

A new pathway for the regulation and  
governance of health research

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of health research**

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## Summary

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Health research underpins the prevention and treatment of ill health and brings benefits across the UK population. It provides patients with early access to new and innovative treatments, it improves the quality and efficiency of health services for the wider public and it attracts investment and jobs into the UK.

The UK's first-class universities and hospitals, vibrant medical science industries, strong health research charities and unified healthcare systems have all contributed to our traditional status as a world leader in health research. In recent years, steps taken by the National Institute for Health Research (NIHR) in England, and similar initiatives in the devolved nations, have created the infrastructure and facilities to increase the standing of the NHS as an academic and commercial research partner.

Yet despite these strengths, there is evidence that UK health research activities are being seriously undermined by an overly complex regulatory and governance environment. This is evidenced by a fall in the UK's global share of patients in clinical trials, and by the increased time and costs of navigating the UK's complex research approval processes. As a specific example, a recent analysis from Cancer Research UK showed that after its funding for a study has been agreed, it now takes an average of 621 days to recruit the first patient. In short, the current situation is stifling research and driving medical science overseas.

In spring 2010 the Academy of Medical Sciences was invited by Government to review the regulation and governance of health research involving human participants, their tissue or their data. A working group chaired by Sir Michael Rawlins FMedSci was convened to undertake the review. The group received over 300 submissions from across industry, academia, the NHS, charities and public sector bodies, as well as from regulators themselves. There was a broad consensus about the key

problems, and a clear desire from those consulted to see the position improved.

As researchers strive to develop new and better treatments, to improve health services and to tackle the challenges of an aging population, there is – more than ever – a need for a regulation and governance pathway that protects the safety and interests of patients without introducing unnecessary bureaucracy or complexity. The Academy therefore welcomed the Government's support for health research in the 2010 Health White Paper and its commitment to '*consider the bureaucracy affecting research...and bring forward plans for radical simplification in light of the Academy's review*'. The recommendations in this report are intended to deliver a level of change that will substantially improve the regulation and governance pathway – as well as the culture within which it operates – for the good of patients, the public and the economy.

### **Regulation should safeguard patients and facilitate research**

Patients, the public and researchers have a common interest in ensuring that research is conducted safely and effectively. In this report, we argue that the application of regulation should be both *proportionate* and *symmetrical*. A 'one-size-fits-all' approach to regulation damages us all. Instead, regulation of health research should be proportionate to the risks and benefits to individuals and society. Those involved with regulation and governance must recognise that the current approach is asymmetrical; approving an inappropriate study is clearly unacceptable, but delaying or prohibiting an appropriate study harms future patients as well as society as a whole. We propose that the UK's regulation and governance framework around health research should be underpinned by the following four principles:

1. To safeguard the well-being of research participants.
2. To facilitate high-quality health research to the public benefit.
3. To be proportionate, efficient and coordinated.
4. To maintain and build confidence in the conduct and value of health research through independence, transparency, accountability and consistency.

### **A complex and bureaucratic regulatory environment is stifling health research in the UK**

The existing regulation and governance pathway has evolved in a piecemeal manner over several years. New regulatory bodies and checks have been introduced with good intentions, but the sum effect is a fragmented process characterised by multiple layers of bureaucracy, uncertainty in the interpretation of individual legislation and guidance, a lack of trust within the system, and duplication and overlap in responsibilities. Most importantly, there is no evidence that these measures have enhanced the safety and well-being of either patients or the public.

Despite recent attempts to improve individual parts of the regulation pathway, significant challenges remain:

#### ***Delays and duplication in obtaining research permissions from NHS Trusts.***

The current process for obtaining research permissions across multiple NHS sites is inefficient and inconsistent, characterised by NHS Trusts reinterpreting assessments already undertaken by regulators such as the National Research Ethics Service and duplicating checks that could be done once across a study. Local negotiation of research contracts and costings are a further source of delay. Together with the lack of agreed timelines within which approval decisions are made, the governance arrangements within NHS Trusts are the single greatest barrier to health research.

#### ***Complexity and inconsistency across the regulation pathway.***

Researchers must navigate numerous approval and permissions processes, coordinated by multiple bodies with overlapping responsibilities. Further complexity is added by different legislative and regulatory arrangements across the devolved nations. Approval processes are often undertaken in series, rather than in parallel, and conflicting advice by different bodies leads to inconsistency, confusion and variable standards.

#### ***A lack of proportionality in the regulation of clinical trials.***

The broad scope and 'one-size-fits-all' approach of the EU Clinical Trials Directive (CTD) places an unnecessary regulatory burden on clinical trials of both new products and established drugs. The Medicines and Healthcare products Regulatory Agency (MHRA) provides timely authorisation of clinical trials but there are concerns about its interpretation of the EU Directive, the lack of consistent advice to investigators and sponsors, and the approach taken during some clinical trial site inspections. In combination, this situation is hampering clinical trials and discouraging academic and commercial health research sponsors from conducting their studies in the UK.

#### ***Inappropriate constraints on access to patient data.***

Patient information is used extensively within the NHS to underpin all aspects of service delivery, and is routinely shared in a secure and confidential manner with members of clinical care teams. Access to patient data is vital for many important research uses, for example to identify causes of disease, to determine the long term effects of treatment and to show how public health can be improved, for example, by the better provision of services. However, access to patient data for research is currently hampered by a fragmented legal framework, inconsistency in interpretation of the regulations, variable guidance and a lack of clarity among investigators, regulators, patients and the public.



***A healthcare culture that fails to fully support the value and benefits of health research.***

The Academy has long argued for a step change in the culture and attitude of the NHS towards research. Although some NHS Trusts recognise the importance of research as the bedrock of effective and evidence-based healthcare, NHS managers have traditionally been under intense pressures to deliver immediate healthcare targets. There are few equivalent incentives to encourage support from NHS staff for health research. Together with their concerns about the obligations of an overly complex regulation and governance pathway, this can cause NHS Trusts to give research a low priority. As a result, the NHS is still perceived as a difficult and unpredictable place in which to conduct clinical studies.

**Clearing the path: streamlining the regulation and governance pathway**

In this summary we present only the major recommendations that address the problems identified during our review. Further recommendations can be found in the relevant sections of the report. We recommend the following:

***Creating a new Health Research Agency to rationalise the regulation and governance of all health research.***

The Agency should have two major functions: *A National Research Governance Service* that would:

- Eliminate inefficiency and support NHS Trusts and researchers by undertaking all NHS research governance checks just once. This will ensure common standards and a consistent interpretation of the requirements.
- Oversee new arrangements that enable Trusts to determine local research feasibility within agreed timelines.
- Allow Trusts to focus on monitoring local capacity, conduct and performance.

*A single system for ethical approvals.*

This system would encompass the responsibilities for both general ethical approval (the National Research Ethics Service), as well as specialist approvals and licenses (for studies involving patient data, human tissue, gene therapy or human stem cells etc.). Bringing together the regulatory functions that are currently fragmented across multiple bodies will:

- Provide clarity on the interpretation of legislation, develop best practice, remove inefficiencies by pooling resources, and reduce timescales.
- Establish a single point of contact and source of advice to support investigators and sponsors.
- Ensure transparency and accountability to healthcare professionals, patients and the wider public.

The new Health Research Agency (HRA) should work alongside systems in the devolved nations to create an efficient, seamless approach. Its success in simplifying research governance and approval processes should be formally reviewed on a periodic basis.

***Improving the UK environment for clinical trials.***

To address the challenges identified around clinical trials, improvements need to be made at both the European and UK levels. The Department of Health and Department for Business, Innovation and Skills – supported by the MHRA and other UK stakeholders – should seek to ensure that the CDT is revised to:

- Reduce the scope of the Directive.
- Ensure that approval and monitoring requirements are proportionate to risk.
- Simplify the requirements for safety reporting to improve the quality of drug safety data and monitoring.

The relationship between the new HRA and MHRA will be crucial in improving the current system and should be enshrined in a duty of consultation between the two organisations. The HRA and MHRA should work in consultation to:

- Ensure a more proportionate approach to clinical trials regulation.
- Provide consistent and clear guidance on the interpretation of the scope of the EU Clinical Trials Directive.
- Improve the approach and process of Good Clinical Practice (GCP) monitoring inspections so that they form a proportionate and constructive part of the regulatory process.
- The UK Data Protection Act should be reviewed to identify and amend aspects requiring clarification and to inform proposed revisions to the EU Data Directive.

***Providing access to patient data that protects individual interests and allows approved research to proceed effectively.***

We urge the Government to evaluate progress in implementing the recommendations of the 2008 Data Sharing Review. Specifically, we recommend that:

- 'Safe havens' are established as a matter of urgency to allow access to data for approved research.
- Accredited investigators and research team members should be considered part of a clinical care team to enable them to identify patients eligible for approved studies.
- The core role of health research in the delivery and improvement of the NHS should be more widely communicated to healthcare staff at all levels.
- Health research should be formally and irreversibly embedded into NHS leadership and governance processes by the following: the use of appropriate metrics and incentives; training the NHS workforce to ensure it can support health research; and ensuring that within each Trust there is an executive director with specific responsibilities to promote health research.

***Embedding a culture that values research within the NHS.***

To support improvements to the regulation and governance environment, a cultural change is required within the NHS to embed health research as a core function, to foster a more facilitative approach to research governance and to promote public and patient engagement in research. We recommend that:

**Guide to the report**

- In **Chapter 1** we provide a brief introduction to the **opportunities for UK health research** and the **challenges presented by the current regulation and governance pathway. A guide to the existing regulation pathway is provided in Annex I.**
- In **Chapter 2** we set out the **principles** on which we believe the regulation and governance pathway should be based. These principles form the basis for the discussion, conclusions and recommendations that follow in the later chapters.
- In **Chapter 3** we outline the importance of a supportive **culture and attitude towards research** on the part of patients and the public, the NHS and other stakeholders.
- **Chapter 4** deals with the issue of **NHS R&D approvals** and includes discussion of a proposed **National Research Governance Service**. This is also revisited in **Chapter 9**.
- Specific issues relating to **clinical trials, use of patient data in research, use of human tissue and research ethics**, are discussed in **Chapters 5, 6, 7 and 8** respectively. Each of these chapters contains specific conclusions and recommendations related to those areas, and **Chapter 9** considers how they might be dealt with by a proposed **new Health Research Agency**.
- The overall **conclusions** of the report and a description of our proposed **new regulation and governance pathway** are set out in **Chapter 10**.

# 1 Introduction

## 1.1 Overview

Health research provides the knowledge that underpins improvements in healthcare and allows people to live longer and healthier lives. By improving our understanding of medical conditions, and by developing new ways to treat and prevent disease, health research brings great benefit to individuals, their families and society. Throughout this report we demonstrate the health and economic benefits of undertaking this research in the UK. For example:

- Patients gain early access to innovative medicines, devices, procedures or diagnostic techniques.
- Healthcare professionals gain early experience and expertise in the selection and use of new therapeutic interventions.
- Evidence to support public health interventions is relevant and available quickly to healthcare professionals and policymakers.
- Commercial health research brings substantial economic and social benefits, for example, the UK's pharmaceutical sector is estimated to invest approximately £11.8 million per day in research and development (R&D), more than any other industrial sector, and employs over 72,000 people.<sup>1</sup>

Health research relies on the involvement of the public, patients and healthy volunteers (section 1.4). Regulation and governance mechanisms are in place to safeguard research participants from the potential risks of research, while also ensuring that high quality research can take place for public benefit. The regulation and governance pathway needs to manage these risks and benefits in a proportionate manner.

As the population ages and the NHS attempts to improve quality and efficiency, the need for a fertile health research environment has never been more important. It is essential

to have a regulatory system that facilitates research without unnecessary bureaucracy or complexity. There are concerns that public and private investment, the UK's research assets, and the strong public support for research are failing to be maximised because of the stifling regulatory and governance environment. The threat to the UK's traditional position at the forefront of health research is evidenced by a fall in the UK's global share of patients in clinical trials and the increasing cost and time taken to get research approved (section 1.2).

In spring 2010, the Department of Health for England commissioned the Academy of Medical Sciences to conduct a review of the regulatory and governance environment for health research in the UK, with a particular focus on clinical trials (section 1.3).<sup>2</sup> Professor Sir Michael Rawlins FMedSci chaired the Academy working group established to undertake this review. The recommendations made to reduce and streamline the regulatory burden — without undermining effectiveness — have been informed by evidence from over 300 individuals and organisations across the health research community.

## 1.2 Regulation and governance

### 1.2.1 Health research: a UK strength

The UK has traditionally been a world leader in research to understand and treat disease. Our scientific publications produce over 12% of the world's citations in both the clinical and health sciences and we have created nearly a quarter of the world's top 100 medicines (for example, see Box 1.1).<sup>3,4</sup> The UK's success has been due to our superior academic health research base, our coordinated landscape of private, public and charity funders, the NHS and the support of the public for research (Box 1.2).

1 Association of the British Pharmaceutical Industry (2010). *The pharmaceutical industry's contribution to the UK economy and beyond*. <http://www.abpi.org.uk/pdfs/The%20Pharmaceutical%20Industry%20Contribution%20to%20the%20UK%20Economy%20and%20Beyond.pdf>

2 For further information see <http://www.acmedsci.ac.uk/p118pressid63.html>

3 Department for Business, Innovation and Skills (2009). *International comparative performance of the UK research base*. [http://www.bis.gov.uk/assets/biscore/corporate/migratedd/publications/i/cpruk09v1\\_4.pdf](http://www.bis.gov.uk/assets/biscore/corporate/migratedd/publications/i/cpruk09v1_4.pdf)

4 Academy of Medical Sciences (2010). *Reaping the rewards: a vision for UK medical science*. <http://www.acmedsci.ac.uk/download.php?file=/images/publicationDownload/Reapingt.pdf>

### Box 1.1 Monoclonal antibodies

Research supported by the UK Medical Research Council in the 1970s and 1980s led to the development of monoclonal antibodies and, in particular, to humanised versions of these antibodies that are suitable for therapeutic use. Antibody therapies now constitute a third of all new drugs for a variety of major diseases, including cancer and arthritis, and the market is forecast to grow to over \$43 billion by 2012.<sup>5</sup> Adalimumab (Humira®) is one example of an antibody therapy that is now used to treat various inflammation diseases such as adult and juvenile rheumatoid arthritis, psoriatic arthritis and Crohn's disease. By August 2009, Humira was being used by 370,000 patients in 80 countries and it is estimated to become one of the world's top earning pharmaceutical products with sales reaching \$10 billion by 2016.<sup>6</sup>

### Box 1.2 Health research: a UK strength

The ability of the UK to continue to deliver health benefits to the public, patients and society requires us to maximise the opportunities available from the following:

- The **National Health Service** (NHS). Almost all health research involving human participants is undertaken in NHS hospitals and GP practices. An NHS culture that is supportive of research is therefore vital. The NHS treats the largest group of people within a single healthcare system anywhere in the world, and keeps detailed records on all patients from birth to death. Access to, and analysis of, these data is essential in epidemiological research to improve the safety of medicines, to identify potential participants for clinical trials and to identify those who would benefit most from targeted health interventions.
- Our world-class **universities** and **researchers**. Four of the UK's universities are in the top six in the world.<sup>7</sup> The UK has produced 30 Nobel Prize winners in biomedical research.<sup>8</sup> Recent initiatives such as the Biomedical Research Centres and Units and Academic Health Science Centres have strengthened links between academia and the NHS.<sup>9</sup>
- A vibrant research-intensive **life sciences industry**. Pharmaceutical and biotechnology companies, manufacturers of medical devices and diagnostics, and contract research organisations are an important part of the UK's knowledge economy. They are attracted by the availability of skilled researchers and the NHS. Commercial, academic and charity funded studies often share the same infrastructure and can complement and support each other.
- Thriving **health research charities** (e.g. Wellcome Trust, Cancer Research UK, British Heart Foundation and Arthritis Research UK). Each year, medical research charities invest £1.1 billion in UK health research and facilitate the involvement of patients in research.<sup>10</sup>
- Sustained **public funding** from the MRC and the Department of Health's National Institute for Health Research (NIHR). Both funders support essential infrastructure for health research, as well as funding individual programmes and projects. In October 2010 the Government announced that public funding for health research would increase over the next four years.
- **Patients and the public** who are supportive of research both as research participants and as contributors to health research charities.

5 Datamonitor (2007). *Monoclonal antibodies report part II: Companies – holding mAbs in portfolio promises protection against the looming 2011-12 patent cliff*. Datamonitor, London.

6 EvaluatePharma (2010). *Humira set to steal Avastin's crown*. <http://www.evaluatepharma.com/Universal/View.aspx?type=Story&id=211976&isEPVantage=yes>

7 Times Higher Education (2009). *Top 200 universities*. <http://www.timeshighereducation.co.uk/hybrid.asp?typeCode=438>

8 For further information see <http://www.mrc.ac.uk/AchievementsImpact/NobelPrize/index.htm>

9 H M Government (2010). *Life Sciences 2010: delivering the blueprint*. <http://www.bis.gov.uk/ols>

10 Association of Medical Research Charities (2010). *Challenge for Government*. <http://www.amrc.org.uk/challenge>

### 1.2.2 Regulation and governance: a UK weakness?

In the past ten years the UK's position in health research has been under threat and our global share of research activity has fallen. Trends causing concern include the following:

- In 2002, 46% of EU products in clinical trials were being developed in the UK; by 2007 this had fallen to 24%.<sup>11</sup>
- While data from the MHRA show that the number of trials approved has stayed constant between 2004 and 2008, our global market share of patients in trials has dropped from 6% to 2-3%.<sup>12</sup>
- Almost half of the representatives of major pharmaceutical industries surveyed in 2008 indicated that they expected to reduce the number of clinical trials in the UK.<sup>13</sup>
- Commercial and non-commercial researchers have indicated that the complexity of the regulation and governance pathway is limiting the amount of research they do.<sup>14</sup>

Throughout the course of our review, we found evidence that the regulatory and governance environment has led to delays, increased cost and created unnecessary barriers to the recruitment of patients.<sup>15,16</sup> For example, a recent analysis from Cancer Research UK showed that after its funding for a study has been agreed, it now takes an average of 621 days to recruit the first patient.<sup>17</sup> Most importantly, there is a consensus that these regulatory and governance measures have not – either individually or collectively – enhanced the safety or well-being of either patients or the public.

A survey of UK Life Sciences Leaders in July 2010 identified the regulatory burden as one of four key areas that the new Coalition Government should address.<sup>18</sup> Also in July, the Department of Health's White Paper '*Equity and excellence: Liberating the NHS*' was published.<sup>19</sup> This paper committed to '*consider the legislation affecting medical research, and the bureaucracy that flows from it, and bring forward plans for radical simplification*' in light of the Academy's review.

### 1.2.3 The current regulation and governance pathway

The complexity of the current regulatory and governance process is outlined in Annex I and illustrated in Figure 1.1.

In the past five years several attempts have been made to improve the UK's regulation and governance pathway. These initiatives are outlined throughout this report and include programmes by the National Institute for Health Research (NIHR) to create the infrastructure and facilities to improve the NHS research environment, and efforts by regulators to reduce timelines for clinical trials and ethical approval. In this report we have sought to build on these individual improvements while taking a view of the regulation and governance pathway in its entirety.

## 1.3 The Academy's review of regulation and governance

In January 2010 the Academy published '*Reaping the rewards: a vision for UK medical science*',

11 Bioscience Innovation Growth Team (2009). *Review and refresh of bioscience 2015*. <http://www.berr.gov.uk/files/file49805.pdf>

12 Kinapse (2008). *Commercial clinical research in the UK: report for the Ministerial Industry Strategy Group Clinical Research Working Group*. <http://www.ukcrc.org/index.aspx?o=2873>

13 Association of the British Pharmaceutical Industry (2008). *Bellwether Industry's Confidence In UK Slumps – ABPI/CBI Survey*. [http://www.abpi.org.uk/press/press\\_releases\\_08/200308.asp](http://www.abpi.org.uk/press/press_releases_08/200308.asp)

14 OnCoreUK (2009). *The effect of regulation and governance on research led by pathologists or involving pathology in the UK*. <http://www.oncoreuk.org/documents/EffectofRegulationandGovernanceSurveyReport-onCoreUK2009-09-07o.pdf>

15 Hackshaw A, et al. (2008). *Setting up non-commercial clinical trials takes too long in the UK; findings from a prospective study*. *Journal of the Royal Society of Medicine* **101**, 299-304.

16 Both CR-UK and UCL indicated large increase in the number of staff required since 2003/04 to deal with the administration of Clinical Trial Applications, trial coordination and monitoring, pharmacovigilance (PV) tasks and quality assurance. These staffing increases provide a simple indication of the escalating resources and infrastructure required.

17 The 621 days is the time from decision to support the study to first patient entered at the first site. This is the average time from 25 studies approved by Cancer Research UK's Clinical Trials Awards and Advisory Committee during the period of November 2006 to July 2007.

18 Science, Technology & Innovation Partners (2010). *Life science leaders' survey*. <http://www.standipartners.com/download/2010-UK-Life-Science-Leaders-Survey-Full-Report.pdf>

19 Department of Health (2010). *Equity and excellence: liberating the NHS*. [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_117353](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_117353)

which set out the challenges for an incoming Government.<sup>20</sup> The report proposed that a more fertile research environment could be created, at less cost, by streamlining and improving current regulation, and recommended that this be informed by an independent review of the existing governance framework. In response, the Department of Health commissioned the Academy to conduct this review.

