importantly might undermine rather than support clinical research in the UK.

2.2 GCP Training

Good Clinical Practice training will be needed for all researchers involved in medicinal trials; organisations may take the view that it would be appropriate to extend this requirement to all interventional trials.

There is a need to develop a strategy for the NHS and currently the R&D Forum is looking at the options in discussion with providers of such training.

2.3 Support for Researchers

Resource issues arise from the need to provide appropriate support to researchers in negotiating the regulatory framework.

There is a general feeling that what is needed most is a one-stop shop where all documentation can be completed and kept up-to-date without over-burdening the

researcher, whose main task should be to perform the research (albeit within the guidance of the research governance framework and good clinical practice).

There is concern that without additional funding, essential infrastructure will not develop, and this in the long-term will be to the detriment of clinical research in the UK.

2.4 The Regulatory Environment

The Final Report of the Research for Patient Benefit Working Party recommended that one of the immediate tasks of the newly formed UK Clinical Research Collaboration [UKCRC] should be to set in train a detailed analysis of the cumulative effects of existing regulations with a view to seeking a way of streamlining the overall requirements.

Further, it recommended that the CRC should include as part of its core function the competency and capability to develop, communicate and spread best practice in relation to statutory regulations.

3. SOURCE DOCUMENTS

[Trial Management and Monitoring Guidance – MRC/DH Joint Project on Clinical Trials](#)

[The Medicines for Human Use \(Clinical Trials\)](#)

[Description of the Medicines for Human Use \(Clinical Trials\) Regulations 2004](#)

[EU Clinical Trials Directive: Sponsorship responsibilities in publicly funded trials](#)

[Responsibilities, liabilities and risk management in clinical trials of medicines – DH/Universities UK Joint Statement](#)

[Research for Patient Benefit Working Party: Final Report](#)

[MRC-EU Clinical Trials Directive Policy Statement](#)

[MRC Guidelines for Good Clinical Practice in Clinical Trials](#) *[to be amended in 2004 so that it refers to the EUCTD and UK Regulations]*

Department of Health. The Research Governance Framework for Health and Social Care. Draft 2nd Edition, HM Stationery Office, London, 2003. *[2nd Edition to be revised so that it and the EUCTD are consistent]*

Research Governance in Health and Social Care – NHS Permission for R&D Involving Patients

NHS Research Governance Controls Assurance Indicators

[NHS R&D Forum Guidance via Working Groups, Website and Workshops](#)

APPENDIX 1

Standards In A Quality Research Culture

Quality Research Culture	<p>The organisation supports and promotes high quality research as part of a service culture receptive to the development and implementation of best practice in the delivery of care.</p> <p>There is strong leadership of research and a clear strategy linking research to national priorities and needs, the organisation's business, and to clinical governance.</p> <p>The organisation's research strategy values diversity in its patients or users and its staff and promotes their active participation in the development, undertaking and use of research.</p>
Science	<p>There is a commitment to the principle and practice of independent peer review, with scrutiny of the suitability of protocols and research teams for all work in the organisation.</p> <p>There is close collaboration with partner organisations in higher education and research to ensure quality and relevance of joint work and avoidance of unnecessary duplication of functions.</p> <p>The organisation's human resource strategy includes commitment to support research careers (full and part-time) by earmarking funds specifically for R&D training across the professions. The organisation plays its role in developing research capacity with appropriate training and updating. This includes taking action to ensure the diversity of the workforce reflects society and developing the capacity of consumers to participate.</p> <p>The organisation promotes a high standard of health and safety in laboratory work.</p> <p>Systems are in place to monitor compliance with standards and to investigate complaints and deal with irregular or inappropriate behaviour in the conduct of research.</p> <p>The organisation assesses its research outputs and their impact and value for money.</p>
Ethics	<p>All research which involves patients, users or care professionals or their organs, tissue or data is referred to independent ethical review to safeguard the dignity, rights, safety and well-being of the participants.</p> <p>Research is pursued with the active involvement of service users and carers including, where appropriate, those from hard to reach groups such as the homeless.</p> <p>If organs or tissue are used following post mortems, informed consent is obtained from relatives, and there is commitment to respectful disposal of material.</p>