**1.3.1 Terms of reference**

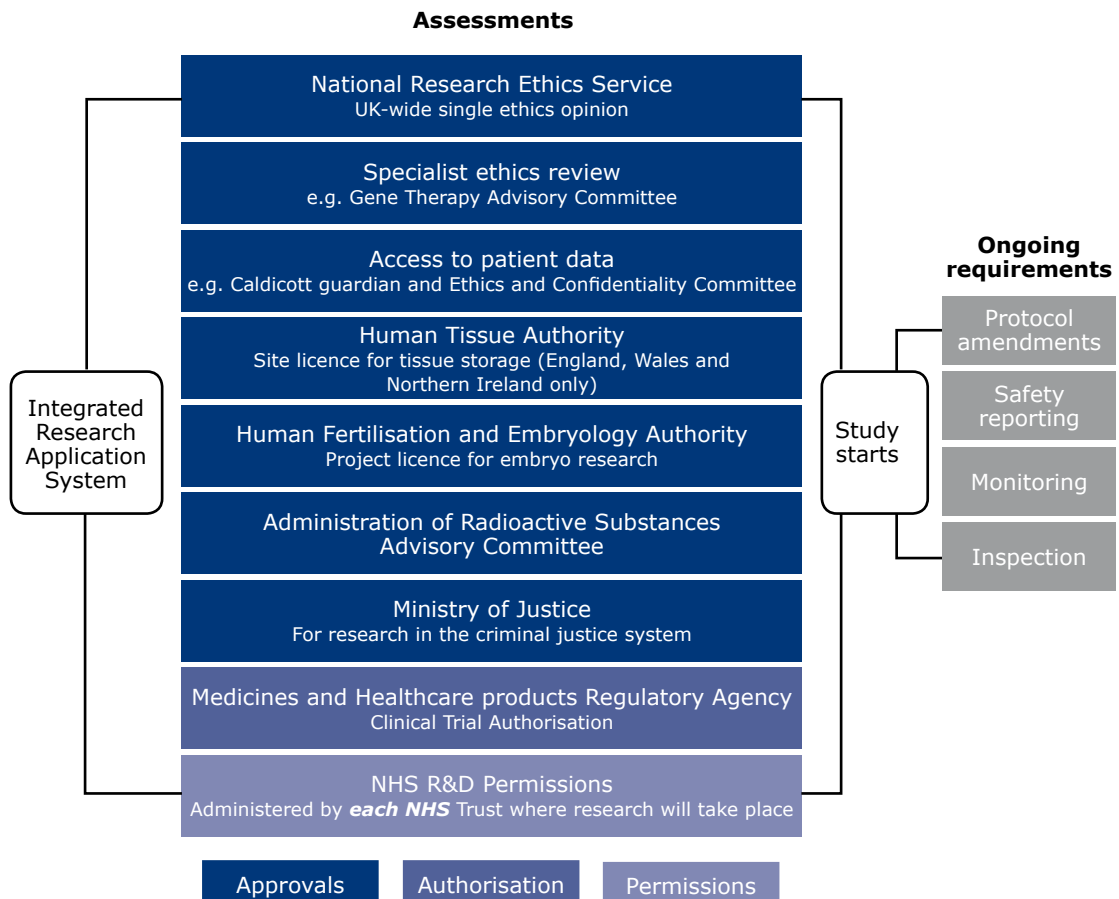
The study was launched in May 2010 with the following terms of reference:

- To review the regulatory and governance environment for health research in the UK, with a particular focus on clinical trials.
- To identify key problems and their causes, including unnecessary process steps, delays, barriers, costs, complexity, reporting requirements and data collection.

- To make recommendations with respect to the regulation and governance pathway that will achieve the following: increase the speed of decision-making; reduce complexity; and eliminate unnecessary bureaucracy and cost. In making recommendations for change, the need to ensure the protection of the safety of participants, as well as the need for appropriate arrangements for governance and accountability, have been central.

During the course of the Academy’s review, the Department of Health set out proposals to reorganise ‘arm’s-length bodies, including the suggestion that a single regulator of research should be established.<sup>21</sup> The Academy was asked to consider the possible scope and function of this new body in the context of this review (see Chapter 9).

**Figure 1.1: The current regulation and governance pathway**



20 Academy of Medical Sciences (2010). *Reaping the rewards: a vision for UK medical science*. <http://www.acmedsci.ac.uk/download.php?file=/images/publicationDownload/Reapingt.pdf>

21 Department of Health (2010). *Liberating the NHS: report of the arm’s-length bodies review*. [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_117691](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_117691)

### 1.3.2 Geographical scope

England, Scotland, Wales and Northern Ireland have separate healthcare systems with different administrative arrangements. Although this review was commissioned by the Department of Health in England we have tried, in so far as it has been possible, to take a UK-wide approach. Stakeholders made it clear that the system for permissions, approvals and authorisations in the NHS must be joined up across the UK. A coordinated UK approach will become even more important in the face of growing competition from other nations who are investing in, and enhancing, their health research capacity.

### 1.3.3 Conduct of the study

Professor Sir Michael Rawlins FMedSci chaired the Academy working group established to undertake this review, which included health researchers and clinicians from academia, industry, the NHS, and the charity sector, experts in bioethics and law, a representative of a patient charity, and a lay member. Observers from the MHRA, the Department of Health and the Department of Business Innovation and Skills also joined the initial working group meetings to clarify factual points but were not present for the discussion of the conclusions and recommendations of the study. A list of working group members and observers can be found in Annex II.

Two calls for evidence were issued to inform the review:

- The project was launched with an initial call for evidence in May 2010 to determine the priorities for the study.
- A second call for evidence was launched in July 2010 to seek responses to the Department of Health's announcement that it was considering the creation of a new arm's-length body to regulate research.

In addition to considering the written responses to the calls for evidence, the working group held evidence sessions with Wendy Fisher

(NHS R&D FORUM), Sir Nick Partridge (Chair of INVOLVE and Chief Executive of the Terrence Higgins Trust), Mr Marc Taylor (Department of Health) and Professor Kent Woods FMedSci, (Chief Executive, MHRA).

The Chair and individual working group members also had discussions with other stakeholders, including many of the regulatory bodies and with representatives from the devolved administrations, at various stages of the project. The Association of British Pharmaceutical Industry (ABPI) and the Bioindustry Association (BIA) organised a meeting to discuss key issues for industry and working group members and the secretariat spoke to the UK Clinical Research Collaboration (UKCRC) Board and its Regulation & Governance sub-group.

The Academy also supported the Association of Medical Research Charities and INVOLVE in organising a Patient and Public Involvement (PPI) workshop for patients and their representatives interested in health research. The workshop provided an opportunity for participants to discuss their hopes and concerns around regulation and governance.<sup>22</sup>

We thank all those who contributed to this study, including all those who submitted evidence (Annex IV). We are very grateful to Cancer Research UK and the Wellcome Trust for each seconding a member of their staff to the study on a part-time basis and to the NIHR for making a contribution towards the costs of the study. The report was reviewed by a group appointed by the Academy's Council (Annex III) and it has been approved by the Academy's Council.

## 1.4 What do we mean by health research?

This report focuses on the regulation and governance of research involving human

<sup>22</sup> Association of Medical Research Charities & INVOLVE (2010). *Patient perspectives on the regulation and governance of medical research*. <http://www.invo.org.uk/pdfs/AMRCINVOLVERegulationWorkshopReport211210.pdf>



participants, their tissue or their data. We use the term health research but the terms 'clinical research' and 'medical research' are also commonly used. Health research has many aims, including:

- To understand the biology of disease and prevent ill health.
- To find new ways to treat disease and improve the quality of life for people living with ill health.
- To develop new diagnostic and therapeutic interventions (for example new medicines, devices, or surgical techniques).
- To monitor the efficacy and safety of interventions once they are in use.

Our review focuses on approaches to health research that are broadly labelled as 'experimental medicine', 'clinical trials', and 'epidemiology', and that involve human participants, their tissues or their data. The regulation and governance of research involving animals is outside the scope of this report.

#### **1.4.1 The involvement of patients and healthy volunteers**

Much health research relies on the involvement of patients and healthy volunteers usually in a hospital or other healthcare setting. Without the participation of patients and volunteers – or access to their tissue and/or data samples – the research that led to the advances described in this report would not have been possible. The UK has a long history of public support for health research, as evidenced by the large number of participants in clinical trials and

population studies (e.g. UK Biobank) and the generous contributions to medical research charities such as Cancer Research UK and the British Heart Foundation. Personal involvement in research studies can bring direct benefits to participants themselves, who experience enhanced care and monitoring, play a more active role in their healthcare and often gain earlier access to new medicines.

As well as the many benefits of health research, there are risks. For most health research studies these risks are minimal. However, for some studies there may be potential consequences to participants such as extended hospital stays, the possibility of the experimental treatment being ineffective, or risk to physical well-being due to adverse effects. For studies involving patient data, the potential risk may relate to security of personal information. There are also other potential issues that impact on the decisions of those organising, hosting or delivering research (often healthcare providers). For example, risks to the quality of the study data and the perceived risk of legal action due to negligent or non-negligent harm. Alongside the potential benefits of research, it is these risks that a regulation and governance pathway should manage in a proportionate manner.

#### **1.4.2. Experimental medicine**

Experimental medicine is a broad term, with varying definitions. It is most often used to describe research that aims to identify the mechanisms (pathophysiology) of disease. This

### **Box 1.3 Experimental medicine: understanding obesity**

Obesity has been categorised as an epidemic by the World Health Organization and is often associated with high blood pressure. A Medical Research Council funded team from the University of Cambridge has increased our understanding of the underlying disease mechanisms. Their work has included revealing that the melanocortin 4 receptor (MC4R) gene, which works in the brain to control body weight, is a key link between the body's systems for controlling weight and blood pressure.<sup>23</sup> MC4R deficiency is the most common form of inherited human obesity. Together with Lilly Inc in the USA, the team demonstrated that a new drug that increases the action of MC4R causes an increase in blood pressure in overweight individuals.



might include determining the genes linked with susceptibility to a given disease (which can indicate a potential therapeutic target) or using an existing drug to better understand underlying disease mechanisms (see Box 1.3). It can generate new hypotheses that can be explored in the laboratory. The term is also used to describe work done to demonstrate proof-of-concept evidence of the validity and importance of new discoveries or of treatments in development. Experimental medicine can overlap with Phase I clinical trials (see below).

### 1.4.3 Clinical trials

Clinical trials are research studies designed to assess the safety and efficacy of therapeutic interventions. Such interventions can include drug treatments, vaccines, devices, screening (see Box 1.4), surgical procedures, approaches to disease prevention and improving public health, radiotherapy, physical and psychological therapies, educational programmes or methods of diagnosis. Much of the focus of this report is on Clinical Trials of Investigational Medicinal Products (CTIMPs), which involve studying a

drug in humans, often with an emphasis on new or relatively new drugs (although studies defined as CTIMPs can vary, as discussed in Chapter 5).

Trials of new medicines provide important information not only about their effectiveness but also how quickly they are absorbed, how often they need to be taken, and the nature and frequency of any adverse side effects. Before it reaches the market, safety and efficacy of a new medicine must be demonstrated through a series of stages that are often defined as follows:

- **Phase I** studies are about determining how the body metabolises and responds to the drug and how it will tolerate increasing doses. These usually involve small numbers of healthy volunteers.
- **Phase II** studies involve small groups of patients to test whether the drug works for the disease for which it has been developed and determine the most appropriate dose.
- **Phase III** studies involve larger groups of patients (1,000-5,000) to determine if the

### Box 1.4 Ten thousand people each year will avoid bowel cancer through screening

About 1 in 20 people in the UK will develop bowel cancer during their lifetime. In the UK it causes over 16,000 deaths a year, making it the second biggest cause of death by cancer. In 2010, a 16-year study funded by Cancer Research UK, the Medical Research Council and the National Institute for Health Research was completed, which demonstrated that bowel cancer can be prevented with a simple, once-in-a-lifetime, five-minute screening test.<sup>24</sup> The test uses a flexible tube (named the Flexi-Scope) to examine the lower bowel for the presence of polyps, which are then burnt or snipped off. Polyps occur in around one in five people over 55, and in 1 in 20 people they develop into cancer.

The study revealed that 10,000 people each year will avoid bowel cancer as a result of incorporating the Flexi-Scope test into the national bowel screening programme. The study also suggests that deaths from the disease will drop by almost half (43%) among those who attend screening, saving up to 3,000 lives a year.

In addition to saving lives, the screening programme could also reduce the costs associated with treating people with bowel cancer. Research commissioned by the Department of Health suggested that if a screening programme based on this test was effective this could save an average of £28 for every person screened. In October 2010 the Government confirmed that Flexi-Scope would be rolled out nationwide over the next four years.<sup>25</sup>

<sup>24</sup> Atkin W, et al. (2010). *Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial*. *Lancet* **375** (9726), 1624 – 1633.

<sup>25</sup> For further information see <http://www.screening.nhs.uk/cms.php?folder=3014>

medicine is both safe and effective.

- **Phase IV** trials or post-marketing studies are used to learn more about the drug and its long term benefits and risks.

The later phases are usually undertaken across many sites, often in more than one country and involving larger numbers of patients. The cost and complexity therefore increases as a new drug progresses through these phases. Drug development is a very expensive business – some estimates put the total cost of bringing a single new medicine to market at between \$0.5 and \$1.4 billion.<sup>26</sup>

Some studies do not focus on the development of a new drug, but on alternative uses of an existing drug. Such studies will generally have a lower associated risk than trials of a completely new drug. Trials may also focus on determining whether well-established treatments are effective and safe (e.g. Box 1.5). Trials of non-drug interventions will follow different stages from those listed above.<sup>27</sup>

#### 1.4.4. Epidemiological research

Epidemiological research aims to understand factors associated with disease. It includes investigating events such as causes of death, the adverse consequences of certain behaviours such as smoking (Box 1.6), reactions to preventative regimes, or the provision and use of health services. Studies in this broad

discipline range from examining the possible causes and prevention of infectious (e.g. HIV/AIDS) and non-infectious (e.g. cancer) diseases to examining poisoning caused by environmental agents. Epidemiological studies use data on health, lifestyle, environment and genotype.

They include methods such as the following:

- Cohort studies that follow a defined population to investigate disease outcomes. For example the Million Women Study<sup>29</sup> involves more than one million UK women aged 50 and over has been used to study aspects of women's health such as the link between hormone replacement therapy and various cancers (Box 6.2).
- Case-control studies to compare possible causal factors in individuals with and without a specified condition. This involves collecting data from case and control groups at a particular point in time. One of the best known case-control studies is the long-term programme of research into the link between smoking and cancer (Box 1.6).
- Ecological studies, which, rather than examining associations at an individual level, compare aggregated population groups. For example, researchers might analyse hospital admissions for respiratory conditions by comparing severe asthma attacks with the local air quality to examine links between specific pollutants and impact on human health.

#### Box 1.5 Halting ineffective treatments: surgical stockings

In small trials of patients undergoing surgery, graduated compression stockings had been shown to reduce the risk of deep vein thrombosis (DVT). National stroke guidelines had extrapolated from these trials and recommend their use in patients with stroke - despite only a small amount of evidence. Research led by the University of Edinburgh, published in 2009, showed that thigh-length graduated compression stockings are not effective at preventing venous thromboembolism in patients with stroke. As a result, clinical guidelines published in the UK and internationally were changed and it is estimated that the NHS may save £7 million and 320,000 hours of nursing time a year by cutting the use of stockings for approximately 80,000 people with stroke.<sup>28</sup> This study involved patients in hospitals across the world. It was funded by the Medical Research Council, the Chief Scientist Office of the Scottish Government and the medical charity Chest Heart and Stroke Scotland.

26 Adams CP, Brantner VV (2010). *Spending on new drug development*. Journal of Health Economics **19**, 130–141.

27 Medical Research Council (2008). *Developing and evaluating complex interventions: new guidance*.

[http://www.mrc.ac.uk/consumption/idcplg?IdcService=GET\\_FILE&dID=15585&dDocName=MRC004871&allowInterrupt=1](http://www.mrc.ac.uk/consumption/idcplg?IdcService=GET_FILE&dID=15585&dDocName=MRC004871&allowInterrupt=1)

28 The CLOTS Trials Collaboration (2009). *Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): a multicentre, randomised controlled trial*. The Lancet **373(9679)**, 1958–1965.

29 For further information see <http://millionwomenstudy.org/>

### Box 1.6 Reducing smoking-related deaths

Research funded by the MRC, Cancer Research UK and the British Heart Foundation since the 1950s has shown that people who smoke have lower life expectancy, that passive smoking is harmful and that stopping smoking can reduce the risk of lower life expectancy.<sup>30</sup>

In 1950, Doll and Hill published the results of a case-control study<sup>31</sup> showing an excess of smokers amongst patients with lung cancer compared with patients with other diagnoses. They confirmed these findings in a prospective cohort study of British doctors.<sup>32</sup> These individuals have been tracked ever since to see what illnesses they died of. Among the first results was that the death rate from lung cancer among heavy smokers was 20 times the rate in non-smokers.<sup>33</sup>

Over the next half-century, researchers collected more data and the extensive dangers of smoking gradually emerged. This research has resulted in national public health campaigns and a dramatic reduction over the past 50 years in the number of smokers. It has also led to bans on smoking in workplaces and public places after sustained exposure to passive smoking was shown to be harmful. A year after the ban in Scotland was introduced there was a 17% fall in admissions for heart attacks compared with annual reduction in admissions for heart attacks of 3% per year in the decade before the ban.<sup>34</sup>

30 MRC (2010). *Impact of MRC research*. <http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC007392>

31 Doll R & Hill AB (1950). *Smoking and carcinoma of the lung; preliminary report*. *BMJ* **2**(4682), 739-748.

32 Doll R & Hill AB (1954). *The mortality of doctors in relation to their smoking habits: a preliminary report*. *BMJ* **228** (i), 1451-1455.

33 Doll R & Hill AB(1956). *Lung cancer and other causes of death in relation to smoking; a second report on the mortality of British doctors*. *BMJ* **2**, 1071.

34 Pell J, et al. (2008). *Smoke-free legislation and hospitalizations for acute coronary syndrome*. *The New England Journal of Medicine* **359**, 482-91.



## 2 Our principles and vision for the regulation and governance pathway

### 2.1 Introduction

Regulation and governance need to promote high-quality research but also to maintain public and professional trust in an area that relates directly to individual safety and dignity. The various checks and assessments in place need to safeguard research participants and the public from potential risks, while recognising that reliable and valid research evidence is needed to provide effective medical interventions. An overly complex and burdensome regulation and governance pathway does not, in itself, necessarily protect participants from potential risks or facilitate research. Indeed, many respondents to this review suggested that, rather than increasing safety, elements of the current environment were detrimental because of the focus on form-filling and administration – a ‘box-ticking’ approach – rather than engaging with patient and public safety issues.

The complexity of the current regulatory and governance environment has developed cumulatively. New regulatory requirements and checks have been introduced over time to improve on previous arrangements, in response to individual cases of actual and alleged clinical malpractice, or as a consequence of legislation. Each new requirement was well-intended but the combined effect has been the layering of new bodies or checks onto existing functions. A key aim of this report is to consider the regulation and governance pathway as a whole and its net impact on patients, the public and UK health research.

This chapter outlines a vision for regulation and governance that identifies four principles to be used as a benchmark against which to assess the current regulatory framework and to test our proposals for change.

### 2.2 Our vision for regulation and governance

Other bodies have developed broad principles to underpin regulation. In the UK the Hampton Principles, and those developed by the Better Regulation Executive, are particularly relevant to the Academy’s review and focus on ensuring that regulation and its implementation is more risk-based.<sup>35,36</sup> However, respondents to the calls for evidence, and participants in the Patient and Public Involvement (PPI) workshop, were provided with an opportunity to consider their own priorities in the context of the UK environment for health research.

Based on the responses received we have developed a vision that incorporates the traditional functions of a regulator (in setting, monitoring and enforcing standards) with a desire to improve the regulatory and governance environment for patients and researchers (e.g. by providing clear and consistent guidance). This ideal system would achieve the following:

- Protect participants’ safety and promote high-quality health research.
- Apply regulatory and governance requirements in a way that is proportionate to the potential benefits and harms of the research.
- Raise research standards with an emphasis on promoting compliance rather than simply policing non-compliance.
- Outline clearly the roles and responsibilities of the various stakeholders.
- Have the authority and expertise to provide patients, clinicians, researchers and the public with clear guidance and advice.
- Be consistent (including across the UK), transparent and accountable.

- Be independent of Government.
- Provide a single point of entry and exit for research applications and enable all checks and approvals to be undertaken without duplication or causing unnecessary delay.
- Facilitate and encourage public and patient participation in research.
- Engender trust among all stakeholders including the public, the professions, healthcare providers and administrators.
- Enhance the UK's viability and attractiveness as a site for clinical trials, experimental medicine and epidemiological studies through ambitious and internationally competitive time-frames by which all regulatory and governance assessments must be completed.

The desire for a regulation and governance pathway that is proportionate to the risks and benefits of research was emphasised in many of the written submissions (Box 2.1). Respondents heavily criticised the largely one-size-fits-all' approach of the current system, which can distract attention from the most hazardous research and inhibit valuable, lower risk, research that could lead to better and safer interventions.

## 2.3 Principles

Our principles are intended to provide a benchmark by which to evaluate the current regulatory pathway and to reflect our vision when proposing changes to it. The principles should be considered together and a balance needs to be achieved to ensure they are met as fully as possible. There needs to be clarity and transparency on how this balance is met.

### ***Principle 1: safeguard the well-being of research participants***

This is the most important principle and deals directly with individual involvement in research. It enshrines the need to safeguard the well-being of research participants. The need to protect physical well-being is at the core of this principle, but it also recognises the need to safeguard the use of an individual's data or tissue.

Clearly, there are very different issues to be considered when assessing the physical well-being of individuals participating in, for example, a trial of a new drug compared with the use of anonymised patient data in an epidemiological study. A regulation and

### **Box 2.1 A proportionate approach to regulation and governance**

Health research provides benefits for patients and the public, but is also associated with potential risks. For some studies there may be a possible direct risk to a participant's physical safety. At other times, when research involves accessing an individual's personal data, additional care may be needed to uphold an individual's entitlement for confidentiality and, usually, the requirement for consent. It is important to recognise that there are also risks to the public associated with *not* undertaking research. Reliable evidence is needed to assess potential new treatments before they are used and to evaluate the most effective and safe application of interventions already in use.

In turn, the potential benefits of research will also vary and although a favourable benefit-harm balance is fundamental, the acceptable balance between benefits and risks varies. For example, a healthy individual would expect there to be minimal harm from volunteering to help study a new diagnostic test. In contrast, a patient with a life-threatening disease may be willing to accept some uncertainty to take part in a higher risk, first-in-man trial of a potential new medicine. It is important that the regulation and governance pathway recognises these differences and that, rather than focus simply on process, it is proportionate.

governance framework needs to be flexible enough to ensure that appropriate safeguards are in place across the spectrum of research studies.

Informed patient consent is essential to ensure that this principle can be met and should be a key component of a regulation and governance pathway - a point that was emphasised at the PPI workshop. In some circumstances, seeking consent is not possible or required (see Chapter 6) and in such circumstances there is a need to communicate to patients and the public the safeguards that are in place.

***Principle 2: facilitate high-quality health research to the public benefit***

This principle seeks to ensure that research is undertaken to the benefit of the public and wider society and recognises the harms caused by inappropriately prohibiting or delaying research. The regulation and governance system not only has a key role in protecting individuals participating in research but also in ensuring that they have the opportunity to gain advantage from innovative medical advances. Regulators must be accountable and ensure that they do not unnecessarily obstruct research. The regulatory system should ensure high-quality and reliable data are produced, captured and published – and that poor quality or fraudulent research is identified.

It is in the public's interest to have opportunities to take part in research if they wish to do so. The regulation and governance framework should support NHS organisations in offering all individuals the opportunity to become involved, if they are eligible, in a research study.

As discussed in Chapter 1, health research in the UK provides considerable economic benefits. For these to continue, the regulatory and governance environment must not create unnecessary barriers and should support and maintain a vibrant life sciences industry.

***Principle 3: be proportionate, efficient and coordinated***

The individual components of the regulation and governance pathway need to work in an integrated manner. The various checks and assessments need to be coordinated, with unnecessary and duplicated checks removed. The system should be cost-effective and continually improved through self-assessment, formal review, feedback, and opportunities to appeal decisions. The regulatory environment should be efficient and deal with the risks and benefits of research in a proportionate manner (see Box 2.1), i.e. characteristics that foster a system that can support and meet Principles 1 and 2.

***Principle 4: maintain and build confidence in the conduct and value of health research through independence, transparency, accountability and consistency***

This principle focuses on the importance of building confidence and trust in the conduct and value of research among patients, and the public, as well as across the NHS, industry and research community. The independence of regulatory bodies from Government is considered fundamental to meeting this principle, but all stakeholders involved in research have an important role to play.





## 3 Culture around health research

### 3.1 Introduction

As described in Chapter 1, health research involves a diverse range of stakeholders. They include the healthcare professions, patients and the public, non-commercial organisations such as the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) and health research charities such as Cancer Research UK and the Wellcome Trust. Universities, commercial organisations and the — as well as the various regulatory and governance agencies — are also critical elements of the research environment.

In this report we use the term 'culture' to refer collectively to the understanding, attitudes and behaviours that stakeholders demonstrate towards health research. The culture of these stakeholders — and their mutual interactions — is an important factor in the amount of research undertaken, and the efficiency and application of the regulation and governance pathway. Submissions to this review indicated a general perception that cultural barriers need to be broken down if the UK is to realise its research potential. Regulatory and governance bodies such as the National Research Ethics Service (NRES) and the Medicines and Healthcare products Regulatory Agency (MHRA) clearly play a leading role in setting the tone. The current approach taken by these bodies is described in later chapters. This chapter focuses on culture with regard to three groups: patients and the public, the NHS, and the research community.

### 3.2 Patients and the public

Patients and the public are essential partners in health research. In some cases it can be difficult to distinguish between 'patients' and 'the public'. The comprehensive nature of the

NHS means that most of the public can be considered patients because they are registered (and have records stored) with their GPs. This was described by one contributor to the review who simply referred to 'patients' and 'potential patients'. Patient groups play an increasingly significant role in research, particularly by increasing the recruitment of patients into clinical trials. Yet attendees at Patient and Public Involvement (PPI) workshop felt that such groups were still under used by other stakeholders in the research environment.

#### 3.2.1 Support for health research

At the broadest level, patients and the public have a vested interest in research. They contribute to its funding through taxes and by donations to health research charities. They also benefit from the advances of research and new knowledge and treatments it can generate. Although it is difficult to capture and communicate the range of public views on research, in general there is strong public support for health research in the UK:

- Large numbers of participants have been recruited to clinical trials and population studies. For example, the UK Collaborative Trial of Ovarian Cancer Screening<sup>37</sup> and UK Biobank<sup>38</sup> have recruited their targets of 200,000 and 500,000 individuals (respectively) with minimal objection to the use of their healthcare data.
- The attitudes of over 1,000 adults towards participating in health research were examined in the Wellcome Trust Monitor survey.<sup>39</sup> 71% of participants indicated that they would be willing to give blood or tissue samples for research and 62% were willing to test a new treatment for a disease from which they were suffering.
- Public engagement initiatives in relation to specific issues, such as the use of patient data, generally show that research is warmly supported (see Box 6.6).

38 For further information see <http://www.ukbiobank.ac.uk/>

39 Butt S, et al. (2009). *Wellcome Trust Monitor: survey report*. [http://www.wellcome.ac.uk/stellent/groups/corporatesite/@msh\\_grants/documents/web\\_document/wtx058862.pdf](http://www.wellcome.ac.uk/stellent/groups/corporatesite/@msh_grants/documents/web_document/wtx058862.pdf)

However, such support is not unconditional and public confidence could be damaged by actions that are perceived to be an abuse of the system. An effective regulation and governance system has an important role in building and maintaining public trust and securing a 'social licence' for health research.<sup>40</sup>

### **3.2.2 Engagement with health research and its regulation**

The general view of respondents and participants at the PPI workshop – and a view shared by the Academy – was that it is essential patients and the public:

- Understand the role and importance of research as an integral part of the care system.
- Inform the priorities, design, and implementation of research and the regulation pathway.

Respondents to our review considered it important that patients appreciate that high-quality clinical service in the NHS is underpinned by research – and that this research relies on the participation of patients, as well as access to their tissues and data. PPI workshop participants highlighted the importance of public communication about different types of health research.

In general, there was a consensus that a more sophisticated dialogue with the public is needed, where the 'rights' of patients to the best healthcare are discussed in the context of their 'responsibilities' towards improving the evidence upon which that healthcare is based. Establishing such a dialogue would enable the public to become genuine partners in the research process. It is our view that the public should be encouraged to consider the impact that their involvement in research could have on them as individuals, and on society as a whole. Organisations such as INVOLVE and the Association of Medical Research Charities (AMRC) have key roles to play in providing coordinated information for patients and the public on the role and benefits of health research (see Recommendation 1).

To be effective, regulation and governance should be informed by public views. Several of the responses highlighted areas where the current regulation and governance does not accurately represent majority opinion. For example, the Royal College of Pathologists' Lay Committee and attendees at the PPI workshop both considered the regulation around the use of tissue from living subjects to be disproportionate in relation to most patients' concerns (see Chapter 7). Attendees at the workshop felt that patients should routinely be offered the option that tissue excess to diagnostic requirements could be used for research.

There are a large number of organisations working to improve patient and public engagement with health research, including (but not limited to) UK Clinical Research Collaboration (UKCRC), INVOLVE, regulators themselves, the medical Royal Colleges, research charities and disease specific patient groups. However, there are other opportunities to increase patient and public involvement in regulatory and governance processes (see Chapter 9). Attendees at the PPI workshop emphasised the following:

- Patients should expect research to be an integral component of the NHS.
- Generating a national ambition and appetite for research should be seen as a responsibility of both the NHS, those who work in it, and patients.
- Patients should be seen as partners in the shaping, conduct and scrutiny of health research activity, as well as in its regulation and governance.
- Good communications and professional attitudes are fundamental to creating the right culture for research including issues around consent.
- Regulation and governance should support and remove barriers to – not hinder – patient participation and involvement in health research.

- Public involvement in the regulation and governance of research must be robust, well-informed and properly resourced.
- Any move towards the creation of a single research regulator (see Chapter 9) should not be at the cost of losing expertise and experience within the existing regulatory system.

*NHS. Research enables the NHS to improve the current and future health of the people it serves. The NHS will do all it can to ensure that patients, from every part of England, are made aware of research that is of particular relevance to them. The NHS is therefore putting in place procedures to ensure that patients are notified of opportunities to join in relevant ethically approved research and will be free to choose whether they wish to do so.*<sup>43</sup>

### 3.3 The NHS

Two groups of NHS staff play key roles in health research and its regulation:

- Healthcare professionals, who undertake many elements of health research (including patient recruitment, administering interventions, and collecting data).
- NHS Trust management, who provide oversight of research by granting permission for clinical studies that are sponsored, or hosted, by the Trust.

Mechanisms have been put in place in an attempt to implement these aspirations. For example, the NHS Operating Framework for 2009/2010 contained a target to double the number of patients involved in clinical trials. We are disappointed that this target is not included in more recent versions of the Framework, although since 2010 Trusts must include figures on patient recruitment as part of their Quality Accounts.<sup>44,45</sup> Trusts have also been encouraged to set goals for research in their organisation and to publish the average time it takes for the local research approval process to be completed.<sup>46</sup>

#### 3.3.1 Embedding research as a core NHS activity

The Academy has long championed the opportunities for UK research available through the NHS, and we welcome steps taken to embed research as core NHS activity (Box 3.1). The White Paper on the NHS in England, *'Equity and Excellence: Liberating the NHS'*, states that *'the Government is committed to the promotion and conduct of research as a core NHS role'* and the 2011/12 NHS Operating Framework highlights that *'continued research and the use of research evidence in design and delivery of services is key to achieving improvements in outcomes'*.<sup>41,42</sup> These reiterate the messages in the NHS constitution that *'Research is a core part of the*

It was clear from the PPI workshop that patients and their representatives see research as an integral part of the NHS, and some went so far as to suggest that the NHS should be renamed the *'National Health and Research Service'*. It will be vital to seize opportunities to enhance the culture of research among forthcoming changes to the structure of the healthcare system.

41 Department of Health (2010). *Liberating the NHS: legislative framework and next steps*  
[http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/@dh/@en/@ps/documents/digitalasset/dh\\_122707.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_122707.pdf)

42 Department of Health (2010). *The operating framework for the NHS in England 2011/12*.

[http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/@dh/@en/@ps/documents/digitalasset/dh\\_122736.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_122736.pdf)

43 Department of Health for England (2009). *The handbook to the NHS Constitution*.

[http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/@dh/@en/@ps/@sta/@perf/documents/digitalasset/dh\\_109785.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/@sta/@perf/documents/digitalasset/dh_109785.pdf)

44 Department of Health (2008). *The NHS in England: the operating framework for 2009/10*.

[http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_091445](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_091445)

45 Department of Health (2010). *The operating framework for the NHS in England 2010/11*.

<http://www.connectingforhealth.nhs.uk/systemsandservices/infogov/links/operatingframework2010-2011.pdf>

46 Department of Health (2009). *Requirements to support research in the NHS*.

[http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/documents/digitalasset/dh\\_102098.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_102098.pdf)

### Box 3.1 The National Institute for Health Research: strengthening clinical research.

Since the publication of the Academy report '*Strengthening Clinical Research*', in 2003, several important initiatives have been implemented.<sup>47</sup> The most significant has been the creation of the National Institute for Health Research (NIHR).<sup>48</sup> The NIHR aims to create a coherent 'health research system' by coordinating and funding research in the NHS in England.

The working group welcomes the considerable achievements of the NIHR in improving the clinical research environment in England. For example, the Clinical Research Networks have improved the conduct and delivery of research within specialties and increased participant recruitment levels. Recent data show that the National Cancer Research Network has contributed to a situation whereby one in every six cancer patients is involved in research.<sup>49</sup> This is the highest level in the world. We also welcome the parallel efforts of the devolved nations as well as the many instances of collaborative working across all four nations to facilitate UK wide studies.

There are some important examples of what can be achieved when the right framework and culture are put in place. The Northwest Exemplar (Box 4.1) is a programme that aims to demonstrate the improved clinical trial performance that is possible when the NIHR Clinical Research Network (CRN) works closely with partners in the pharmaceutical and biotechnology industries and across the NHS. Emerging findings from this initiative have indicated that the involvement of Trust Chief Executives, Industry Medical Directors and Network Clinical Directors has been the key to the initiative's success.

#### 3.3.2 Research culture among NHS staff

Despite the recent efforts outlined above, respondents to our review raised serious concerns about the approach to research among many NHS healthcare professionals, managers and administrative staff.

##### *Communicating the value of research*

Some responses indicated that healthcare professionals fail to understand the process of health research, its potential value, and the safeguards in place to protect patients. This

can hinder and restrict patient recruitment. Specifically, the National Cancer Research Institute (NCRI) Consumer Liaison Group was concerned that healthcare professionals can be 'paternalistic', too protective of patients, and potentially prevent them from participating in research studies. Such an approach conflicts with our Principles 1 and 2. It was perceived that healthcare professionals also lack the time and incentives to become involved in research. This was a source of considerable frustration to PPI workshop participants, summed up in the following remarks: '*We do research because that's how you get better treatment. I'd like to see that carved in stone above every hospital door*'; '*Research needs to be a core part of the NHS and a routine part of any first appointment letter – the NHS approach should be anticipatory that patients will want to take part in research*'.

There was a strong view expressed to the working group that the cultural disconnect with research is particularly prevalent in general practice and primary care. These settings could provide considerably greater opportunities for the engagement of a wider proportion of the

47 Academy of Medical Sciences (2003). *Strengthening clinical research*. <http://www.acmedsci.ac.uk/download.php?file=/images/publication/pscr.pdf>

48 For further information see <http://www.nihr.ac.uk/>

49 Cameron D, et al. (2010). *Four-fold increase in recruitment of cancer patients to NCRN portfolio studies between 2001 and 2010: a tale of investment bringing returns*. Presentation at NCRI Cancer Conference, 7-10 November 2010. <http://www.ncri.org.uk/ncriconference/2010abstracts/abstracts/PP39.htm>

population in health research. The opportunities and challenges of research in general practice were discussed at an Academy workshop held in 2008.<sup>50</sup>

#### *Embedding research in NHS processes*

It was clear from the call for evidence that respondents believe that a cultural step change is needed before research is treated as a core NHS activity throughout the UK. We hope that communicating the role of health research in the delivery and improvement of NHS care to healthcare and management staff at all levels in the NHS will go some way to address this (Recommendation 1). However, this needs to be complemented by steps to formally and irreversibly embed health research into NHS leadership and governance processes (Recommendation 2).

Respondents particularly emphasised the need for a change in the attitude and behaviour of NHS managers. Some perceived health research to conflict with managerial goals for service delivery because research requires key resources including staff time and access to facilities and equipment. This problem is compounded by the tensions between short-term NHS targets and the longer-term nature of research and its impact on clinical practice. Although clinical services are clearly a priority, it is important that NHS managers recognise that research is an essential component of good clinical services.

Recommendation 2 outlines several initiatives aimed at embedding research as a core function of the NHS. These include the need to address the current cultural and practical barriers around the provision of excess treatment costs (ETCs) (see also section 4.5.4). Studies attracting ETCs are those most likely

to change clinical practice and should therefore be supported. However, concerns within Trusts about recovering ETCs are a major barrier and a cause of significant delay to some non-commercial research. In theory, ETCs are covered by the commissioning budget but the mechanisms in place for Trusts to claim these costs are impractical and create a further disincentive for research. The provision of ETCs must be streamlined.

In addition to the initiatives outlined in Recommendation 2, the Academy has previously recommended that the UK's Clinical Excellence and Distinction Awards should be retained because of their important role in providing incentives to clinicians to devote time to research.<sup>51</sup> These Awards are currently under review and we recommend that the UK Health Departments should use the Awards to recognise contributions to the operational effectiveness of clinical studies in addition to the achievements of research leaders at the local level.

Cultural change in the NHS needs to be accompanied by a transformation in the approach taken to regulatory and governance checks within individual Trusts. NHS Trusts and primary healthcare sites have important responsibilities and liabilities around research whether they are acting as research sponsors or hosts. However, the prevailing risk-averse culture towards research leads to over-cautious approaches in many NHS Trusts. This is evidenced in the time taken to approve individual research studies and the duplication of minor checks and administrative processes. Chapter 4 focuses on how the current NHS R&D permissions process, identified in the evidence as the major bottleneck to health research in England, must be streamlined.

50 Academy of Medical Sciences (2009). *Research in general practice: bringing innovation into patient care*. <http://www.acmedsci.ac.uk/download.php?file=/images/publication/12569153801.pdf>

51 Academy of Medical Sciences (2010). *Response to the consultation for the review of compensation levels, incentives and the Clinical Excellence and Distinction Award schemes for NHS consultants*. <http://www.acmedsci.ac.uk/download.php?file=/images/publication/CEAconsu.pdf>

### 3.4 Researchers

Evidence received by the working group indicated that researchers themselves can be responsible for delays to approval processes, for example, by providing incomplete or incorrect applications. Indeed, the content of submissions to this review betrayed a lack of awareness among some researchers of the details of the current regulatory and governance pathway. Issues around the provision of suitable support for researchers to navigate the regulation and governance pathway are considered in other parts of this report, including Chapters 8 and 9. However, we strongly emphasise that it is essential for researchers to take responsibility for producing a correct and complete research application, using the guidance and support available to them.

Previous reports have noted that researchers are likely to complain about the burden associated with regulation and governance.<sup>52</sup> In some cases this criticism is justified. For example, respondents highlighted the unnecessarily demanding requirements

of some regulators including the rejection of applications due to minor deviations in document file names, or the need to submit empty documents (simply to 'tick a box') when the content is irrelevant to a particular study. Such inappropriate demands are a significant reason why researchers apparently fail to provide complete or correct applications.

We also recognise, however, that it is essential for researchers to understand the generic benefits that appropriate regulation and governance brings and the role it plays in building public confidence in research. They are sometimes poor at expressing the potential value and impact of their studies both to their colleagues and to the wider public. It is important that researchers take responsibility for clearly communicating these messages and to contribute to increased engagement in research among the public and the NHS. Research funders and other stakeholders – particularly the health research charities that act as a bridge between patients, clinicians and researchers – have an important role in helping to communicate the value of research in a responsible manner.

## Recommendations

*To support recommendations made throughout this report to improve the regulatory and governance pathway, cultural change is required within the NHS to embed health research as a core function, to foster a more facilitative approach to research governance and to promote public and patient engagement in research. All those involved in health research and its regulation have a role to play in supporting this culture change and in enabling the UK to realise its potential as a world leader in health research.*

**Recommendation 1:** The UK health departments, with the support of other government departments, should communicate the core role of health research to all NHS staff, and continue to work with organisations such as INVOLVE and AMRC to provide coordinated information for patients and the public about the role and benefits of health research.

**Recommendation 2:** To embed research as a core function in the NHS we recommend that:

- a. The Director General of NHS R&D should serve as a member of the proposed NHS Commissioning Board in England.
- b. Key metrics and indicators of research activity should be developed by the proposed new Health Research Agency (HRA) (Recommendation 13), in consultation with stakeholders, and included in the next NHS Operating Framework. These metrics should include timelines for assessment of local feasibility, delivery and recruitment under the new National Research Governance Service (NRGS) model (Recommendation 3). The use and publication of these metrics should allow the research performance of Trusts to be compared and scrutinised by the Trust Board, research funders and the public.
- c. An executive director of each NHS Trust should be responsible for promoting research within the organisation and report on current research activity (including metrics) at each Board meeting.
- d. Challenges around the definition and allocation of research costs remain a major disincentive for Trusts to engage in research. The forthcoming re-organisation of NHS commissioning arrangements provides an important opportunity to improve the provision of Excess Treatment Costs and remove the current difficulties this creates for non-commercial research.
- e. All those involved in training healthcare professionals, including the General Medical Council, the Nursing and Midwifery Council, the General Pharmaceutical Council, medical schools and the medical Royal Colleges, should ensure that the NHS workforce is aware of the important role of health research and equipped to engage with studies taking place in their Trust. This should include providing support to patients who are considering whether or not to participate in research.





## 4 NHS research and development

### 4.1 Introduction

Most UK health research involving patients is undertaken in the NHS and it is therefore crucial that the regulatory and governance processes in the NHS support the Principles outlined in Chapter 2.

As described in Chapter 3 the NHS is, to a large extent, still perceived to be a challenging and inconsistent research partner by both the academic and commercial research communities. In recent years, several initiatives have increased the standing of the NHS as a health research collaborator. The most significant improvements have resulted from the establishment of the NHS National Institute for Health Research (NIHR) in England (see Chapters 1 and 3). Significant investment in the research infrastructure has been complemented by new systems and processes to improve the mechanisms in place to assess and deliver research. Several of these initiatives, for example the creation of Comprehensive Local Research Networks (CLRNs)<sup>53</sup>, and an Integrated Research Application System (IRAS)<sup>54</sup>, are covered elsewhere in this report.

Despite some progress, the research potential of the NHS is largely unfulfilled. Research projects are being funded and granted the necessary ethics and regulatory approvals, but are then being significantly delayed or prevented because of the challenges in obtaining permission from the individual NHS Trusts involved. There was consensus in submissions from across all sectors that the current process of obtaining NHS R&D permission is the most significant barrier to health research in the UK, particularly for multisite studies. The process is cumbersome and bureaucratic with a focus on procedures rather than outcomes. This chapter describes the following problems that are endemic in the current system:

- Duplication and reinterpretation of checks by NHS Trusts that are the responsibility of national regulators such as the Medicines and Healthcare products Regulatory Agency (MHRA) and National Research Ethics Service (NRES).
- Inconsistency in the interpretation of checks, such as requirements to access patient data, among and within Trusts.
- Replication of study-wide checks by each individual Trust involved in the study.
- Lengthy negotiation of contracts and costings by each Trust.
- Lack of oversight of the NHS permission process and absence of a clear mechanism for an overall agreement to begin a multisite study.

The negative impact of this situation is felt by both commercial and non-commercial research organisations and across all research disciplines. There is a clear and obvious need for a step change in how NHS R&D permissions are granted. In this chapter we propose a new approach for R&D permissions and the creation of a new National Research Governance Service for England (NRGS). How this service will interplay with other aspects of the regulation pathway for health research is considered in Chapter 9.

### 4.2 Undertaking research in the NHS

Individual NHS Trusts vary significantly in their research activities. Trusts linked to leading teaching hospitals and universities are likely to initiate a larger proportion of research studies than those without such associations. To ensure that research can deliver benefits and meet the needs of all UK patients it is crucial that research takes place efficiently across the *entire* health service. This is especially important for research studies that are limited by the size of the patient population, e.g. for rare diseases. It is often the case that studies take place in

<sup>53</sup> For further information see <http://www.crnc.nihr.ac.uk/>

<sup>54</sup> For further information see <https://www.myresearchproject.org.uk/SignIn.aspx>

multiple countries to reach the numbers of patients required to achieve sufficient power. It is a significant loss to patients in the UK if, as suggested by the evidence, studies simply cannot recruit patients owing to delays in attaining NHS permission (see section 4.4.1) - with consequent reputational risk to the NHS as an effective clinical trial environment.

Each NHS organisation is a separate legal entity and has a legal duty of care for its patients. It is the view of NHS Trusts that fundamental elements of NHS R&D permission are not therefore transferable among NHS sites. This means that each NHS Trust is required to review and assess every research application. Before a Trust will grant R&D permission a series of checks are undertaken. From the perspective of an individual NHS Trust these checks can be categorised as addressing one of three issues:

- Is the Trust aware of the potential financial implications of the research and are suitable arrangements in place?
- Has the Trust made the necessary arrangements to support the activity and are the resources in place?
- Is the Trust aware of the potential impact of the research in terms of risk and are all the activities for which they are responsible compliant with the law?

The evidence submitted to this review suggests the approach taken by many NHS Trusts focuses overly on the third question, contributing to a risk-averse culture perpetuated by concerns around indemnity and harm. This mindset is perhaps understandable given the complexity of the regulation framework and uncertainty around the interpretation of certain guidance and legislation (see section 4.4.3). However, the approach taken by many Trusts appears to give priority to safeguarding the organisation over the potential benefits of research to patients and the public. This risk-averse approach is often described in the context of protecting patients, although there is no evidence that this attitude, which delays or stops research,

results in greater safety of patients and the public. The approach neither meets Principle 1 (safeguarding patients) or Principle 2 (promoting research for public benefit).