	<p>If animal use is unavoidable the highest standards of animal husbandry are maintained under veterinary supervision.</p>
Information	<p>Information is available on all research being undertaken in the organisation. This is held on a database, which contains details of funding, Intellectual property rights, recruitment, research outputs and impact.</p> <p>The organisation ensures that patients, users and care professionals have easy access to information on research. Special arrangements are made to ensure access to information for those who are not literate in English or who may need information in different formats because of a disability, e.g. braille.</p> <p>Those agreeing to be involved in research (including the relatives of deceased patients who have consented to the use of organs or tissue in the research) are informed of the findings at the end of the study.</p> <p>An information service provides access from a single point to all up-to-date regulatory and advisory documentation pertaining to research governance, together with procedural guidance, for example, for applications to research ethics committees.</p> <p>There is a research dissemination strategy, which addresses different media and writing styles for different audiences.</p>
Finance & IPR	<p>The organisation is aware of the activity involved in supporting research and of what it costs. Research expenditure is planned and accounted for.</p> <p>The organisation demonstrates financial probity and compliance with the law and rules laid down by HM Treasury. It complies with all audit required by external funders or sponsors and has systems in place to deter, detect and deal with fraud.</p> <p>When research findings have commercial potential the organisation takes action to protect and exploit them, in collaboration with its research partners and – when appropriate – commercial organisations.</p>

APPENDIX 2:

Exemplar: NHS Controls Assurance Criteria for Research Governance

CRITERION	COMPLIANCE	COMMENTS
Criterion 1: Board level responsibility for research governance is clearly defined and there are clear lines of accountability throughout the organisation, leading to the Board.	100%	Good reporting structure in place
Criterion 2: There is a designated person with responsibility for the management of all research undertaken by the organisation	100%	Well established project approval and management system is in place. R&D Director accountable to the R&D Planning Group and Clinical Governance committee
Criterion 3: The organisation ensures financial probity in all matters concerning research governance	100%	Well established R&D financial management systems which are subject to regular internal and external audit
Criterion 4: The organisation has a written agreement with research partners documenting the allocation of research responsibilities	90%	Agreements in place for all externally funded projects (funding agreements, commercial research agreements & indemnity). <i>Action identified for project specific responsibilities for non-commercial multi-centre trials</i>
Criterion 5: The organisation has arrangements in place to issue NHS honorary contracts to non-NHS researchers	100%	System well established. Core part of RG-PAS process. New application form and contract developed
Criterion 6: All research undertaken by the organisation complies with statutory legislation and guidance	90%	Trust approval not issued until all other regulatory approvals are in place. Will implement GCP training to facilitate compliance with UK Regulations. <i>Action identified in information governance - use of databases</i>
Criterion 7: There is a system in place to record all adverse events arising from any research undertaken by the organisation and staff are made aware of and, where necessary, trained in adverse incident reporting requirements	80%	Two systems at present - research reporting of outcomes and hospital incident reporting system of all patient injuries, near misses and unexpected reactions. <i>Action relates to multiplicity of reporting - need to simplify to reduce delay, clarify definitions etc</i>
Criterion 8: All research undertaken by the organisation has a nominated sponsor	70%	All commercial trials have a nominated sponsor. Sponsorship arrangements for most non-commercial studies will be relatively straightforward with joint sponsor model. <i>Action is formal confirmation.</i>

Criterion 9: The organisation has a system in place to detect and deal with research misconduct and fraud	90%	Considerable emphasis on prevention via training, project management, statistical support etc. Major studies are monitored plus data quality checks etc. New RG policy will define process to investigate allegations. <i>Action: increased monitoring and audit activity planned.</i>
Criterion 10: The organisation has systems in place to identify the involvement of consumers in research and to ensure that consumers are involved in the development and execution of research projects	80%	Examples of involvement where appropriate (e.g. HELP MI consent process). No systematic involvement in all studies. <i>Action: this is an area of continuing quality improvement</i>
Criterion 11: There are systems in place to inform service users and members of the public about research undertaken within the organisation	100%	Successful research open days, web site, information booklet developed.
Criterion 12: All research is appropriately disseminated	85%	Time and finance provided for conferences. Dissemination facilitated by R&D support and library services. <i>Action is to identify what % projects get written up and what additional help required</i>
Criterion 13: The organisation has systems in place for the appropriate management of intellectual property	90%	Several IP opportunities have been explored. <i>Action is to increase awareness and professional technology transfer via the new Hub</i>
Criterion 14: The organisation ensures that all relevant staff are aware of their roles and responsibilities with regard to the research governance framework	90%	Research Governance workshop is mandatory training. Major studies have trial management protocol which defines trial specific responsibilities. <i>Action is to implement training to facilitate compliance with UK Regulations</i>
Criterion 15: Key indicators capable of showing improvements in research governance and/or providing early warning of risk are used at all levels of the organisation, including the Board, and the efficacy and usefulness of the indicators is reviewed regularly	80%	Previously used research governance indicators. Will use controls assurance criteria from now on. Number of patients in studies / number of research episodes would be useful additional information but requires significant database developments <i>Action: to be defined</i>
Criterion 16: The system in place for managing research governance, including risk management arrangements, is monitored and reviewed by management and the Board in order to make improvements to the system	100%	Controls Assurance system now in operation - designed to provide Board with appropriate information for risk management. Policies are reviewed and updated very two years
Criterion 17: The Board should seek independent assurance that an appropriate and effective system of research governance is in place and that the necessary level of controls and monitoring are being implemented	100%	Regular finance audits, CHI audit, NHS R&D HTA site visit, NSCAG site visit, MHRA inspections. Internal audits will be conducted as part of controls assurance process.