In practice, the three questions listed above are currently addressed for each individual research application at each Trust, by undertaking checks at the following levels (the examples provided reflect individual checks that are part of the current system described in section 4.3):

- Confirmation that external approvals, licences and authorisation have been granted. This involves reassessing, for example, that ethical approval has been granted (see Chapter 8) or that, where required, a clinical trial authorisation has been obtained (see Chapter 5).
- Undertaking a study-wide assessment of the suitability of the research to be conducted in the NHS. This looks at issues that are common across all sites involved in a study including, for example, is the researcher (or Chief/Principle Investigator) leading the study suitably qualified? Is study sponsorship in place with appropriate indemnity arrangements? Are the study-wide pharmacovigilance arrangements clearly described and appropriate?
- Checking the local arrangements at each individual Trust involved in a study. Local checks can be divided into the following:
  - An assessment of the local governance arrangements - for example, are local pharmacovigilance requirements in place? Is the research on that site in accordance with the Data Protection Act and NHS confidentiality policy? Are appropriate arrangements in place for the local research team?
  - An assessment of local delivery issues. This covers questions such as; are the local resources, equipment and facilities suitable for the study? Have all the relevant internal authorisations within the research site been granted from pharmacy or radiology departments?

There is no central body with responsibility for overseeing consideration of these issues and each NHS organisation currently provides permissions on a site by site basis. In the absence of top-down guidance as to how checks should be interpreted, Trusts have evolved their own processes leading to a diversity of approaches and a host of inconsistencies. The following section briefly reviews the current process before using the evidence, and case studies received, to describe the challenges this creates.

### 4.3 Gaining R&D permission: the current process

Each individual Trust involved in a study reviews the research and provides local R&D permission. This function is undertaken by Trust R&D offices. The current practices of R&D offices were developed in response to the Research Governance Framework (RGF) for Health and Social Care.<sup>55</sup> Introduced in 2004, the RGF requires NHS organisations to undertake a series of checks before granting local NHS permission. The manner by which the RGF was introduced, whereby each organisation implemented the principles at a practical level on an individual basis, has led to inconsistencies in the requirements of individual NHS Trusts (see section 4.4).

Systems currently in place to facilitate and support the R&D permission process do not remove responsibility from an individual Trust but attempt to seek approval across all Trusts involved in a study in a coordinated way. These processes include:

- Comprehensive Local Research Network (CLRNs): Each of the 25 CLRNs funds a research management and governance workforce whose role is to assist investigators in obtaining permission for their studies. The support of CLRNs

and other NIHR initiatives such as the Coordinated System for NHS Permission (CSP) are only applicable to NIHR Clinical Research Network (CRN) Portfolio research.

- NIHR Portfolio: In England, the Department of Health has determined that studies (clinical trials and other well designed studies which involve the NHS) that are funded by NIHR, other areas of Government, and specified NIHR non-commercial Partners are automatically eligible to be included in the NIHR Portfolio and gain support from CLRNs.<sup>56</sup> In England studies included in the NIHR Portfolio have access to infrastructure support and access to training courses on Good Clinical Practice (GCP).
- NIHR Coordinated System for gaining NHS Permissions (CSP). For studies on the NIHR Portfolio this provides coordinated provision of documents and sets out 37 checks to be undertaken. It separates CSP checks into:
  - Global governance checks, which are applicable to the study as a whole and should be undertaken once by a Lead CLRN.
  - Local governance checks that recognise that NHS permission is required at each site, and are assessed using a Site Specific Information (SSI) Form.
- NIHR Research Support Services (RSS). RSS is intended to complement CSP and: provide NHS Trust R&D Departments with guides to risk management, competencies and training needs, establish a monitoring system for collecting and publishing performance information and agree delivery timelines for use in the NHS.

It is clear from the evidence that as a result of these national initiatives, a few Trusts have developed more efficient local processes to grant NHS permission in a timely manner (see Box 4.1).

<sup>55</sup> Department of Health (2005). *Research governance framework for health and social care: second edition*. [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_4108962](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962)

<sup>56</sup> For further information see [http://www.crnc.nihr.ac.uk/about\\_us/processes/portfolio](http://www.crnc.nihr.ac.uk/about_us/processes/portfolio)

### **Box 4.1 North West Exemplar programme**

The North West (NW) Exemplar Programme sought to demonstrate that improved clinical trial governance is possible when the NIHR's Clinical Research Network works closely with partners in the pharmaceutical and biotechnology industries.<sup>57</sup> The Programme has fostered 20 industry sponsored studies that have been adopted by the NIHR Clinical Research Network running at sites in the North West Strategic Health Authority.

Data collected show that clear and open communication, together with streamlined processes, have been at the core of the Exemplar's success. As a result the median time from R&D form validation to NHS permission at the first site has reduced from 98 days to 53 days for Exemplar studies.

The North West Exemplar Programme has demonstrated that the NIHR infrastructure, coupled with direction from senior management, can lead to R&D staff working together with clinical staff to provide patients with the opportunity to benefit from health research studies. The Exemplar has helped to showcase the potential of District General Hospitals in delivering high-quality research.

#### **4.3.1 Differences across the devolved administrations**

Many of the processes described above are applicable to England only and different systems for obtaining R&D permission have evolved across the UK. This creates further complexity in obtaining R&D permission for UK-wide studies. All of the current systems require input from all participating Trusts or Health Boards and, for applicable studies, differentiate between 'global' (study-wide) and 'local' (site specific) permissions. Details on the system used in Scotland to coordinate NHS permissions across all Trusts is provided in Box 4.2.

The new model for facilitating NHS R&D approvals proposed at the end of this chapter (section 4.5) highlights the need for greater alignment across the UK and cooperation across the nations to facilitate a move towards a coordinated UK approach. This should build on lessons from the UK Wide Compatibility Group, a forum for discussion and resolution of issues related to NHS R&D permissions for cross border research.<sup>58</sup>

#### **4.4 NHS R&D permission: the major bottleneck in health research**

The great majority of submissions to this review identified problems with acquiring NHS R&D permission as the rate-limiting step in the regulatory and governance pathway. The following problems were highlighted:

##### **4.4.1 Delays and lack of timelines.**

A large number of respondents highlighted the long delays in obtaining NHS R&D permission for multicentre studies across participating Trusts. Submissions emphasised the variation in local processes by quoting the range in approval times:

- A submission from Kidney Research UK showed how, for one trial, time taken to receive R&D permission varied from around 5 to 29 weeks.
- A study of stroke survivors took between 1 to 35 weeks to receive permission from the various NHS Trusts involved.

### Box 4.2 NHS Research Scotland

NHS Research Scotland (NRS) is a collaboration between the Chief Scientist Office and the unified NHS Boards in Scotland.<sup>59</sup> Each of the four main university NHS Boards in Scotland are allocated responsibilities on behalf of the entire country, while NRS regional arrangements allow less research active NHS Boards to be linked to the four main Boards. The NRS Permissions Coordinating Centre coordinates the flow of R&D paperwork and permissions across Scotland for multicentre studies.

For generic R&D issues, permission is given by one NHS Board and this decision is accepted by all other Boards in Scotland. Both local and generic review timescales are closely monitored so that studies that might exceed the 30 day target time-frame are clearly identified. National performance metrics are published.

The NRS permissions 'clock' does not start until a complete document set has been submitted. The Chief Scientist Office recently published the NHS R&D permission times for July – September 2010, with the median permission time for non-commercial studies standing at 16 working days, and 15 working days for commercial studies.<sup>60</sup>

- The time taken between submission of site-specific information and NHS approval ranged from 5 to 50 weeks for a multicentre trial comparing two types of emergency intervention for ruptured aortic aneurysm (the IMPROVE trial).<sup>61</sup>

The key consequence of delays and unpredictability in the permission process is the negative impact this has on the ability to recruit patients and initiate trials. Respondents identified delays in NHS R&D permission as responsible for the following:

- Shortening the window of opportunity for recruitment, owing to it taking several months to approve a trial.
- Pharmaceutical companies reducing their target for patient recruitment in the UK because of the difficulties in getting trials started.
- Many multi-national trials not having a UK site owing to the inefficiency in recruitment of patients as a result of the lengthy NHS R&D permissions process.

Significant delays can also lead to trials being cancelled and the loss of associated benefits for patients and the UK.

#### 4.4.2 Duplication of checks

A major cause of delay is duplication of effort with each Trust rechecking, for example, whether the study has appropriate ethical approval or whether approval to access patient data has been granted. Evidence suggests that duplication is occurring in the following areas:

- Individual Trusts each rechecking the same issues across a multisite study.
- Duplication of aspects of approvals and authorisations that are the responsibility of organisations such as NRES or MHRA.

For studies in England, CSP was intended to reduce these problems.<sup>62</sup> Although CLRN is supposed to undertake 'global' checks just once, the evidence suggests this is not the case and that 'global' checks are being repeated locally (see Box 4.3). Many respondents also highlighted that CSP has contributed to a 'two-tier' system as it is only available for NIHR

59 For further information see [http://www.nhsgrampian.org/nhsgrampian/nrspcc.jsp?pContentID=7170&p\\_applic=CCC&p\\_service=Content.show&](http://www.nhsgrampian.org/nhsgrampian/nrspcc.jsp?pContentID=7170&p_applic=CCC&p_service=Content.show&)

60 Chief Scientist Office, Scotland (2010). *Research matters. Newsletter of the Chief Scientist Office.*

<http://www.scotland.gov.uk/Resource/Doc/334432/0109346.pdf>

61 The IMPROVE Trial Management Committee (2010). *Getting research in the NHS started.* The Lancet **375**, 2072.

62 For further information see [http://www.crncc.nihr.ac.uk/about\\_us/ccrn/bbc/rmg/NIHR+Coordinated+System+for+gaining+NHS+Permission+\(NIHR+CSP\)](http://www.crncc.nihr.ac.uk/about_us/ccrn/bbc/rmg/NIHR+Coordinated+System+for+gaining+NHS+Permission+(NIHR+CSP))

Portfolio studies. There is a need to build on the principles underpinning CSP and further revise the process for undertaking study-wide or 'global' checks. This should be achieved in England by establishing a common process for all studies and providing clear advice to all Trusts that all licences and authorisations that are the responsibility of regulators outside of the NHS are in place (see Chapter 9), and by providing a new mechanism to ensure single and consistent assessment of all study-wide checks (see section 4.5).

Duplication within the current system also involves the repetition of certain 'checks' on an application-specific basis. Current examples include the need to check, each time research is undertaken at a site, whether certain site licences are in place, or whether a Criminal Record Bureau certification is held each time a researcher leads on a study.

### **Box 4.3 Coordinated system for NHS permission (CSP)**

Many respondents highlighted the positive objective of CSP and its attempts to streamline the R&D approval process. However, there were variable reports on how well CSP has worked in practice owing to the following:

- Continued repetition of 'global' checks.
- Inconsistencies and lack of clarity from R&D departments in relation to the interpretation of research governance principles.
- Lack of timelines and long delays in providing approvals.
- Lack of transparency (e.g. researchers not being made aware of easy to address issues), leading to unnecessary delays in obtaining Trust management approval and recruitment.
- Limited number of IT software accounts, leading to delays.

A submission from one leading university suggested that the introduction of CSP had increased workload fourfold to sixfold and extended the approval process for each study by an average by 10 days. In contrast, Cancer Research UK has worked with the NIHR Clinical Research Network Coordinating Centre to evaluate the impact of CSP and found the time taken to obtain all relevant regulatory approvals (equivalent to 'NHS permission') had fallen from an average of 250 days to 75 days in the first year of CSP. This research was, however, based on early data from only seven trials, some of which will have been clearly over the average time of 75 days. Furthermore, the qualitative findings from this study echo some of the concerns highlighted above.

The CSP Unit has worked with stakeholders to identify areas in need of further improvement and provided the Academy's review with an overview of activities to be undertaken between October 2010 and March 2011, including the following:

- The need to reduce the number of checks in CSP substantially (by at least 10).
- Ensuring that global checks address problems once and draw on responsive expert advice.
- Simplifying the process for handling amendments through CSP.
- Developing a proportionate approach to the use of site specific information forms, principle investigator authorisations and provision of CVs, using a matrix for defining proportionate review appropriate to the study type and nature of activities at site.

Respondents to the call for evidence highlighted the potential for these 'generic' issues (that are not study specific because they differ between protocols) to be dealt with by accreditation or through statements from Trusts on their local arrangements and capabilities. Removing some of these issues from the standard R&D permission process was identified as a real opportunity for streamlining the system and reducing timelines.

#### **4.4.3 Lack of consistent advice and interpretation**

As currently interpreted, the roles of R&D offices include a diverse selection of responsibilities ranging from checking external regulatory requirements, funding and contractual arrangements, supporting research applications and the production of reports on recruitment.

Much of the local variation in individual Trusts and duplication and delays described above appears to be due to uncertainty and variation in how requirements and legislation are interpreted. Examples include the following:

- Local discussion of contracts and costing (see section 4.4.6).
- Uncertainty around requirements to access patient data for research (see Chapter 6).
- Inconsistency in interpretation of the requirements for compliance with Good Clinical Practice (GCP) inspections. Combined with the approach taken by some GCP inspectors, the preparatory work required for an inspection – not to mention the anxiety caused by the actual and perceived requirements – is a major factor in contributing to the risk-averse approach within the NHS (see 5.5.4).

One submission from an international medical technologies company suggested that an application had been delayed by 10 weeks at one Trust, owing to confusion around the completion of a data protection form. When the applicant tried to explain how the issue had been resolved elsewhere the data protection

officer responded by stating that how other Trusts viewed and dealt with data protection issues was immaterial. As stated in Chapter 6, advice and guidance on data issues is currently fragmented, however, it is unacceptable that individual Trusts interpret legislation such as the Data Protection Act in a varied and inconsistent manner.

#### **4.4.4 Variation in performance across Trusts**

In the context of the current system, it is understandable that the roles of local R&D staff are complex and challenging. However, local variation is a major contributing factor to the challenge of obtaining NHS permission across a multi-site study. In addition to the variation experienced in the interpretation of individual checks, some respondents commented on the varying quality of some Trust R&D offices and highlighted examples of poor communication between R&D offices and local participating Trusts.

In one evidence submission, an academic clinical trial unit stated that for every multicentre study that has been set up in the past three years, there were several R&D offices which delayed the process because of lost documentation. In one case a trial monitor from the unit visited an R&D office to help staff search for missing documents. Other respondents reported problems including a poor understanding of the relevant regulations, high staff turnover with inadequate handover and uncertainty about what should be reviewed leading to requests for irrelevant documents.

#### **4.4.5 Inconsistency in the process.**

Lack of clarity and knowledge leads to some organisations introducing systems over and above those required. As many studies are multicentre, and some are cross-border, significant time and funding is wasted negotiating the different systems. The evidence identified inconsistency in areas such as issuing Honorary Contracts for staff. One CLRN explained how they have developed



a centralised policy for issuing Honorary Contracts for 12 NHS Trusts and three higher education institutions that is considered by researchers to work well. However, there is a lack of consistency across CLRNs, with some sites not implementing the Research Passport Scheme.<sup>63</sup> As previously stated, several submissions to the review highlighted the variation caused by some Trusts adopting a different assessment process for Portfolio and non-Portfolio studies, leading to a 'two-tier' system. The review was provided with examples of instances where Trusts had refused to participate in a clinical trial because it had not been adopted by NIHR.

#### **4.4.6 Local negotiation of contracts and costs**

A common cause of delay described by respondents concerned local negotiations and disagreements around contracts and costings. One example provided by the British Heart Foundation was the PATHWAY study (Prevention And Treatment of resistant Hypertension With Algorithm based therapy). This study took more than a year to begin because of delays in governance and funding issues. The study involves three clinical trials in eight centres (five based in England and three in Scotland). The longest delays occurred in agreeing the contracts between the lead site at the University of Cambridge and seven of the other centres. Some sites wanted separate agreements for each trial, amounting to 21 contracts for the University of Cambridge to prepare for just one grant.

The evidence also identified that there is a lack of clarity around research costing. Uncertainty about what constitutes a research cost, an excess treatment cost and service support cost continues to delay progress (see section 4.5.4).

## **4.5 The creation of a new National Research Governance Service (NRGS)**

The current process for NHS R&D permissions highlights a fundamental tension between the concept of a 'single standardised system' (which is desirable from the point of view of speed and efficiency in trial set-up), and the reality of an NHS structure which devolves responsibility, including the legal duty of care, to individual NHS Trusts. Many of the issues experienced by respondents result from this unresolved tension. The NIHR have previously stated, '*Lack of standardised systems and processes, as well as the lack of an agreed risk-based approach to granting permissions and managing research projects, has led to inconsistencies when interpreting the principles set in the RGF and relevant legislation, such as the Human Tissue Act.*'<sup>64</sup>

A new approach needs to be taken to eliminate the heterogeneity of Trust activity and the following sections outline a more streamlined process for NHS R&D permissions.

### **4.5.1 Roles and responsibilities: a streamlined system**

We recommend that a new National Research Governance Service (NRGS) should be established in England. The NRGS would be a core component of the proposed new Health Research Agency (HRA) described in Chapter 9. The NRGS would reduce the bureaucracy and increase the speed of NHS R&D permissions by replacing multiple, inconsistent checks by individual NHS Trusts, with a single, consistent, efficient process for obtaining NHS R&D permission (see Recommendation 3). The creation of the NRGS should be a priority to maximise the benefits of changes elsewhere in the regulation pathway and to ensure the NRGS is fully integrated in the new HRA from the outset. The NRGS would:

63 For further information see [http://www.nihr.ac.uk/systems/Pages/systems\\_research\\_passports.aspx](http://www.nihr.ac.uk/systems/Pages/systems_research_passports.aspx)

64 NIHR (2010). *Best research for best health. Implementation plan 4.1g. Bureaucracy busting: research support services.*

[http://www.nihr.ac.uk/files/pdfs/Implementation%20Plan%204.1g%20Bureaucracy%20Busting.%20NIHR%20Research%20Support%20Services%20\(PDF\).pdf](http://www.nihr.ac.uk/files/pdfs/Implementation%20Plan%204.1g%20Bureaucracy%20Busting.%20NIHR%20Research%20Support%20Services%20(PDF).pdf)



- Perform all study-wide NHS governance checks once, ensuring consistent national standards and clear and consistent interpretation of requirements for compliance.
- Recommend research projects as suitable for undertaking in the NHS, subject to assessment by Trusts of local feasibility and delivery.
- Maintain up-to-date records on NHS staff that are appropriate to conduct research studies, including whether they have passed Criminal Records Bureau (CRB) checks.
- Introduce timelines for providing NHS R&D permission.
- Provide model agreements and agreed costing structures.

Individual NHS Trusts would then need to undertake local checks to assess feasibility and delivery, and to confirm their willingness to participate in a study, within – we propose – 20 working days. By transferring all study-wide checks to the NRGs, the function of Trust R&D offices would evolve to focus on monitoring local capacity, performance and conduct. The publication of metrics on research activity is a key aspect of this shift in approach (see Recommendation 2b and section 4.5.2).

In implementing this new model consideration should be given to the role of regional research ‘representatives’ to build confidence in, and understanding of, the centralised element, and to support Trusts in implementing procedures to streamline local assessment and delivery.

Current initiatives designed to improve R&D permissions are progressing through encouragement and consensus, but lack a real driver. The NRGs would provide clear guidance and leadership on a new permission process for studies in England, including NIHR Portfolio and non-Portfolio studies. The NRGs should work with systems in the devolved nations to establish a mechanism to achieve UK wide permissions. To this end, many respondents highlighted the success of NRES

in achieving close working and a memorandum of understanding between the national systems across the UK.

This new model would complement recent investment and allow, for example, CLRN to focus on supporting high-quality research and recruiting patients. Alongside the recommendations made in Chapter 9, the creation of the NRGs would clearly separate issues and decisions around:

- Funding and infrastructure (NIHR).
- Local capacity, monitoring and delivery (NHS Trusts).
- Study-wide checks and oversight of the NHS permissions process (NRGs).
- Regulation, licences and authorisations (the new HRA, see Chapter 9).

#### **4.5.2 Incentives and metrics**

The NIHR should develop a system to formally assess the performance of Trusts in approving and carrying out research when allocating funding. The process should be transparent and metrics should be published on Trusts’ research activities, including use of the streamlined NRGs model and timelines for assessment of local feasibility, delivery and recruitment. The failure of Trusts to provide prompt and reasonable local R&D approval should be formally considered when assessing participation in wider NIHR initiatives or providing support to Trusts for research (see Recommendation 4). Chief Executives of NHS Trusts should be closely involved in the design of the NRGs model to ensure it addresses their concerns and removes some of the existing disincentives to undertaking research.

#### **4.5.3 Indemnity**

It is our understanding that the NHS Litigation Authority has received no claims relating to research. However, we understand that a fear of litigation persists within the NHS and contributes to a risk-averse approach and a lack of confidence in checks undertaken by others. The success of our new model is dependent on

individual Trusts having confidence in the NRGS and delegating the responsibility for study-wide checks. Trusts, through providing confirmation of local governance and feasibility, would grant final NHS permission, in line with their legal duty of care for patients.

One of the possible mechanisms for cementing this division of roles would be to ensure clarity on responsibility for different aspects of research indemnity so that there is confidence that:

- If research causes harm due to errors in the permission process this is the responsibility of the regulator (in our proposed model this would be the new Health Research Agency).
- If research causes harm through negligence of staff, this is a Trust responsibility (in the same way that clinical negligence is covered by the existing Clinical Negligence Scheme for Trusts).
- If research causes harm through poor design or conduct of the study this is the responsibility of the sponsor.

#### **4.5.4 Contracts and costing of research**

The NRGS would support Trusts in providing an efficient assessment of local feasibility and delivery by providing model agreements, templates and agreed costing structures. The development of a model Clinical Trial Agreement for commercial research has greatly streamlined the processes for industry-sponsored studies and the use of a similar approach for non-commercial research would be of significant benefit.

Many researchers have highlighted the problems faced when attributing costs to non-commercial clinical studies, with various Trusts using different cost tariffs, leading to negotiation and delays. The costs of R&D in the NHS are currently split into three categories:<sup>65</sup>

- Research costs, which: are the costs of R&D itself and *'include the costs of data collection and analysis...and can include the pay and indirect costs of staff employed to carry out the R&D'*.
- NHS Support costs, including the additional patient-related costs associated with the research, which would end once the R&D activity has stopped, even if the patient care continues to be provided.
- Treatment costs, which are the patients' costs and which would continue to be incurred if the patient care service in question continued to be provided after the R&D activity had stopped. Excess treatment costs (ETCs) are the difference (if any) between the total treatment costs and the costs of the standard treatment.

Commercial studies pay ETCs but, as highlighted in section 3.3.2, difficulties in accessing funds to cover ETCs are a major barrier to undertaking non-commercial research.

The forthcoming re-organisation of NHS commissioning arrangements provide a timely opportunity to address this (see Recommendation 2d).