APPENDIX 3:

Implementation of the UK Regulations on Clinical Trials: Guidelines for Universities

Universities which act as Sponsor to clinical trials should consider the following “best practice guidelines” in considering how to respond to the UK Regulations on Clinical Trials and accompanying UK legislation.

In many areas universities may find themselves meeting “best practice” already – in others there will be room for improvement.

It is being commonly found that a key action which is required is providing appropriate training to staff: in finding such provision universities are recommended to establish what is already available within their local NHS Trusts or through bodies such as the NHS R&D Forum.

BEST PRACTICE	CURRENT PRACTICE	ACTIONS REQUIRED
A. Council level responsibility for research governance is clearly defined and there are clear lines of accountability throughout the University leading to Council		
B. There is a designated person with responsibility for the management of all clinical research undertaken by the University at an operational level; the University can demonstrate effective oversight of its portfolio		
C. The University ensures financial probity in all matters concerning clinical trials		
D. All clinical research protocols undergo independent peer review, ethical approval and appropriate insurance cover is in place for all trials		
E. The University has a written agreement with research partners documenting the allocation of responsibilities		

under the Directive and, as appropriate, research governance		
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F. The University's trialists hold NHS honorary contracts if undertaking any trials involving NHS patients		
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G. The University should have procedures in place to reassure itself that all clinical research which it undertakes, complies with statutory legislation and guidance. This includes the Directive, Good Clinical Practice ("GCP") (expected to be cast into a new EU Directive by the end of this year), Good Manufacturing Practice, Human Tissue Act, Data Protection Act, etc		
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H. There is a system in place to record all Adverse Events arising from any research undertaken by the University or Sponsored by the University and that staff are made aware of and are trained in Adverse Event reporting requirements		
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I. All clinical trials undertaken by the University have a nominated Sponsor		
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J. The University has systems in place to detect and deal with research misconduct and fraud		
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K. All clinical research is properly recorded and management information is available		
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L. The University ensures that all relevant staff are aware of		
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their roles and responsibilities and the University can demonstrate training programmes to achieve this		
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M. Key indicators showing the University's effectiveness in successfully running its trials and providing early warning of risk should be developed and used at all levels in the organisation		
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N. Council should seek independent assurance that an appropriate and effective system of clinical trial governance has been established and that the necessary levels of controls and monitoring are implemented		
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APPENDIX 4b

Quality and Risk Management System: Imperial College

Current Arrangements

All applications for clinical projects are processed through local NHS research ethics committees; Imperial College is represented by senior clinical academics who are members of the LREC.

Ongoing review of COREC procedure and how we might use Part D (governance) to help us fulfil requirements

Apart from peer review by external sponsors, projects that are academic led (essentially internally funded) are subject to peer review within the Faculty of Medicine and can involve non-College academic input.

Staff always check that factors like GCP, Declaration of Helsinki and patient consent forms are included in all applications.

A series of presentations about RGF and EUCTD have been given to Heads of Departments and their administrative staff; also a guidance document has been posted on the College intranet

All trial applications require internal approval from Head of Dept and NHS Trust R&D office where necessary.

All applications are routed through our insurance office for confirmation that existing indemnity arrangements apply and identify any additional insurance requirements (occasionally needed for paediatric, GM or obstetric studies)

We have a cooperative agreement with our associated NHS Trusts to work together to effect Governance; discussions are underway about how this will work at an operational level e.g. sponsorship/co-sponsorship responsibilities; it is likely local or project-by-project agreements between College and Trust will be required

We have introduced a dedicated clinical trials database as an interim measure to record relevant data and milestones

New Developments

Internal discussion about forming a Clinical Trial Unit, led by a clinical academic, who would ensure all internally funded protocols were appropriately peer reviewed, offer advice to PIs, be responsible for guidance, monitoring, training and compliance around the Directive. Additional staff are likely to be required to meet this need.

Internal discussion about who is responsible for Governance and the Directive at senior College level; this person should receive regular updates on issues.