## Recommendations

*Obtaining NHS permissions was identified as the single greatest barrier to health research and the rate-limiting step in most studies. Changes are needed to reduce bureaucracy and increase the speed of NHS R&D permissions by replacing multiple, inconsistent, slow checks by individual NHS Trusts, with a single, consistent, efficient process for the NHS as a whole. We therefore recommend that:*

**Recommendation 3:** A new National Research Governance Service (NRGS) should be established as a core component of the new Health Research Agency outlined in Chapter 9. The NRGS should be created as a matter of urgency, to oversee a streamlined, common process for NHS R&D permission for all single and multi-site studies in the NHS in England. The NRGS should provide clear guidance and leadership on a new permission process, including clarity on different aspects of research indemnity. The NRGS would:

- Undertake all study-wide NHS governance checks, ensuring consistent national standards and interpretation of requirements for compliance.
- Recommend research projects as suitable for undertaking within the NHS subject to local assessment of feasibility and delivery.
- Facilitate new R&D timelines that would require participating Trusts to determine local feasibility within 20 working days.
- Maintain up-to-date records on NHS staff to confirm their competence to conduct research, and that, for example, they have the expertise and accreditation relevant to their role in the study and have passed Criminal Records Bureau (CRB) checks.
- Issue model agreements and provide clarity on research costs and payment.

**Recommendation 4:** The National Institute for Health Research should develop a transparent system to formally assess the performance of Trusts in approving and undertaking research and use this to inform its funding allocations.



## 5 Clinical trials of investigational medicinal products

### 5.1 Introduction

Clinical trials are used to assess the safety, efficacy and effectiveness of therapeutic and public health interventions. This chapter focuses on Clinical Trials of Investigational Medicine Products (CTIMPs), as defined by the EU Clinical Trials Directive (CTD), because respondents identified this legislation and its implementation in the UK as a significant barrier.

CTIMPs currently included within the scope of the CTD are a group encompassing trials at different phases of drug development, with a variety of sponsors and host organisations. Sponsors include commercial and non-commercial organisations; data provided to our review show that in the UK in 2009-10 75% of studies requiring clinical trial authorisations were sponsored by industry.

The generalised differences between the aims, activities and level of resource of commercial and non-commercial (e.g. charitable, hospital, academic or public sector) sponsors of clinical trials mean that they are affected by clinical trial regulation in different ways. Despite the differences between the sectors, many of the concerns raised around regulation of these studies are common to both.

This chapter examines concerns about the CTD itself (sections 5.3 and 5.4), as well as issues arising from the incorporation of the Directive into UK law and its interpretation by the Medicines and Healthcare products Regulation Agency (MHRA) (section 5.5).

### 5.2 Current environment overview

#### 5.2.1 European legislation

The European Clinical Trials Directive (2001/20/EC) (CTD or 'the Directive') was introduced in 2001 in an attempt to simplify and harmonise the administration of clinical trials of drugs across Europe.<sup>66</sup> The Directive sets out the laws, regulations and administrative requirements of the Member States relating to the conduct of clinical trials on medicinal products for human use and was intended to:

- Protect the health and safety of clinical trial participants.
- Improve the ethical soundness of clinical trials across the EU.
- Ensure the reliability and robustness of data generated in clinical trials.
- Simplify and harmonise the administrative provisions governing clinical trials to allow for cost-efficient health research.

Clinical trials must be undertaken in accordance with an appropriate standard of Good Clinical Practice (GCP). The CTD and associated GCP Directive (2005/28/EC) set out standards for GCP in CTIMPs. The GCP Directive states that the '*conditions and principles of GCP which apply to all clinical trials*' are '*based on*' International Conference on Harmonisation guidelines on GCP (ICH-GCP).<sup>67,68</sup>

#### 5.2.2 The UK regulatory body: the Medicines and Healthcare products Regulatory Agency (MHRA)

The MHRA is an Executive Agency of the Department of Health and has a wide range of functions, including authorising medicines for sale in the UK and post-marketing safety monitoring.<sup>69</sup> The focus for this review is on the MHRA's role in regulating clinical trials of medicines.

66 European Commission (2001). *Clinical Trials Directive 2001/20/EC*. [http://ec.europa.eu/health/files/eudralex/vol-1/dir\\_2001\\_20/dir\\_2001\\_20\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf)

67 European Commission (2005). *Good clinical practice directive 2005/28/EC*. [http://ec.europa.eu/health/files/eudralex/vol-1/dir\\_2005\\_28/dir\\_2005\\_28\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-1/dir_2005_28/dir_2005_28_en.pdf)

68 International Conference on Harmonisation (1996). *Guideline for good clinical practice*. [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6\\_R1/Step4/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf)

69 For further information see [http://www.dh.gov.uk/en/Aboutus/OrganisationsthatworkwithDH/Armslengthbodies/WhatareALBs/DH\\_063385](http://www.dh.gov.uk/en/Aboutus/OrganisationsthatworkwithDH/Armslengthbodies/WhatareALBs/DH_063385)

The CTD was implemented in the UK as the Medicines for Human Use (Clinical Trials) Regulations (2004). The MHRA is the UK's designated National Competent Authority (NCA) for the implementation of this legislation and its role includes authorising and monitoring CTIMPs, as described in Annex I. In 2009-10 the MHRA received 252 applications for clinical trial authorisations for phase I CTIMPs and 842 for other CTIMPs. The MHRA's services for clinical trial regulation are operated on a cost recovery basis by charging fees.

### 5.3 The impact of the Clinical Trials Directive

Some respondents to the review noted that the Directive has played a role in increasing standards in non-commercial trials, which were previously exempt from MHRA regulation through the 'Doctors and Dentists Exemption' scheme. We outline how the implementation of the Directive catalysed improvements to the UK ethics system in Chapter 8. However, most respondents from both the commercial and non-commercial sectors reported that many of the impacts of the Directive have been negative. Compliance with the Directive has increased the administrative burden and cost of clinical trials for both non-commercial and commercial sponsors with no discernible improvements to patient safety or to the ethical basis of clinical trials.

The EU-wide Impact on Clinical Research of European Legislation (ICREL) study sought to measure the impact of the Directive on key stakeholders between 2003 and 2007.<sup>70</sup> The ICREL study was not without limitations, but reported that ethics committees, as well as commercial and non-commercial sponsors, observed an increase in workload over this period. For example, non-commercial sponsors

responding to the survey indicated that the number of full-time equivalent staff required to manage administrative tasks associated with the clinical trial application has almost doubled from 1.5 to 2.8, with a similar increase in staff associated with pharmacovigilance. The survey also found that after implementation of the Directive, commercial and non-commercial sponsors saw an increase in the time between finalisation of the protocol and first patient recruited, from 115 to 152 days and 144 to 178 days respectively. Furthermore a Cancer Research UK study indicated that the Directive resulted in a doubling of the cost of running non-commercial cancer clinical trials in the UK, in addition to delaying the start of trials.<sup>71</sup>

It is difficult to establish the impact that the Directive has had on the number of studies taking place in Europe, because the Directive has changed the way in which some trials are authorised and no comparable data are available for the period before 2004. MHRA statistics show that the number of clinical trials authorised was stable at around 1,100 to 1,200 per annum between 2004 and 2008, although more recent data indicate a decline in the annual number of authorisations since 2008.

The inadvertent negative impacts of the Directive are now widely recognised and the Directive is currently under review by the EU Commission. The Academy responded to the Commission's public consultation in January 2010 both independently and as part of the Federation of European Academies of Medicine.<sup>72,73</sup> The Commission published a summary of responses to its consultation in March 2010.<sup>74</sup> This showed that although some respondents considered that the Directive had resulted in benefits, most agreed there had been a negative impact on commercial and non-commercial studies.

70 EFGCP (2009). *Impact on clinical research of European legislation*. [http://www.efgcp.be/downloads/icrel\\_docs/Final\\_report\\_ICREL.pdf](http://www.efgcp.be/downloads/icrel_docs/Final_report_ICREL.pdf)

71 Hearn J & Sullivan R (2007). *The impact of the Clinical Trials Directive on the cost and conduct of the non-commercial cancer trials in the UK*. *European Journal of Cancer* **43**, 8-13.

72 Academy of Medical Sciences (2010). *Response to the European Commission consultation on the Clinical Trials Directive 2001/20/EC*. <http://www.acmedsci.ac.uk/download.php?file=/images/publication/ECTDcon>

73 Federation of European Academies of Medicine (2010). *Response to the European Commission consultation on the Clinical Trials Directive 2001/20/EC*. <http://www.acmedsci.ac.uk/download.php?file=/images/publicationDownload/FEAMresp.pdf>

74 For further information see [http://ec.europa.eu/health/human-use/clinical-trials/developments/responses\\_2010-02\\_en.htm](http://ec.europa.eu/health/human-use/clinical-trials/developments/responses_2010-02_en.htm)

### **5.3.1 Inconsistent implementation across Member States**

The Directive was designed to harmonise requirements across the European Union. However, it is widely acknowledged both within and outside the European Commission that the Directive has been inconsistently implemented across Member States. One explanation for this is that although individual Member States were given 36 months to transpose the Directive into national legislation, detailed guidance was only issued by the Commission a month before the deadline. By this time many Member States had already made their own legislative provisions.

The evidence received by the Academy included examples of inconsistencies among Member States both in assessing clinical trial authorisation and in ongoing study requirements, including differences in whether a study was deemed to be within the scope of the Directive:

- Investigators running a non-CTIMP study in France sought to collaborate with a UK university and to expand the study to include a UK site. However, the MHRA considered the study to be a CTIMP, which raised logistical issues because the study was not being run as a CTIMP in France. Because these issues could not be resolved, the study could not be run in the UK.
- A study on nutrition formula for intravenous feeding of newborn babies used in standard clinical practice in the UK was deemed to be a CTIMP in the UK but not in the Netherlands.
- A CTIMP assessing combination chemotherapy in Hodgkin's Lymphoma was considered to include 14 investigational medicinal products (IMPs) in some Member States but only to involve two IMPs in another.

Inconsistencies between Member States increase the complexity of conducting multinational trials with associated increases in time and cost. It is difficult to quantify the

additional resources required to overcome these differences, but the impact is felt by both the commercial and non-commercial sectors. The Academy received several submissions from academic organisations who are now reluctant to initiate multinational studies because of these difficulties.

In light of the problems in obtaining authorisation for multiple Member States, the EU Heads of Medicine Agency Clinical Trials Facilitation Group (CTFG) has developed the Voluntary Harmonisation Procedure (VHP) in an attempt to harmonise and improve the process of obtaining approval from multiple Member States. VHP can be used for studies involving three or more Member States and involves a 30 day initial assessment in individual countries, after which the VHP coordinator at the CTFG collates this information and initiates a teleconference to resolve areas of disagreement. Applications that are considered acceptable are then sent for national assessment with relevant NCAs with a cover note indicating that it was considered appropriate for approval by the participating Member States.

In its response to the European Commission consultation, in January 2010, the MHRA supported VHP as the most suitable mechanism to streamline the authorisation process for multi-country trials. However, the VHP will not reduce inconsistencies in ongoing study requirements and although additional guidance might partly address this, other legislative revisions will be required to remove inconsistencies between Member States' interpretations of the provisions of the Directive.

### **5.3.2 Lack of clarity in definitions in the Directive**

The lack of clarity in some of the definitions included in the Directive is a major contributing factor to its inconsistent implementation across Member States.

In responses to the call for evidence, commercial and non-commercial organisations raised the concern that where regulatory requirements are not clear, sponsors may go above and beyond requirements of the Directive to ensure that they are compliant. This type of 'over-implementation' of the Directive incurs costs and takes more time, as well as creating additional work for the main Research Ethics Committee (REC) for the study (see Chapter 8) and the MHRA. A good example relates to 'substantial amendments'. These are amendments likely to have a significant impact on the safety or physical or mental integrity of the subjects or the scientific value of the trial. They might include changes in the dose, the way an IMP is administered, or new data on an IMP that are likely to impact on the risk assessment. Responsibility lies with the sponsor to decide whether an amendment is substantial and to act on this decision. Evidence received suggests that sponsors err on the side of caution in applying the definition. Other areas in urgent need of clarification include the definitions of 'Suspected Unexpected Serious Adverse Reactions' (SUSARs) and 'investigational medicinal products' versus 'non-investigational medicinal products'.

The European Commission has recognised the issues caused by a lack of clarity in some of the definitions and is issuing new guidance to address the problems, for example on 'substantial amendments' and SUSARs, as an interim measure before the Directive is revised. It is not yet clear to what extent the new guidance will resolve these problems.

## 5.4 Improving the legislative environment

To resolve many of the general concerns with the Directive and to overcome its negative impacts, we strongly support the need for thorough revision of the Directive as set out in Recommendation 5.

In addition, our first call for evidence identified specific concerns that fall into three main categories: the broad scope of the Directive, its 'one-size-fits-all' approach and duplicative safety reporting requirements. The following sections discuss these problems in further detail.

### 5.4.1 Scope

The scope of the Directive was primarily intended to regulate studies examining the safety and efficacy of an IMP. Articles 2(a), (c) and (d) define 'clinical trial', 'non-interventional trial' and 'investigational medicinal products' (Box 5.1). Strict interpretation of these definitions, as applied in the UK, makes the scope of the Directive very broad. For example studies that involve randomisation of participants, or a minimal additional intervention, such as an imaging procedure or taking an additional blood sample, are considered to be CTIMPs even where the product is used under the terms of its marketing authorisation. For example, a study of anti-Tumour Necrosis Factor therapy was designated as a CTIMP because of the addition of a brain scan, despite the fact that the product was being administered according to routine clinical practice. The specific interpretation of the scope of the Directive in the UK is discussed in section 5.5.1.



**Box 5.1 Articles 2(a), (c) and (d) of the Clinical Trials Directive 2001/20/EC:**

The scope of the Clinical Trials Directive is set by the definitions in the following articles:

2(a) 'Clinical trial': any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s) (IMP), and/or to identify any adverse reactions to one or more IMP and/or to study absorption, distribution, metabolism and excretion of one or more IMP with the object of ascertaining its (their) safety and/or efficacy.

2(c) 'Non-interventional trial': a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.

2(d) 'Investigational medicinal product': a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

The consequences of being defined as a CTIMP, discussed in section 5.4.2, can be challenging for some types of study. The designation of studies as a CTIMP can therefore act as a disincentive to undertake these types of study. However, assessing a treatment strategy using minimal intervention and strategies that make simple studies more robust, such as randomisation, should be encouraged because they will contribute to the evidence base to inform future clinical practice. Inappropriately obstructing these is therefore in conflict with Principle 2 (facilitating research for public benefit).

Recommendation 5(a) calls for a reduction in the scope of the Directive to avoid the inclusion of any studies simply on the basis of methodology. The definitions in Article 2 should be amended to clearly identify which products are intended to be included in or excluded from the scope of the Directive.

**5.4.2 Lack of a proportionate approach**

The requirements of the Directive apply equally to a wide spectrum of studies, including the following: the first use of a new product in humans; testing products with a marketing authorisation for a new indication; and even studying products available without prescription. The requirements for all studies that fall within the scope of the Directive include:

- Special arrangements for the handling of IMPs, including labelling and storage.
- GCP requirements which may exceed those expected during routine care.
- Detailed safety reporting requirements.

These 'one-size-fits-all' requirements are not always proportionate to the risks of a study and this exacerbates the problems caused by the broad scope of the Directive.

Some products tested in clinical trials are already licensed and routinely used for both licensed and unlicensed indications. For these products, an understanding of their safety profile means the risks to participants can be well-managed and in many cases will be no greater than those associated with routine care. Drug storage requirements, such as 24-hour temperature monitoring, are widely cited as an example of unnecessary demands imposed on some types of trial. For example, the IMP in the CRASH-2 trial, tranexamic acid, is licensed with no special storage requirements. However, because GCP requires that storage temperatures should be monitored, the MHRA expected temperature monitoring arrangements to be in place. Other examples of this 'one-size-fits-all' approach are given in Box 5.2.

It is important to note that ensuring that regulatory requirements are proportionate to the risk involved in a study would not make studies less safe. Proportionate approaches that provide appropriate protection to participants have been successfully applied to clinical trials in other contexts, for example:

- The US Food and Drug Administration's approval requirements for clinical trials of investigational new drugs depend on the nature of the study and the drug involved (Box 5.3). Studies that are not intended to support significant changes in the labelling of the product are exempt from requirements.
- The Medical Devices Directive categorises devices based on their complexity and the potential risks involved determine the requirements for a trial.<sup>75</sup>

### **Box 5.2 Examples of a lack of proportionate approach**

#### ***Effect of omega-3 fatty acids (fish oil) on non-alcoholic fatty liver disease***

This randomised study was designated as a CTIMP and, as a consequence, the IMP (fish oil) had to fulfil Good Manufacturing Practice (GMP) requirements despite the fact that it is readily available 'off the shelf' in pharmacies. The original fish oil was to be supplied free, but GMP compliance created extra costs for the study, because the fish oil had to be obtained from an alternative supplier and a third party used to undertake labelling and certify batches of the product as suitable for use in the study. Furthermore, the MHRA required a Summary of Product Characteristics to be provided for the fish oil, which led to delays while this was produced. In total, the issues surrounding the IMP status of fish oil took a year to resolve.

#### ***Ventilation of pre-term babies with oxygen***

A study sought to optimise oxygen saturation limits, within a widely used and acceptable range, to formalise the clinical care process for pre-term babies. Because the study was deemed to be a CTIMP, oxygen was required at GMP standards and GCP had to be followed. Pre-term babies are often moved from specialist units to a hospital nearer their home (so called 'step-down units') once this becomes appropriate. In this study a baby had to be withdrawn from the trial, despite the fact that they were continuing to receive ventilation with oxygen under routine care, because the step-down unit was not able to demonstrate GCP compliance.

#### ***Use of fibrinogen during surgery for repair of thoraco-abdominal aortic aneurysm***

Clinical stocks of fibrinogen are routinely stored at room temperature, which is sufficient to ensure patient safety given the stability of the drug. However, to fulfil GCP requirements, fibrinogen used in this trial had to be held in a separate cupboard, with the temperature monitored and documented. These requirements, which go beyond that of standard clinical care, resulted in additional administrative work for the department and raised logistical issues in assigning an exclusive area to store the fibrinogen.

### **Box 5.3 US Food and Drug Administration (FDA): proportionate requirements for Investigational New Drug (IND) applications**

Drugs that are lawfully marketed in the USA are exempt from IND requirements if:

- They fulfil several criteria, for example, if the study is not intended to support significant changes in the labelling or advertising of the product; and
- The risks associated with the use of the product are not significantly increased compared with its marketed use.

FDA guidance notes that phase I oncology trials of marketed drugs may be considered exempt if such therapy is appropriate for the patient population (i.e. if patients have residual cancer) and if there is no alternative effective therapy. Studies of new combinations of cancer drugs that have been described in the literature do not usually require an IND where the doses do not differ significantly from those described.

The amount of information on a particular drug that must be submitted in an IND depends upon such factors as the novelty of the drug; the extent to which it has been studied previously; the known or suspected risks; and the developmental phase of the drug, for example:

- Where a drug is already licensed in the USA a letter of cross-reference from the manufacturer, referring to an earlier IND submission, is sufficient to avoid the submission of further information.
- For plant extracts, already legally marketed within the USA, very little new toxicological data are needed to initiate trials, as long as there are no known safety issues associated with the product and it is to be used at approximately the same doses as those currently or traditionally used or recommended.

Studies on products that are already in widespread use, such as vitamin D, aloe vera extract, omega-3 and routinely-used drugs such as warfarin, are often undertaken by non-commercial sponsors, such as universities or NHS Trusts. These organisations are not well-resourced to fulfil the Directive's requirements and ensuring that these requirements can be met often leads to delays in starting a study and can prevent studies from going ahead. In addition, the compliance requirements set out in the Directive may be particularly difficult to fulfil in the context of studies where the IMP is not conventionally considered to be a drug. Examples of these are included in Box 5.2.

Responses to the call for evidence indicate that the current regulatory approach presents a significant threat to trials on established products that hold potential benefits for the

population through the improvement of clinical practice. Recommendation 5(b) seeks to tackle these concerns through revision of the Directive to ensure that approval and monitoring requirements are proportionate to risk. This approach builds on the broad risk-based categories proposed by the European Science Foundation (Box 5.4). A proportionate approach would need to include a transparent and straightforward mechanism for: determining when studies should be exempt from requirements; where minimal approval and monitoring requirements are appropriate; and where greater requirements for authorisation and monitoring are necessary.

### Box 5.4 The European Science Foundation: a model for a proportionate approach to clinical trial regulation

The following recommendations were included in the European Science Foundation report, 'Investigator driven clinical trials',<sup>76</sup> to remedy the lack of proportionality in the Clinical Trials Directive:

*There is a need to make a distinction between studies whose risk is equivalent to standard (usual) care (including randomised trials that compare already marketed and labelled treatments) and those that are aimed at innovation (e.g. testing a new drug). New categories of clinical studies could be developed in which the study is defined based on the aim of the study and on the risk that the study carries to the patient, to the institution and to public health. Each category of risk would have its specific requirements for issues such as submission to competent authority, insurance, need for a sponsor, monitoring of the trial and so on. We recommend that regulators minimise requirements (submission to ethics committee) for studies whose risk is similar to usual care, and to use a broad risk-based categorisation. For example:*

- *Level A – low risk (such as non-interventional pathophysiology, imaging)*
- *Level B – similar to usual care (equivalent to most phase IV clinical trials)*
- *Level C – moderate risk (most phase III clinical trials)*
- *Level D – high risk (most phase I–II drug trials, gene or cell therapy)*

*Clinical trials should be categorised according to the level of risk that they pose to the patient, investigators and the health service and the regulations governing the clinical trial, including the monitoring procedures, should be adapted to reflect the degree of risk. We recommend that:*

- *All procedures and requirements be adapted to the appropriate level of risk, include the risk-based approach in the CTD requirements and consider exempting low-risk IMP studies from the CTD requirements.*
- *Specific populations (e.g. children) or the use of IMPs outside their licensed indication(s) should not be considered to be automatically 'Level D – high risk'.*

#### 5.4.3 Safety reporting

The Directive sets out specific requirements for safety reporting, including:

- **Adverse reactions reports:** Sponsors must keep a record of all adverse events relating to a clinical trial and report all SUSARs to the MHRA, the relevant ethics committee, and the NCA of any other Member State where the trial is being conducted. The timescales for reporting depend on the severity of the reaction.
- **Annual safety reports:** Sponsors are required to submit an annual safety report to the MHRA and the relevant Ethics Committee, taking into account all new available safety information received during the reporting period.

These arrangements lead to duplication between EU Member States as well as between the NCA and ethics committee(s) within a single Member State. This situation is further complicated in the UK by the fact that some NHS Trusts also request safety reports, although the Directive does not specify this requirement.

The lack of clarity in the definition of SUSARs, and inconsistencies in reporting requirements across Member States, may lead to both over-reporting and under-reporting. Both outcomes will impact on the quality of safety reporting, creating an inaccurate impression of a drug's safety profile that will affect the NCA's ability to assess the risks to participants. This potentially

negative impact on patient safety is in conflict with our Principle 1 (safeguard research participants).

Responses to the first call for evidence highlighted concerns that duplication in reporting across Member States imposes a significant burden on commercial and non-commercial sponsors alike, without increasing patient safety. It is difficult to quantify the level of resource required by an organisation to implement multiple SUSAR reporting but a centralised portal would liberate resources to enable organisations to undertake other important activities such as interpretation of data. The EudraVigilance Clinical Trial Module, run by the European Medicines Agency, has been specifically designed to facilitate the electronic reporting of SUSARs and allow sponsors to submit SUSAR information for the whole of the EU in a single portal. However, this system is still in development and MHRA plans to run the national reporting system alongside EudraVigilance for the foreseeable future.

Reporting of both SUSARs and ASRs must be made to the relevant ethics committees in addition to the NCA. The National Research Ethics Service (NRES) highlights that there is widespread agreement among ethics committees in Europe that these obligations add no value to the monitoring of a trial because the information is already collected by the NCA. In the UK for example, RECs do not act on the safety information they receive. Instead, a Memorandum of Understanding between NRES and MHRA ensures that NRES will be informed of any significant changes to the IMP's safety profile.

Safety reporting can, unquestionably, protect participants. However, duplicate reporting may distort safety data and increase the burden for sponsors without improving patient safety. In Recommendation 5(c) we call for safety reporting requirements to be simplified. This could include removal of the requirement for

SUSARs to be provided to ethics committees and investigators, i.e. ethics committees and investigators would only be informed of significant changes to an IMP's safety profile. Improved safety reporting would also be supported through the further development of a high-standard single EU-wide portal that is acceptable to all NCAs.

## 5.5 UK implementation of the Directive and the MHRA

In addition to highlighting problems with the Directive itself, responses to the review raised specific concerns about the transposition of the Directive into UK law and its interpretation in the UK.

The MHRA's role in clinical trial authorisation was not perceived by respondents as a rate-limiting step and some respondents considered that the MHRA is a part of the regulation and governance pathway that works well. This is consistent with MHRA data showing that all clinical trial authorisation (CTA) applications have been assessed within the 30 day timescale since 2007. Other responses noted that the MHRA has played a role in increasing standards across CTIMPs. However, respondents from across all sectors have raised serious concerns about the operation of MHRA on a day-to-day level.

The UK's share of global patient recruitment into clinical trials fell from 6% to 2-3% between 2000 and 2006, while the share of the core EU Member States fell less dramatically from 21% to 14% during this period.<sup>77</sup> The UK's declining position is further exemplified by data that show the time taken to set up for phase III trials in the UK has been above the European average since 2006, and that in 2009, Germany recruited over 2.5 times more patients than the UK into phase III trials.<sup>78</sup> These data also show that the UK failed to recruit as many patients as France or Spain.

<sup>77</sup> Kinapse (2008). *Commercial clinical research in the UK: report for the Ministerial Industry Strategy Group Clinical Research Working Group*. <http://www.ukcrc.org/index.aspx?o=2873>

<sup>78</sup> GlaxoSmithKline internal data.

### **5.5.1 The need for a proportionate approach in the UK**

As discussed above, the Directive has been implemented inconsistently across the EU. There is a general perception among respondents that other Member States interpreted the Directive more pragmatically and less stringently than the UK. Commercial organisations that work across a range of Member States report that the UK applies a more detailed interpretation of the documentation required for clinical trial authorisation than most other Member States. For example, it is reported that the MHRA is the only NCA in the EU that requires manufacturing site-specific drug substance and drug product batch analysis data, rather than representative data, to register a manufacturing site to support a clinical trial.

The scope of the Directive is a concern in itself, but is exacerbated by the UK's strict approach to the definitions in Article 2. As a consequence some studies that are not considered CTIMPs in other Member States are considered to be CTIMPs in the UK (for examples see section 5.3.1).

These discrepancies appear to be caused by both the rigorous implementation of the Directive in law and on a day-to-day level within MHRA. However, other Member States seem to be able to take a more pragmatic approach. For example, the Netherlands has not included the definition of a non-interventional trial in its legislation. Although the Academy appreciates the difficulties of working within the legislative framework established in the Directive we consider the pragmatic approach taken by other Member States to be more appropriate.

The MHRA considers that in some aspects of interpretation the UK '*compares favourably to other Member States*', but this view was not shared by stakeholders. The UK's interpretation of the Directive was perceived to have greater requirements for compliance than other Member States and was often described as

'*gold-plated*' by respondents. Because the UK regulations closely reflect the wording of the Directive it might be more accurate to say that the UK has adopted and applied a more robust and rigorous interpretation of the Directive.

The MHRA has recognised the need for a more proportionate approach to clinical trial regulation and has established a work stream on risk-stratification in the management of clinical trials as part of a joint MRC, Department of Health and MHRA project called 'Clinical Trials - The Way Forward'. This project is considering both risk-assessment, and associated risk-adapted requirements that could apply to CTIMPs in the context of existing legislation. Since it is likely to be several years before the revision of the EU Clinical Trials Directive, Recommendation 6 urges the MHRA to implement a more proportionate approach within the current legislative framework as a matter of urgency.

### **5.5.2 Availability of consistent advice**

Responses to the call for evidence highlighted concerns around the availability and consistency of advice from MHRA. This is a particular problem for non-commercial organisations because they do not have access to the extensive regulatory support available within industry. For example, one academic group that had previously undertaken five different studies on the effects of licensed drugs on healthy volunteers that had not been classified as CTIMPs by MHRA, found that a sixth similar product was deemed to be a CTIMP. The group discontinued the study. Another academic group received advice from the MHRA in August 2009 that their study was not considered a CTIMP, only to be contacted by MHRA in February 2010 to be told it had been reclassified as a CTIMP and that they needed to apply for a CTA.

Although CTA applications are administered punctually, and within the statutory 30 day requirement, the lack of consistent advice causes serious delays before applications can

be finalised. These delays are not reflected in the statistics. The MHRA's approach to providing advice appears to contrast sharply with that of the US Food and Drug Administration (FDA). Those who have used the US system report that the FDA takes a highly facilitative approach to approvals, which simplifies the process from the applicant's perspective. Clear lines of communication established between the FDA and researchers, are essential to the delivery of this advice, but comparable arrangements are lacking in the UK. Indeed, the evidence indicated that researchers sometimes find it difficult to identify an appropriate contact in MHRA to address their queries. This issue is addressed in Recommendation 7.

### **5.5.3 Engagement with stakeholders**

Non-commercial organisations raised the greatest number of concerns about MHRA and considered that the MHRA had not engaged with the sector sufficiently to understand and respond to their needs. Academic organisations noted that although MHRA's approach to providing guidance has recently improved there is still a lack of suitable written guidance for non-commercial applications, which is compounded by the difficulties in contacting MHRA to get consistent advice. The Directive and UK regulations are heavily influenced by, and suited to, the pharmaceutical industry and therefore non-commercial sponsors have an even greater need for high-quality guidance on how to apply these. For example, MHRA confirmed in its submission that ICH-GCP is not considered to be the legal standard in the UK.<sup>79</sup> However, it has become clear during the course of the review that there is uncertainty among researchers on GCP standards in the UK, with a strong perception that ICH-GCP is a legal requirement. ICH-GCP was developed in 1996 by the pharmaceutical industry to facilitate multinational trials. The guidelines are generally thought to provide useful standards for such studies but are less relevant, and often difficult to apply, to trials in non-commercial settings. By failing to provide constructive advice on its approach to GCP the MHRA has

not taken the opportunity provided by the UK regulations to allow appropriate flexibility.

It is essential that the MHRA engages with its full range of stakeholders and responds appropriately to their needs; this is addressed in Recommendation 7. We consider that it is particularly important that the MHRA develops a better relationship with the non-commercial sector, to develop a constructive partnership towards the regulation of CTIMPs.

### **5.5.4 GCP inspections**

The MHRA undertakes GCP inspections, as summarised in Box 5.5, to ensure that CTIMPs are compliant with the regulatory requirements. Respondents gave mixed views of their experiences. Although some indicated that they had found GCP inspections to be a constructive experience, many raised concerns about the approach taken. For example, respondents reported that inspectors failed to be constructive and in some cases behaved unprofessionally and adopted an intimidating approach.

These concerns were shared by non-commercial and commercial sponsors. A large commercial sponsor reported that inspectors had behaved confrontationally and with a lack of objectivity on two separate visits. For example, at one of these inspections it was perceived that there was a certain 'satisfaction' among the inspectors that a critical finding had been identified. The Association of Contract Research Organisations also reported that MHRA inspections are less constructive than those in other Member States. Many non-commercial organisations shared a similar view, with one reporting that inspectors made inappropriate comparisons with pharmaceutical industry standards. Examples were provided of GCP inspectors considering the protocols or requirements in place for a study to be inappropriate, even when these had been specifically agreed at the time the trial was authorised. Such inconsistencies have effects on subsequent studies. For example, for one study the MRC Clinical Trials Unit was advised by the MHRA Clinical Trials Unit on specific procedures

79 McMahon AD, et al. (2009). *The unintended consequences of clinical trials regulations*. *PLoS Med* **3(11)**, e1000131.



for IMP handling during the authorisation process. However, some site pharmacies refused to take part in the study according to these procedures because a previous inspection finding made them concerned that they would not be complying with requirements.

Some respondents claimed that MHRA inspectors were not inspecting within the legal requirements by applying ICH-GCP standards where that was not the designated standard for the trial; or by expecting Good Laboratory Practice standards (which do not apply to CTIMPs). Recommendation 7 relates to the approach to GCP inspections and calls for the MHRA to improve the training of their GCP inspectors as a matter of urgency and ensure that they are inspecting to relevant standards. The MHRA should also ensure that: inspectors are acting objectively and professionally at all times; they are working constructively with sponsors and that there is consistency across inspections.

The approach taken by GCP inspectors exacerbates the anxiety of organisations facing an inspection (see also 4.4.3). Preparation for GCP inspections is demanding and requires expertise. This is a particular concern for non-commercial organisations, such as NHS Trusts and universities. Substantial resources are often committed to the preparation for inspections to the significant detriment of other work. For example a highly research active non-commercial organisation reported that three full time equivalents of governance office staff were required for 20 days to produce the inspection dossier, in addition to the time each research team member spent on the process. The governance office had to postpone all but essential work to produce the requested dossier in the short timescale available. Cancer Research UK reported that researchers they support have experienced delays in obtaining NHS permissions from R&D offices that have been too busy with preparations for an imminent GCP inspection to process applications. In a

### **Box 5.5 GCP inspections by MHRA**

GCP inspections review standard operating procedures, staff training and experience records, contracts and agreements, equipment and facility records of trial sponsors and hosts. There are two main types of GCP inspections: routine inspections assess the procedures and systems an organisation has in place to support clinical trials; and unannounced triggered inspections which take place in response to a suspected breach of regulatory requirements.

Organisations are given two to three months' notice of a routine inspection. These typically last for four days and a dossier of evidence must be submitted in advance. A sample of studies is reviewed at each site with an emphasis on complex trials.

From 2009, the MHRA started to introduce a formal 'risk-based' inspection programme, although this is still under development. The system is designed so that inspectorate resources are concentrated in those areas that maximise protection of patients while reducing the overall administrative burden to stakeholders. Under this scheme, sponsors and host organisations complete an annual compliance report which, together with MHRA's internal information, is used to determine an organisation's ability to manage risk and comply with GCP. Risk assessments are categorised into high, medium and low, and inspections are prioritised for those organisations with the highest risk category. A small proportion of organisations from the medium and low-risk categories are randomly selected for inspection for control purposes.



separate submission it was reported that, in the six weeks leading up to an MHRA inspection, one trial used over 50% of its MRC-funded staff time in preparing for the inspection rather than focusing on patient recruitment.

In addition to the time taken to prepare for inspection, non-commercial organisations raised concerns about the costs involved, which are reported to be around £20,000-£30,000 per inspection. One respondent noted that their highly research active university and associated local NHS Trust were inspected separately when these could have been undertaken simultaneously.

The Academy considers that the anxiety caused by the actual and perceived requirements for compliance, coupled with the approach taken in some GCP inspections, is a major factor in contributing to the risk-averse approach of NHS Trusts and other organisations to health research. The impacts of a risk-averse approach of NHS Trusts and consequences of this on health research are discussed in Chapters 3 and 4.

It is important that sponsors and host organisations adopt an appropriate attitude to GCP compliance and take their responsibilities seriously. However, it is of concern that the emphasis placed on inspection by the MHRA

leads to a 'tick-box mentality' where sponsors and host organisations focus on obtaining evidence to demonstrate compliance with GCP. This diverts attention and resources away from the delivery of GCP to an appropriate standard. This view resonates with the MHRA's submission to the first call for evidence, in which they noted that *'it is not uncommon for business processes to be developed which far exceed those anticipated or required by the regulations and guidance'*, adding that *'over-emphasis on unnecessary requirements is often to the detriment of critical data, particularly where resources are limited'*.

The impact of MHRA's 'risk-based' approach to GCP inspections is not yet clear but the Academy considers it is essential that the MHRA works with sponsors to foster more collaborative mechanisms to audit GCP, as set out in Recommendation 6. GCP audit should be proportionate to the potential risks of the trials taking place compared with standard care. Alternative systems involving greater use of statistical approaches could also ensure that sponsors take responsibility for assessing risks, monitoring compliance and pro-actively reporting to MHRA.

## Recommendations

*The broad scope and lack of proportionality in the European Clinical Trials Directive have created a major barrier to undertaking studies of established products, without providing greater levels of protection to study participants. Within the UK, despite punctual administration of Clinical Trial Authorisations (CTA), there are concerns about: the way in which Medicines and Healthcare products Regulatory Agency (MHRA) engages with stakeholders; the provision of timely and consistent advice before a CTA is submitted; a lack of proportionality in the MHRA's approach to regulation; and the approach to some Good Clinical Practice (GCP) inspections. In addition to recommendations in Chapter 9, where we outline our proposal for a Health Research Agency, we recommend that:*

**Recommendation 5:** The Government, supported by the MHRA, should seek to influence the European Commission to act quickly to revise the EU Clinical Trials Directive. The Directive should be amended to:

- a. Reduce the scope of the Directive through the revision of the definitions set out in Article 2.
- b. Ensure that approval and monitoring requirements are proportionate to risk.
- c. Simplify the requirements for the reporting of adverse events.

**Recommendation 6:** Before revision of the Clinical Trials Directive the MHRA should adopt a more proportionate approach to clinical trials regulation without delay. This should include implementing the recommendations of their current project on risk stratification and developing alternative and appropriate systems for the audit of GCP. In addition, the MHRA should ensure that GCP inspections are consistent, assessing against relevant standards, and conducted objectively, professionally and constructively at all times.

**Recommendation 7:** The MHRA should increase the quality, consistency and timeliness of advice from its Clinical Trials Unit. The MHRA should designate a clear single point of contact for every CTA application with which applicants can work to overcome problems. The Clinical Trials Unit and GCP Inspectorate must engage more effectively across the full range of stakeholders to promote mutual understanding and provide support that is tailored to the needs of different sectors.

## 6 Use of patient data in health research

### 6.1 Introduction

The use of patient data is essential to research that underpins our knowledge of disease, the development of diagnostic and therapeutic interventions, and the delivery of services.

Patient data is used as follows:

- In epidemiological studies to identify important causes of disease and for research into public health.
- In surveillance for detecting and controlling infectious and non-communicable diseases.
- To evaluate the effectiveness of screening programmes.
- To monitor the safety and efficacy of prescribed drugs, vaccines and devices used in healthcare.
- In audit to highlight areas for improvement in provision of NHS services.
- To identify eligible participants to invite to participate in studies.

To maximise the benefits that research studies deliver it is crucial that data are accessed from across the sample population to reduce bias and highlight any inequalities in healthcare. The study outlined in Box 6.1 highlights the differences in research findings when restricted samples are accessed; and the implications if research findings from these restricted datasets are taken forward. An epidemiological study seeking to identify groups at greater risk of disease should include a range of ethnic and socioeconomic groups so all needs are met when providing NHS services or delivering interventions. The need to engage research participants from across the population will increase further as we build on our understanding of the similarities and differences between individuals to stratify disease and target treatments to specific patient subgroups.

#### Box 6.1 Bias introduced into research findings when incomplete datasets are accessed

A study comparing the care given to affluent and deprived women with breast cancer demonstrates the bias that can be introduced due to challenges in seeking consent.<sup>80</sup> At the time of the initial study in the late 1990s, patient consent was not required for the review of medical records, but was subsequently introduced as a requirement later in the study process. It was therefore possible to reanalyse the findings from the original study and compare these with the findings from the smaller second dataset of women who consented. The study found that the second dataset missed one of the key research findings: that more women from deprived areas, compared with those from affluent areas, presented with locally advanced or metastatic tumours. This second dataset provided a different and misleading research finding relating to access to treatment, because it suggested that significantly more women from deprived areas received radiotherapy compared with women from more affluent areas. If the research finding relating to treatment had been published then it could have prompted unfounded concern and unnecessary further research efforts.

80 Macleod U & Watt GCM. (2008). *The impact of consent on observational research: a comparison of outcomes from consenters and non consenters to an observational study*. BMC Medical Research Methodology, 8 (15), 1-6.

With the development of electronic records across the NHS there is a real opportunity to maximise the potential of patient records in evaluating interventions, in epidemiological studies and in surveillance of infectious and non-communicable diseases. Outlined in Box 6.2, and throughout this report, examples are provided of vital health research that required the use of patient data. The UK has the potential to lead the way in this field but concerted action is needed to maximise our assets, particularly the advantages of having a single national healthcare system.

As highlighted in the principles in Chapter 2, it is essential that regulation and governance

enable all individuals to use opportunities to take part in health research, in an environment that ensures the well-being of research participants. In this Chapter we highlight how the regulation and governance of patient data is currently extremely complex, creating barriers to setting up studies and making patients aware of research opportunities. Recommendations are made to address key problems in this area and should be considered alongside the proposals in Chapter 9 to create a new Health Research Agency (HRA), which once established would play a key role in the regulation and governance of patient data in health research.

### **Box 6.2 The Million Women Study**

The Million Women Study is a national study of women's health involving more than one million UK women aged 50 and over.<sup>81</sup> Between 1996 and 2001, women were invited to join the Million Women Study when they received their invitation to attend breast screening at one of 66 participating NHS Breast Screening Centres in the UK. Around 70% of those attending the programme returned questionnaires sent at the same time as their screening invitation and agreed to take part in the study. Over one in four women in the UK in the target age group are now participating in the study and it is the largest study of its kind in the world. Disease is monitored through self-reporting on recruitment and follow-up questionnaires and by record linkage to the NHS Breast Screening Programme, Cancer Registries and the Office of National Statistics. The large size of study population means that a broad range of health issues can be addressed.

Hormone replacement therapy (HRT) has been a major focus, and the study has shown the full health effects of HRT on a range of different diseases, which has been of great value to women, enabling more informed choices about the use of such treatment. The record linkage allowed unbiased follow-up of participants on a huge scale and the risks of HRT for cancer to be reliably estimated.

The study, led by researchers from the University of Oxford and funded by Cancer Research UK, the NHS, Medical Research Council (MRC) and the Health and Safety Executive, has:

- Shown that women currently using HRT are more likely to develop breast cancer than those who are not using it and the differences in risk between the different types of HRT. However, past users are not at increased risk.
- Confirmed that post-menopausal women who have not had a hysterectomy are at increased risk of endometrial cancer if they take oestrogen-only HRT.
- Supported the findings of a smaller study that showed a small increase in risk of ovarian cancer in women taking HRT.

## 6.2 Use of patient data: key distinctions

Before describing how access to patient data is currently regulated and the challenges this raises, it is necessary to introduce several key concepts and definitions.

### 6.2.1 Different forms of data

Throughout this chapter we use the term patient data to refer to information about individuals that may be used in health research. This information can include both health data (e.g. cholesterol levels or cancer diagnoses) and non-health data (e.g. postcode, ethnic group or occupation). Patient data can be accessed for use in research in several forms:

- *Identifiable data*. These include information in patient records such as patients' names, addresses, postcodes, dates of birth, dates of death and NHS numbers. There are also aspects of health data that could become identifying when they relate to a diagnosis of a rare condition or when combined with other data.
- *Key-coded data* (also called pseudonymised data). These cannot directly identify an individual, but a 'key' is available that enables the patient's identity to be re-linked to the data by a person or technology with access to the 'key'.
- *Anonymised data*. There is no way of linking the data with the original patient record.

### 6.2.2 Access to patient data

This chapter deals with two distinct scenarios requiring access to patient data in health research:

- The direct use of patient data within a research study that does not require any direct contact by the researcher or research team with patients. This could include epidemiological studies that require access to linked but anonymised or key-coded data and require no patient follow-up; or to studies that access identifiable data without consent with appropriate approval for example by the Ethics and Confidentiality Committee of the National Information Governance Board.

- The use of patient records to identify suitable persons in order to invite them to participate in a research study.

In both of these scenarios, the approach of many regulatory and professional bodies is to 'consent or anonymise', meaning that consent is sought from patients to use data or the data are anonymised before sharing with researchers.

The use of patient records to identify suitable persons to invite to participate in a research study, whether it is a clinical trial or a simple questionnaire, raises its own challenges. One mechanism is for individuals to give generic consent to be contacted about suitable research opportunities, before considering whether they consent to take part in a specific study (a concept called 'consent for consent'). This is a challenging concept to put into practice and previous consideration has been given to whether an 'opt-in' or 'opt-out' system for registering generic interest in research is desirable. Opt-in would require patients to proactively register whereas in an opt-out system, favoured by the Academy, all patients are registered and receive information on suitable research opportunities, unless they indicate otherwise.

The development of what are known as 'safe havens' (or honest brokers) has become a well established concept around the use of data in research in recent years. Safe havens are secure environments for coding and handling data and have three key characteristics (as outlined in the Data Sharing Review):<sup>82</sup>

- They provide a secure environment for processing identifiable personal data.
- Only 'approved researchers' can gain access to the data.
- There should be penalties for anyone who abuses personal data.

### 6.2.3 Sources of data

In most cases, patient data that can be used in health research are collected by the NHS. These include records at GPs' surgeries or hospitals, collected as a routine part of patient care. It is important to note that these data are used extensively within the NHS to underpin all aspects of service delivery and, as such, are routinely shared in a secure and confidential manner with members of clinical care teams. Data are also shared within organisations undertaking clinical audit or to evaluate compliance to NHS standards. Data that are relevant for use in health research are also collected or held by other bodies such as the Ministry of Defence and the Office for National Statistics.

It is an important aspect of research studies using patient data that these different sources of data can be brought together and linked. This is usually initially at the level of the individual data subject, even if the datasets are subsequently only made available to researchers in anonymised or key-coded form. Technological and methodological advances in approaches to linkage that preserve confidentiality are a priority of many recent data initiatives (e.g. the Scottish Health Informatics Programme; for more information see section 6.4.3). It is essential that efforts to link data reliably and securely are not undermined by the regulation and governance pathway, and that linkage across different health sectors, government departments and geographical areas is possible.

## 6.3 The complexity of the current environment and previous attempts to address key problems

### 6.3.1 Over-arching challenges

It was clear that respondents consider the complexity of the current arrangements for regulating the use of patient data as a significant barrier to health research. Current problems include the following:

- The legal framework around access to

patient data is complicated and involves UK statutory legislation, common law decisions, and various EU Directives (see section 6.4.1).

- There are numerous sources of guidance but no one body is responsible for overseeing decisions relating to the use of patient data in health research (see section 6.4.2). Bodies currently involved include the Information Commissioner's Office, the General Medical Council, the MRC, and the British Medical Association. Each body differs in its focus, context and jurisdiction and, as a consequence, they can offer inconsistent advice.
- The development of initiatives to allow researchers to access anonymised data from 'safe havens' is still progressing (see section 6.4.3).
- There are no clear mechanisms to allow researchers to search through patient records to identify eligible patients to invite to participate in a study (see section 6.4.4).
- There have been several public engagement initiatives in this area, but a lack of consistent public information (see section 6.4.5).

The current situation leads to confusion and inconsistency when applying for and using patient data in research. For example:

- The approvals process is different across the devolved nations. Section 251 of the NHS Act (2006) grants the National Information Governance Board's Ethics and Confidentiality Committee (ECC) advisory powers in relation to the use of identifiable patient data without consent. However, these powers only apply to England and Wales. Scotland and Northern Ireland have a similar approach but without the same statutory basis.
- Different and overlapping mechanisms are in place depending on the data set involved. For example, if a research study involves anonymised data from the Yellow Card Scheme<sup>83</sup> or the General Practice Research Database<sup>84</sup> then an independent committee (ISAC) advises the Medicines and

Healthcare Regulation Authority (MHRA) on authorisation. If the same study also needs to access identifiable data without consent from across the UK it would involve additional applications to the ECC (England) and the Privacy Advisory Committee (Scotland).

It is evident that there is much uncertainty about the legal requirements among researchers and healthcare professionals. Many argue that the complexity of the current landscape, combined with an over-emphasis on privacy and autonomy, has created a conservative culture around access to data

which does not always best serve the needs of research or, more importantly, the needs of patients within the NHS.

### **6.3.2 Previous efforts to address these problems**

Many of these problems, described in further detail in section 6.4, have been explored previously in reports such as the Academy's report on Personal data for public good (2006)<sup>85</sup> and the Data Sharing Review (2008)<sup>86</sup> (Box 6.3).

#### **Box 6.3 Previous efforts to improve access to patient data for research**

Both of the reports below contained specific recommendations to bring about change in this area:

##### **Personal data for public good: using health information in medical research (2006).**

The Academy of Medical Sciences report included recommendations that:

- Identifiable data can be used for health research, without consent, provided that such use is necessary and proportionate with respect to privacy and public interest benefits.
- Relevant bodies including the Patient Information Advisory Group, (now the National Information Governance Board (NIGB)), Information Commissioner's Office, Research Ethics Committees, NHS research governance offices and General Medical Council should accept the above interpretation in their guidance and approval decisions.
- The UK's Department of Health, working with the UK Clinical Research Collaboration, should develop public engagement programmes around the purpose and value of using personal data in health research.

**The Data Sharing Review (July 2008).** Undertaken by Mr Richard Thomas, the Information Commissioner and Sir Mark Walport FMedSci, the Director of the Wellcome Trust, the report recommended that:

- 'Safe havens' should be developed as an environment for population-based research and statistical analysis in which the risk of identifying individuals is minimised; and that a system of approving or accrediting researchers who meet the relevant criteria to work within those safe havens is established.
- Government departments and others wishing to develop, share and hold datasets for research and statistical purposes should work with academic and other partners to set up safe havens.
- The NHS should develop a system to allow approved researchers to work with healthcare providers to identify potential patients, who may then be approached to take part in clinical studies for which consent is needed.

<sup>85</sup> The Academy of Medical Sciences (2006). *Personal data for public good: using health information in medical research*. <http://www.acmedsci.ac.uk/download.php?file=/images/publication/Personal.pdf>

<sup>86</sup> Thomas R & Walport M (2008). *Data sharing review report*. <http://www.justice.gov.uk/reviews/docs/data-sharing-review-report.pdf>

Although several of the recommendations in these reports have been taken forward, many of the problems remain:

- The Academy's 2006 report highlighted the uncertain legal basis for identifiable patient data to be used without consent. There has been progress in this area, with the creation of the ECC within the National Information Governance Board in 2009, providing a clear recognition of the continued need for certain research studies to have access to data in this manner. However, a lack of clarity remains on mechanisms for accessing data without consent, which is complicated by the multiple sources of guidance that exist.
- The Data Sharing Review recommended the creation of 'safe havens' to access data. The work of the Research Capability Programme (section 6.4.3) is an example of the development of such a 'safe haven'. However, researchers cannot yet make use of its services and information demonstrating that these safeguards are in place cannot be communicated to the public. There is a need for the further development of additional safe havens to allow government departments and others to develop, share and hold datasets for research, as well as for researchers to innovate and evaluate methods for record linkage.

The evidence submitted to this review highlights that the core problems around access to patient data have not changed significantly in recent years. We urge the Government to evaluate progress on taking forward the recommendations from the Data Sharing Review, and to ensure that the fundamental changes outlined in that report are now taken forward at pace, alongside the recommendations described below.

## 6.4 Problems and challenges

Although other reports have looked at issues around access to patient data in isolation, a primary objective of this review was to consider the regulation and governance pathway as a whole to identify remaining bottlenecks and challenges. In the evidence that we received there was a strong emphasis on barriers to using data in research together with the delays, unpredictability and unnecessary drain on resources that these cause. Improvements to the process of gaining NHS R&D permissions (Chapter 4) and to the culture of research (Chapter 3) will help to address these issues. However, the specific challenges around the regulation and governance of access to patient data remain a clear priority, with a need for strong commitment and communication from the Government as to how these will be addressed.

This chapter now focuses on key issues that this review has identified and associated recommendations in four key areas: the legislative framework; governance; the development of safeguards and identifying patients to invite to participate in research. Recommendations in these areas, although standalone, will be further enhanced by the establishment of a Health Research Agency that we propose in Chapter 9. The roles of the HRA will include addressing the fragmented nature of guidance relating to patient data (Recommendation 16) and methods to harmonise differences in the regulatory and information governance regimes across the four nations. An additional focus of this chapter is on public engagement on access to patient data for use in research, which draws on the themes explored in Chapter 3.



#### 6.4.1 Legislative framework

The complex legal framework relating to the use of data in the UK has contributed to many of the problems experienced when applying for and using patient data in research. It can be difficult to establish whether specific problems stem from the text of the legislation, its implementation, or the culture in which it is applied. However, it is apparent that clarity is required to provide researchers and the public with as much certainty as possible (see Box 6.4).

The EU Data Protection Directive 95/46/EC<sup>87</sup> will be revised during 2011; the Ministry of Justice has already begun an exercise to review the Data Protection Act in the UK.<sup>88</sup> This should provide an opportunity for clearer interpretation of the Act, in relation to the use of patient data in research, as well as a chance to introduce further clarity into its text. The key aspects that should be considered are as follows:

- Definitions relating to consent requirements and the associated processes.
- How the Data Protection Act fits with the rest of the regulation pathway in relation to access to patient data for use in research for benefit to patients.
- The proportionality of the Data Protection Act.

- Clarity on roles and responsibilities for data controllers and data processors focusing on the impact in NHS R&D offices.

In Recommendation 8 we outline the need for review of this key piece of legislation.

#### 6.4.2 Governance

Those responsible for research approval decisions involving patient data have to make judgements within an uncertain legal framework, which leads to variable interpretations. Many of the problems about the use of patient data result from variable implementation of regulations, differing interpretations by various bodies, and different sources of guidance.

Although there are numerous sources of guidance on access to data this advice often varies. When a research study is further challenged by the need to recruit from a particular patient population, for example patients with rarer conditions or those who are critically ill, delays to recruitment due to inconsistencies in governance can have a significant impact. Combined with a lack of interoperability between different datasets, this can lead to delays in setting up studies and insurmountable barriers.

#### Box 6.4 Case study from Cancer Research UK

In 2007, Cancer Research UK funded a programme grant of £1.6 million to support three studies seeking to recruit 600 patients and spanning six forms of cancer. A change in the interpretation of data legislation over the course of the study meant that researchers with honorary contracts, that had previously been viewed as part of the clinical team, no longer were. These researchers were therefore no longer able to screen patients' records to identify those eligible to approach for the study. The change led to ethical approvals for the studies being placed on hold or revoked until NIGB guidance was received.

The total delay to recruitment was approximately 10 months, during which time patients were unable to take part in research designed to improve patient care. The increased workload for the research team to adapt to the new guidelines was estimated to be 43 working days in addition to an increased burden (estimated at 50 hours) on clinical staff who were required to introduce patients to the research team.

87 European Parliament (1995). *Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.* <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:EN:HTML>

88 For further information see <http://www.justice.gov.uk/consultations/call-for-evidence-060710.htm>

Uncertainty around data protection issues was commonly cited during our consultation as an area where improvement is required. The submission from the National Institute for Health Research (NIHR) Clinical Research Network emphasised the duplication that exists in the current system. At present, the provision of information on the use of patient data is a requirement for ethics review and, where appropriate, for ECC approval. Many NHS organisations also require local assessments, often by Caldicott Guardians (see next paragraph), and request additional forms to be completed for this purpose. This duplication by NHS R&D offices of checks that have been undertaken by another body is something that we are seeking to avoid with the creation of the National Research Governance Service (NRGS) (Chapter 4).

A Caldicott Guardian is a senior person within each Trust with responsibility for protecting the confidentiality of patient and service-user information and enabling appropriate information-sharing.<sup>89</sup> The experience of researchers is that Caldicott Guardians work to different standards owing, in part, to how local processes have evolved, as well as a lack of clarity about the interpretation of the legislation. This inconsistency creates delays, especially for multi-site studies, and affects researchers wishing to use anonymised data and those seeking to access data to identify patients suitable for a clinical trial. In Recommendation 9 we propose that the role of Caldicott Guardians should focus on facilitation and delivery, rather than duplicating the approval process provided by the REC and ECC and risking inconsistencies across Trusts.

### 6.4.3 Development of safeguards

Wherever possible the most desirable approach is for researchers to access anonymised patient datasets. There are several initiatives in place to deliver this and enable high-quality research using patient data:

- The Scottish Health Informatics Programme (funded by the Wellcome Trust, Medical Research Council and the Economic and Social Research Council) aims to create a research portal that provides rapid and secure access to the type of data that investigators require.<sup>90</sup>
- The Health Information Research Unit of Wales (funded by the Wales Office for Research and Development) aims to harness the potential of routinely collected data to support and undertake research.<sup>91</sup>
- In England, a Health Research Support Service (supported by the NIHR) is being developed to enable investigators to analyse a wide range of healthcare information while protecting the privacy of patients.<sup>92</sup> The first stage of this service is currently being piloted with a limited number of data sources.

To ensure that Principles 1 and 4 are met, it is vital that the work to develop safe havens is accelerated. The health departments should continue their work to establish safe havens through the Research Capability Programme and its equivalents in the devolved nations. In particular, the Research Capability Programme should roll out the full system as soon as possible, incorporating lessons learnt from the pilot, to ensure the UK is maximising opportunities in this area. If necessary, legislation should be introduced that would enable safe havens to operate as laid out in the Data Sharing Review, so that researchers have access to secure data and that patient safeguards are fully met.

<sup>89</sup> For further information see [http://www.dh.gov.uk/en/Managingyourorganisation/Informationpolicy/Patientconfidentialityandcaldicottguardians/DH\\_4100563](http://www.dh.gov.uk/en/Managingyourorganisation/Informationpolicy/Patientconfidentialityandcaldicottguardians/DH_4100563)

<sup>90</sup> For further information see <http://www.scot-ship.ac.uk/>

<sup>91</sup> For further information see <http://www.wales.nhs.uk/sites3/page.cfm?orgid=580&pid=14733>

<sup>92</sup> For further information see [http://www.nihr.ac.uk/systems/Pages/Research\\_Capability\\_Programme.aspx](http://www.nihr.ac.uk/systems/Pages/Research_Capability_Programme.aspx)

#### **6.4.4 Identifying patients to invite to participate in a research study**

Accessing patient data to identify eligible patients to invite to participate in a study is vital to ensure that patients from all sectors of society are provided with the opportunity to participate in research. In addition it is increasingly important that research studies are able to maximise use of patient records to specifically target those patients who are eligible for the research in question, particularly as interventions that are tailored to specific populations of patients are further developed.

There was an extensive discussion at the PPI workshop on the issues relating to the use of patient data in research. Participants discussed the pledge in the NHS Constitution, and in the Health White Paper, on the importance of patients being made aware of research that is of particular relevance to them.<sup>93</sup> When participants in the workshop discussed this they indicated that what they sought was information to make choices and the 'right' to make that choice (regardless of whether there is an 'opt-in' or 'opt-out' system of being informed of opportunities). Many felt that currently the choice is not presented to patients and that others were making decisions on their behalf. The pledge in the NHS Constitution was also mentioned in many of the written responses to this review and, although seen as an important development, it was felt that the wording was not as strong as it could be and that the NHS Constitution has had little direct impact on culture and practice.

Evidence from two national research studies demonstrates that a small number of patients complain about receiving direct invitations to participate in research. The UK Collaborative Trial of Ovarian Screening is one of the largest ever randomised controlled trials, covering 13 NHS Trusts in England, Wales and Northern Ireland, with successful recruitment of more than 200,000 women. Of the 1.2 million

women invited to participate in the study only 32 complained about being contacted.<sup>94</sup> UK Biobank reported from its integrated pilot phase that approximately 1 person from every 1,000 invitations indicated that they did not want to participate because of concerns that their contact details had been provided to UK Biobank by the NHS.<sup>95</sup>

In response to the call for evidence, submissions outlined the continued difficulties researchers experience in identifying eligible patients to invite to participate in studies. The evidence highlighted that there are no clear mechanisms in place to allow members of a research team to search patient records for eligible trial participants. Instead, they are dependent on clinical team members who often do not do it, even if payment is offered, owing to their uncertainty of the legal framework, time restraints or the level of priority afforded to research in the Trust (See Box 6.5).

The Research Passport scheme for honorary NHS contracts was seen by many researchers as a potential solution to this problem.<sup>96</sup> The scheme is designed to streamline procedures associated with issuing honorary contracts or letters of access to researchers who have no contractual arrangements with the NHS organisation hosting the research. This allows them to undertake research in the NHS that affects patient care, or requires access to NHS facilities. The introduction of research passports is seen by some researchers to be an improvement; however, some feel that it is a cumbersome scheme which adds further delay. The Wellcome Trust highlighted in their submission that it can take between 6 and 12 months for some post-doctoral researchers to receive their research passports. In addition to the delays to study set-up that the passports can cause, they do not give researchers the ability to access datasets in the same manner as a member of the clinical care team.

93 For further information see [http://www.nihr.ac.uk/awareness/Pages/awareness\\_constitution.aspx](http://www.nihr.ac.uk/awareness/Pages/awareness_constitution.aspx)

94 Menon U, et al. (2008). *Recruitment to multicentre trials – lessons from UKCTOCS: descriptive study*. *BMJ* **337a** 2079.

95 UK Biobank Coordinating Centre (2006). *UK Biobank: report of the integrated pilot phase*.

<http://www.ukbiobank.ac.uk/docs/IntegratedPilotReport.pdf>

96 For further information see [http://www.nihr.ac.uk/systems/Pages/systems\\_research\\_passports.aspx](http://www.nihr.ac.uk/systems/Pages/systems_research_passports.aspx)

**Box 6.5 Case study: swine flu**

In autumn 2009 the Clinical Research Network fast-tracked studies into pandemic flu in response to the high national priority given to rapid research into the disease. This involved coordinating research in 314 NHS organisations across 640 research study sites, and driving through fast set-up times. As a result 57% of NHS research sites granted permission to start the study within two days of the Research Ethics Committee's favourable opinion. The ability of NHS organisations to undertake rapid risk assessment was a key factor in the success of fast-tracking set-up of these studies. However, these studies also highlighted some of the inconsistencies in approach that remain in the system.

In one NIHR-funded study of swine flu conducted across several sites there was a need to send out questionnaires to patients who had been identified through anonymous datasets as eligible for inclusion in the study, to ask them whether they would like to consent to be involved. The involvement of the research team was required to print out address labels to send out the questionnaires. At one site the local Research Ethics Committee and university governance teams would not approve the research team having access to patient's names and addresses before they had consented to take part in the study, and therefore a member of the clinical care team was required to take on this role. Although a member of the clinical care team agreed to undertake this activity, they were unable to complete it due to other (understandable) priorities. Consequently, for that site, instead of 200 questionnaires only 30 were sent out.

There is a need for mechanisms that allow approved researchers to access patient records in confidence, so as to be able to identify eligible patients for specific research studies. The definition of a clinical care team should be clarified so that approved members of research teams are considered members of the clinical care team and therefore have the same contractual obligations (i.e. the same sanctions for any breach of confidentiality) (see Recommendation 10).

**6.4.5 Public engagement**

There is a need to better communicate to the public and patients what is meant by the use of patient data in research, and to improve public engagement in discussions relating to policy decisions in this area. This was summed up in a quote from the Primary Care Research Network: *'A public campaign is needed to increase awareness of research as something that anyone in the UK could be involved with. From a primary care perspective, if all patients were informed via their GP practice that their*

*record could be searched by appropriately qualified people to determine their eligibility for taking part in locally approved research (with an integrated opt-out), then that would speed finding participants.'* Participants at the PPI workshop felt that there is a need to inform not only patients, but the public more widely of the value of conducting research using patient data, while clearly articulating the safeguards that are in place and the opportunities to 'opt-out'.

There is concern that often those involved in collecting patient data for clinical care (e.g. GPs) have been regarded as representing the patient viewpoint on this issue. In December 2009 the UK Clinical Research Collaboration (UKCRC) Subgroup on Public Awareness commissioned market research into the attitudes of patients and GPs on the use of patient data for research purposes, to potentially inform the foundation for their planned public awareness campaign.<sup>97</sup> One of the findings from this market research was the apparent lack of understanding of the value of research using patient data amongst

the GPs who took part and their reluctance to facilitate access to patient data for research purposes. This was in marked contrast to the largely positive response from the patients on this issue.

Building on previous public engagement projects (Box 6.6), the UKCRC Subgroup on Public Awareness has initiated a programme to develop information materials that provide patients, the public and healthcare professionals with information about the use of

data in health research. We recommend that this work should continue and that the primary aim of these materials should be to provide information on what is meant by the use of data in health research and that this should inform decisions relating to 'opt-out'. This programme will require the continued support of the UK health departments and should be integrated with our recommendation around improving public information on the core role of health research in the NHS (see Recommendation 1).

### Box 6.6 Review of public engagement on use of patient data

The following reports have examined public views on the use of patient data. The individual reports should be referred to for detailed findings and information on the methods and samples used.

- **NHS Connecting for Health.** *Using patient information in the NHS* (2009).<sup>98</sup> This report found that the 96 participants were generally happy for their data to be used in research as long as anonymity was ensured and they were approached by someone they knew and trusted, such as their GP.
- **Royal Academy of Engineering.** *Young people's views on the development and use of Electronic Patient Records* (2010).<sup>99</sup> Of 3,000 young people surveyed, most were not against the idea of anonymised data being used in medical research; 50% said that they would want to be asked for consent each time researchers used their anonymous record.
- **New Economics Foundation.** *Exploring public views on personal electronic health records (October 2010)*.<sup>100</sup> Surveyed 6000 people and found: that 57% of adults and 67% of young people were enthusiastic about the benefits of switching to digital patient records; and that patient consent would be essential for using identifiable data for research.
- **Wellcome Trust/University of Surrey.** *Public Attitudes to Research Governance* (2006).<sup>101</sup> Based on interviews and focus groups with 89 people; the report found participants were willing to provide personal data for biomedical research providing its use had been explained to them. Concerns remained over whether promises of anonymity and security could be fully relied on.
- **MRC/Ipsos MORI.** *The Use of Personal Health Information in Medical Research* (2007).<sup>102</sup> Interviewed a sample of 2,106 UK adults and found that 69% were 'likely' to allow the data to be used for health research purposes.
- **Academy of Medical Sciences.** *Personal data for public good: using health information in medical research* (2006).<sup>103</sup> Consulted with a wide range of patient representatives and found research using personal data was strongly supported. Public engagement was identified as one of the most important tasks in developing future arrangements for appropriate governance for the use of health information in health research.

98 NHS Connecting for Health (2009). *Using patient information in the NHS*.

<http://www.connectingforhealth.nhs.uk/engagement/public/consultations/hsreport.pdf>

99 Royal Academy of Engineering (2010). *Privacy and prejudice: young people's views on the development and use of electronic patient records*.

[http://www.raeng.org.uk/news/publications/list/reports/Privacy\\_and\\_Prejudice\\_EPR\\_views.pdf](http://www.raeng.org.uk/news/publications/list/reports/Privacy_and_Prejudice_EPR_views.pdf)

100 New Economics Foundation (2010). *Who sees what? Exploring public views on personal electronic health records*.

[http://www.neweconomics.org/sites/neweconomics.org/files/Who\\_Sees\\_What.pdf](http://www.neweconomics.org/sites/neweconomics.org/files/Who_Sees_What.pdf)

101 Wellcome Trust/University of Surrey (2006). *Public attitudes to research governance: a qualitative study in a deliberative context*.

[http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy\\_communications/documents/web\\_document/wtx038443.pdf](http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/wtx038443.pdf)

102 Medical Research Council/Ipsos MORI (2007). *The use of personal health information in medical research*.

[http://www.mrc.ac.uk/consumption/idcplg?IdcService=GET\\_FILE&dID=10983&dDocName=MRC003810&allowInterrupt=1](http://www.mrc.ac.uk/consumption/idcplg?IdcService=GET_FILE&dID=10983&dDocName=MRC003810&allowInterrupt=1)

103 Academy of Medical Sciences (2006). *Personal data for public good: using health information in medical research*.

<http://www.acmedsci.ac.uk/download.php?file=/images/publication/Personal.pdf>

## Recommendations

*The legal framework around access to patient data is complicated involving UK legislation, case decisions, and an EU Directive. There are also a wide range of bodies involved in producing advice, each of which differs slightly in their focus, context and jurisdiction. This has resulted in conflicting interpretations of the regulation among stakeholders and a lack of clarity for patients and the public. Aspects of these problems are dealt with in our recommendations in Chapter 9, where we outline our proposal for a Health Research Agency. We urge the Government to evaluate progress on taking forward the recommendations from the Data Sharing Review (2008) and to ensure that the fundamental changes outlined within it are taken forward at pace, alongside the recommendations below. We recommend that:*

**Recommendation:** The Ministry of Justice should undertake a thorough review of the UK Data Protection Act to identify aspects that require clarification in relation to health research so as to inform the planned revisions to the EU Data Directive and subsequent amendments to the UK Data Protection Act. As a priority, clear guidance on interpretation of these aspects of the Act should be provided for researchers and healthcare professionals by the Information Commissioner in conjunction with the proposed new Health Research Agency.

**Recommendation:** The role of Caldicott Guardians should not include the approval of research studies. Instead it should focus on facilitating the delivery of research studies for which approvals relating to data have already been granted by other bodies.

**Recommendation:** As recommended in the Data Sharing Review, a system should be developed to allow approved researchers to work with healthcare providers to identify potential patients to be contacted about research studies in which they might wish to participate. The Information Commissioner's Office and the new Health Research Agency should work with the health departments and other stakeholders to provide definitive guidance on this issue. This should state that researchers, or appropriate members of a research team such as research nurses, working on an ethically approved study should be considered part of a clinical care team for the purposes of accessing data to identify patients eligible to be contacted about research studies. The initial contact with these patients about a research study would be by a member of the patient's clinical care team (i.e. not a researcher).

## 7 Use of tissue and embryos in research

### 7.1 Introduction

Many research studies are underpinned by the use of human tissue to improve understanding of how diseases start and progress, and what keeps us healthy. The use of human tissue samples for research into, for example, cancer leads to improvements in diagnosis through the identification of biomarkers that help to develop new and more targeted treatments. Most clinical trials require tissue samples (e.g. blood, saliva, urine or tissue biopsies) from trial participants to be taken on a regular basis, to establish the impact of interventions. With the increasing role that genetic profiling will play in health research, access to tissue samples is an ever more vital element of research studies. Examples of types of research involving human tissue include: developing screening tests for different types of cancer, testing new treatments for conditions such as heart disease, and researching how stem cells could be used to treat conditions such as multiple sclerosis (see also Box 7.1).

In many instances tissue is removed during the course of regular clinical investigation or treatment, and there may be some tissue remaining after the procedure that can be used for

research. At the PPI meeting we heard of patients' desire for such tissue to be used in research:<sup>104</sup>

*'A lady I knew who had had radiotherapy couldn't undergo it a second time when her cancer recurred. She had to have her ovaries removed and was asked if she would donate them for research. It made losing them so much more bearable. It's so important to have choice.'*

Tissue for research can only be used with a person's consent, unless it has been adequately anonymised or the material is used for a specific research project approved by a recognised Research Ethics Committee (REC). A person may also give consent for their tissue to be used for research after their death. As in the case of the use of patient data (Chapter 6), it is important that transparent processes are in place to support Principle 1 (safeguard participant well-being).

Human embryos up to 14 days old can be used in research designed to increase knowledge about serious disease or its treatment. Such research is conducted primarily through the isolation of embryonic stem cells that are grown and transformed into specialised cells (e.g. muscle or nerve cells) through *in vitro* cell culture.

#### Box 7.1 Example of use of tissue in research: UK Biobank<sup>105</sup>

UK Biobank is a major UK health research initiative with the aim of improving the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses including cancer, heart disease, diabetes, arthritis and forms of dementia. It has reached its goal of recruiting 500,000 people aged 40-69 years.

Participants in UK Biobank are asked to attend a local assessment centre for two to three hours to answer health questions, to have some standard measurements taken and to give small samples of blood, saliva and urine. These samples and the health related information are stored by UK Biobank and will be used in an anonymised form by researchers for multiple different studies.

UK Biobank is funded by the Wellcome Trust, the Medical Research Council, the Department of Health, the Scottish Government, British Heart Foundation and the Northwest Regional Development Agency. The project is also supported by the NHS.

<sup>104</sup> Association of Medical Research Charities & INVOLVE (2010). *Patient perspectives on the regulation and governance of medical research*. <http://www.invo.org.uk/pdfs/AMRCINVOLVERegulationWorkshopReport211210.pdf>

<sup>105</sup> For further information see <http://www.ukbiobank.ac.uk/>



## 7.2 Current environment overview

The following sections outline current legislation and roles of the Human Tissue Authority (HTA)<sup>106</sup> and Human Fertilisation and Embryology Authority (HFEA).<sup>107</sup>

### 7.2.1 Human Tissue

The Human Tissue Act (2004) for England, Wales and Northern Ireland covers the removal, storage and use of 'relevant material'.<sup>108</sup> It is perceived by the research community that the development of the Act was largely influenced by the public reaction to events at Alder Hey Hospital, which involved the unauthorised removal, retention and disposal of human tissue and organs. Many respondents felt that this has led to particularly stringent legislation in relation to the use of human tissue from living subjects.

In comparison, evidence that we received highlighted the Human Tissue (Scotland) Act (2006) as offering some flexibility on the use of tissue for research compared with the Act that covers England and Wales. Scottish legislation on human tissue is confined to post-mortem tissue.<sup>109</sup>

### 7.2.2 Human embryos

The Human Fertilisation and Embryology (HFE) Act (1990) established the HFEA.<sup>110</sup> The original scope for research on embryos under that Act was limited, but was expanded in 2001 by Regulations to enable work leading to the creation of human embryonic stem cell lines. The Act was further amended in 2008 to permit work on human admixed embryos, i.e. human embryos containing some animal material.

The existing law sets out several requirements for the regulation of research on human embryos, notably the following: that such research can only be conducted under licence (which is backed up by inspection); that

the licensing decision rests with an HFEA Committee (with a majority of lay members); and that the decision is based on two tests of whether the research is 'necessary or desirable' and that the use of embryos is 'necessary'.

## 7.3 Problems identified

It is important to highlight that, as with ethical approval (Chapter 8), it is clear that many people feel that significant progress has been made in the regulation and governance of tissue and embryos, and that compared with an area such as use of patient data there is a much clearer regulation and governance pathway.

Few of those who responded to our first call for evidence focused on the HFE Act and the role of the HFEA. One reason for this could be due to the small number of project licence applications (36 projects were licensed in 2006-07).<sup>111</sup> However, it most likely reflects a broad view that the regulatory processes relating to research applications involving embryos work reasonably well. The response to the Government's proposal to abolish the HFEA (section 9.2.1) has been met with concern by many stakeholders. It is notable that the role of the HFEA in facilitating recent debate about the use of human admixed embryos in research has earned it the confidence of researchers and the wider stakeholder community. We do not make any specific recommendations about the regulation of research involving human embryos, but the role of the HFEA in our new pathway for the regulation and governance of health research is outlined in Chapter 9.

### 7.3.1 Human tissue legislation

The Human Tissue Authority regulates the storage of human tissue for research based on the definition of 'relevant material' in the Human Tissue Act (2004). Section 53(I) of the Act states it should be applied to 'relevant

<sup>106</sup> For further information see <http://www.hta.gov.uk/>

<sup>107</sup> For further information see <http://www.hfea.gov.uk/>

<sup>108</sup> For further information see <http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/legislation/humantissueact.cfm>

<sup>109</sup> Human Tissue Authority (2006). *Human Tissue (Scotland) Act 2006: a guide to its implications for NHS Scotland*.

[http://www.hta.gov.uk/db/documents/Information\\_about\\_HT\\_\(Scotland\)\\_Act.pdf](http://www.hta.gov.uk/db/documents/Information_about_HT_(Scotland)_Act.pdf)

<sup>110</sup> Department of Health (2008). *Human Fertilisation and Embryology Act 2008*. <http://www.legislation.gov.uk/ukpga/2008/22/contents>

<sup>111</sup> Human Fertilisation and Embryo Authority (2008). *Human embryo research in the UK*.

[http://www.hfea.gov.uk/docs/HFEA\\_Human-Embryo-Research-06-07.pdf](http://www.hfea.gov.uk/docs/HFEA_Human-Embryo-Research-06-07.pdf)



*material... which consists of or includes human cells*'. The only listed exceptions to this definition are the following: '*gametes*', '*embryos outside of the human body*' and '*hair and nail from the body of a living person*'. Therefore the current legislation is applied to – and there is a need for a HTA licence for – research involving bodily fluids (e.g. blood serum and plasma) and bodily waste products that include human cells (e.g. urine, faeces and saliva).

Respondents highlighted the broad scope and application of the Human Tissue Act to materials such as urine, faeces and saliva as the main barrier to research involving human tissue. Obtaining and maintaining an HTA licence was described as a costly and time consuming exercise. Although obtaining a licence was considered important for certain tissues, for example samples of tumours from biopsies or surgery, respondents felt it was not appropriate or necessary for samples of blood plasma and urine. It was suggested in submitted evidence that problems created by the current over-application of the Act are exacerbated for research conducted in universities, as both the institution (the university) and the premises (e.g. each department) have to be licensed. There was a strong belief among those we consulted that the current situation unnecessarily increases costs and bureaucracy and was not the intention of the Act, which was introduced to prevent inappropriate retention of body parts and whole organs, i.e. any repeat of events similar to those at Alder Hey.

The HTA is obliged to regulate according to the terms of the Act and its remit does not extend to applying a proportionate approach to the range of materials within the Act's scope. It has previously drawn attention to the need to clarify the definition of 'relevant material' and amend the legislation.

We consider that the current application of the Human Tissue Act does not present a proportionate approach. Nor is it consistent for hair and nails to be excluded from the Act whereas materials such as saliva and urine are

retained. To address these issues and ensure a proportionate approach to the regulation and governance of the use of tissue from living subjects, we recommend that further materials are made exempt from the Act and are explicitly listed in the Authority's explanatory notes and guidance (Recommendation 11).

Finally, there are differences in law and practice between Scotland and the rest of the UK in the regulation of research involving human tissue, which cause delays in setting up multicentre trials - even though Scotland applies similar standards to the rest of the UK but on a non-statutory basis. We understand that the Chief Scientist's Office in Scotland is currently investigating the potential for the HTA to inspect its 14 Health Boards to provide reassurance to researchers that appropriate standards are being met. This may further reduce the differences between the regulation and governance of research involving tissue between the devolved nations. Respondents highlighted the advantages of the regulation of human tissue in Scotland. In considering changes in the types of material included in the Human Tissue Act, we suggest that an analysis of the impact of the Act on health research be undertaken using the approach taken in Scotland as a comparator. In Chapter 9 we outline the important role that a new Health Research Agency could play in facilitating a UK-wide approach to regulation and governance.

### **7.3.2 Human tissue governance**

Although it is the responsibility of the HTA to grant a licence for research involving human tissue, this is an area where NHS R&D offices frequently undertake additional checks. Respondents felt this has resulted in increased stringency with which the regulations are being interpreted at the NHS R&D level, making the practicalities of using human tissue samples for research excessively complicated (see Box 7.2). Given that licences are provided by the HTA, and ethical approval for specific projects is granted by RECs, there should be no need for R&D offices to query these aspects of research projects. The

**Box 7.2 R&D permissions and tissue**

Evidence submitted to our review described an instance of a project with REC approval 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 assessments were required under the Research Governance Framework, because tissue collection centres were not deemed research sites. However, most of the NHS R&D departments of the recruitment centres *still* insisted that their clinicians make formal applications through the site-specific assessment process, leading to significantly increased time and cost, with no discernable positive impact on patients' or participants' interests.

focus at the NHS R&D permission level should be on ensuring that generic capacity to undertake research using human tissue is in place (e.g. consistent use of Material Transfer Agreements). We discuss the need to avoid NHS R&D offices 'rechecking' approvals such as these in Chapter 4.

One contributing factor to the variable approach at NHS Trust level is the lack of clear and consistent guidance on the regulation and governance of research involving tissue. Although a large amount of guidance has been produced to assist researchers navigating the approvals process, we received considerable evidence that the lack of consistent guidance on the approvals that are required to access tissue for research continues to be problematic. One example where clearer guidance is needed relates to consent options for setting up tissue banks. A number of respondents appeared unaware that it is possible to apply for 'generic' ethical approval for HTA-licensed tissue banks via a voluntary scheme

operated by the National Research Ethics Service. An OnCore UK survey of 242 researchers was undertaken in 2009, of whom 73% described themselves as active in research using human tissue or biological samples. More than half of the respondents (60%) to this survey said that they found doing research difficult because of access to appropriate guidance, with 70% reporting that the provision of guidance by different sources is confusing and unhelpful.<sup>112</sup> As a result, some healthcare workers and potential researchers are put off participating in or assisting with research in this area (in the survey 13% of respondents said that they do not conduct research as a consequence of lack of access to appropriate guidance). Strikingly, 83% of respondents said that they would increase their research activity if there was an easily accessible source of consolidated guidance endorsed by all regulators.

The regulation and governance of human tissue is addressed further in Chapter 9.

**Recommendation**

*There has been much progress in the approach to regulation of human tissue in research across the UK, with stakeholders indicating that they are largely clear on the requirements. However, the regulatory approach taken in England is seen to be disproportionate, whereby the broad definition of 'relevant materials' in the Human Tissue Act does not appear to have been determined against any specific categories of risk, and there is a lack of consistency in approach to the materials listed as exemptions. We therefore recommend that:*

**Recommendation 11:** Hair and nails from living subjects are already excluded from the materials covered by the Human Tissue Act. To ensure a proportionate approach to the regulation and governance of the use of tissue from living subjects, the following exclusions should be introduced: plasma, serum, urine, faeces, and saliva.

## 8 Ethics review

### 8.1 Introduction

All research studies in the NHS that involve human participants, their tissue or data must successfully undergo ethics review. Research proposals are reviewed to consider whether they provide sufficient protection for the interests and safety of research participants and to enable ethical research that is of benefit to society. In most cases, health research studies are reviewed through the National Research Ethics Service (NRES). The Department of Health's report on the arm's-length bodies review in July 2010 proposed that the National Patient Safety Agency (NPSA), which houses NRES, would be abolished.<sup>113</sup> This issue is considered further in Chapter 9.

This chapter examines recent advances in UK ethics review and highlights opportunities for further improvement. There was clear consensus from the responses received that the process for ethics review has been dramatically enhanced in recent years through streamlining of the process and the introduction of timescales. However, some respondents raised remaining concerns about review by NHS Research Ethics Committees (RECs), including the lack of proportionality in the system.

Alongside NHS R&D permissions, ethics review is a core assessment for all health research studies and we return to its central role in the regulation and governance pathway in Chapter 9.

### 8.2 Ethics review in the UK

#### 8.2.1 Overview

Ethics review in the UK is largely based upon the Declaration of Helsinki, which is an internationally recognised framework that sets out the principles for conducting ethical health research.<sup>114</sup>

In the UK a range of bodies are involved in ethics review. The appropriate body for review will depend on the type of research being undertaken:

- NRES incorporating the NHS RECs and the Social Care Research Ethics Committee.
- Independent Ethics Committees (IECs), designated by the Appointing Authority for phase I Ethics Committees (AAPEC), review phase I Clinical trials of Investigational Medicinal Products (CTIMPs) that take place outside of the NHS.
- The Gene Therapy Advisory Committee (GTAC) undertakes ethics review of research on gene or stem cell therapies.
- Ministry of Defence (MoD) research ethics committees, collectively known as MoDREC, review studies involving MoD personnel.
- University ethics committees.

University ethics committees operate on an independent basis, with no external oversight or authority, and generally consider issues of an ethical nature arising from teaching or research in their institution. Because all health research in the NHS is reviewed by RECs, which are centralised to ensure that review is undertaken to UK-wide standards, there is not generally a requirement for a separate university ethics committee review. University ethics committees are therefore not considered further in this report.

#### 8.2.2 The National Research Ethics Service

NRES is the overarching body for NHS RECs in England. NRES was established in 2007 and is part of the NPSA. NRES comprises the 85 NHS RECs in England, the unpaid members that serve on those committees, local REC staff and the NRES division at the NPSA. NRES provides: ethical guidance and management support to RECs, a quality assurance framework for the ethics services; and training programmes. NRES administered 6,321 applications in England between April 2009 and March 2010.

<sup>113</sup> Department of Health (2010). *Liberating the NHS: report of the arm's-length bodies review*.

[http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/@dh/@en/@ps/documents/digitalasset/dh\\_118053.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_118053.pdf)

<sup>114</sup> World Medical Association (1964). *Declaration of Helsinki: ethical principles for medical research involving human subjects*. <http://www.wma.net/en/30publications/10policies/b3/index.html>

There is no charge for ethics review by a REC and costs are covered by the NRES budget of £10.1 million, provided by the Department of Health.

The role of RECs is set out in the Research Governance Framework and the opinions given by RECs sit within a wider legal framework, including the Mental Capacity Act (2005), Human Tissue Act (2004) and similar legislation in the devolved nations.

### **8.2.3 REC review in the regulation and governance pathway**

Because positive opinion from a REC is required for all studies that take place in the NHS, this review forms a core component of the regulation and governance pathway. There are important interdependencies between REC review and other assessments, including the following:

- A positive REC opinion is a condition of NHS R&D permissions (Chapter 4).
- Other regulatory and governance organisations take into account ethical considerations and therefore these assessments potentially overlap with those of RECs. Examples include the Human Tissue Authority (HTA) and the Human Fertilisation and Embryology Authority (HFEA) (Chapter 7); and the Ethics and Confidentiality Committee (ECC) of the National Information Governance Board (Chapter 6).
- A role for RECs in CTIMPs is set out in the EU Clinical Trials Directive (CTD) (see section 8.3), which created a statutory role for ethics committees in safety reporting in clinical trials (Chapter 5).

NRES has taken a proactive approach in improving aspects of the wider regulatory environment in the UK by liaising with organisations involved in specialist ethics review. It has also interacted with other parts of the regulation and governance pathway to reduce bureaucracy and streamline processes. For example, NRES has Memoranda of Understanding with Medicines and Healthcare products Regulation Authority (MHRA), AAPEC and GTAC to clarify the roles and responsibilities of these parties in relation to CTIMPs.

## **8.3 Recent progress in streamlining ethics review**

NRES and its predecessor, the Central Office for Research Ethics Committees (COREC), have made substantial improvements to the process of ethics review. The development of a single UK-wide opinion has been an important success in streamlining regulatory and governance processes in the UK.

The CTD, transposed into UK law as the Medicines for Human Use (Clinical Trials) Regulations (2004), imposed a requirement for Member States to issue a single opinion on ethics review for CTIMPs, within 60 days. The four UK administrations have produced a Standard Operating Procedure (SOP), to fulfil this requirement. This has enabled a single UK-wide ethics opinion to be provided for multicentre trials across the UK. In addition to CTIMPs, this arrangement has been adopted for all other studies and an average time from application to ethics opinion is now around 35 days. Current timelines and a brief description of the current system are included in Box 8.1.

### **Box 8.1 Streamlining ethics review: a single UK-wide opinion**

Depending on the type of study, an application for ethics review can be made directly to a REC in the area where the study is to be conducted, or to a REC allocated by NRES. Allocations are facilitated by a telephone booking service (the NRES Central Allocation System). Applications are submitted through the Integrated Research Application System (IRAS) and for multi-site studies a single application is made to the 'main REC' allocated for the study. The main REC is responsible for all aspects of the ethics review and, where site-specific assessment is required, these issues are taken into account as part of the single opinion. This ensures that the opinion given by the main REC applies to all UK sites where the research will take place. NRES has set a 40 day operational target for ethics review which is 20 days less than the statutory timescale.

Key improvements in REC review since 2004 include the following:

- In 2004 the time taken for review was unknown but widely criticised. The current average is around 35 days.
- The number of applications per year has fallen from 9,760 in 2004 to 6,321 because of the elimination of duplicate reviews of protocols for multi-centre studies.
- The number of RECs has been reduced from 200 to 85.
- NRES has also dramatically reduced the number of locations of NRES staff.

### **Box 8.2 IRAS: progress and future development**

IRAS is a web-based system that allows information required for most regulatory and governance assessments to be entered in one place. It captures the information required for assessments, including the following:

- National Research Ethics Service.
- Gene Therapy Advisory Committee.
- Administration of Radioactive Substances Advisory Committee (ARSAC).
- Ministry of Justice.
- Medicines and Healthcare products Regulatory Agency (MHRA).
- Ethics and Confidentiality Committee of the National Information Governance Board (NIGB).
- Human Fertilisation and Embryology Authority (HFEA).
- NHS R&D permissions.

IRAS was developed in a collaboration that included the UK Health Departments and the UK Clinical Research Collaboration partners. It is now hosted within NRES.

IRAS is generally considered to have been successful in streamlining the application process for regulatory and governance assessments. However, some responses to our call for evidence raised criticisms. For example, the requirements listed in IRAS for a Clinical Trial Authorisation did not match the requirements expected by MHRA at the time the application was made. Other responses noted where change could bring even greater value from the system including improvements to navigation, increased flexibility to suit a wider range of studies, 'multi-authoring' capabilities and track changes, joint training sessions between representatives of the regulators covered by IRAS and shortening (and re-organising) of some parts of the form. It is likely that some of these issues will be addressed as part of improvements that are already planned to make the system easier to navigate and to enable collaboration between researchers when completing applications.

Although the remit of NRES is confined to England, its interaction with counterparts in the devolved nations has been an essential component of its success. NRES provides some functions to ethics services of the devolved nations and the IECs and also hosts two UK-wide services:

- The National Research Ethics Advisory Panel (NREAP) was established to deal with strategy, quality assurance and service development of RECs and to improve the research environment in the UK.
- IRAS provides a single portal for regulatory and governance applications. Box 8.2 highlights the progress made and potential improvements identified in the Academy's call for evidence.

The process for a single UK-wide ethics opinion has been achieved through collaboration and agreement between the ethics services across the four administrations. This has required procedures to overcome legislative differences between the administrations including, for example, use of human tissue and mental capacity legislation. This single national system compares favourably with the Institutional Review Board (IRB) and Research Ethics Board (REB) approvals in the US and Canada respectively, since IRBs and REBs are not subject to statutory timescales and currently neither the US nor Canada has a mechanism for obtaining a single approval for multicentre studies. A single UK-wide opinion is therefore a significant achievement and provides an excellent demonstration that streamlining across the four administrations is possible. How collaboration between the UK administrations could further improve the regulatory and governance environment for health research is discussed in Chapter 9.

RECs currently operate under separate policies for England and the devolved nations. However, a harmonised version of Governance Arrangements for Research Ethics Committees (GAfREC) is currently being developed to incorporate legal and policy developments since 2001 and will apply through all four countries. The developments and recommendations set out in this report should also be incorporated into GAfREC.

## 8.4 Building on progress

The balance of evidence submitted to this review highlights that ethics review is rarely a rate-limiting step. This view is consistent with NRES statistics that show that the average application time is currently around 35 days (Box 8.1). It is important that the momentum achieved by NRES is maintained and that opportunities are taken to further reduce timescales and enhance the quality and efficiency of the process.

### 8.4.1 A proportionate approach to ethics review

The need for a proportionate approach to regulation and governance is discussed in Chapter 2. It is particularly important to adopt a proportionate approach to ethics review because of the diversity of research that undergoes this assessment, which includes: questionnaires for staff and patients, minimally interventional studies and clinical trials of new drugs. The benefits of a proportionate approach are recognised in both the US and Canadian ethics review systems, as discussed in Box 8.3.

### Box 8.3 Proportionality in ethics review in the USA and Canada

Institutional Review Boards (IRBs) in the USA and Research Ethics Boards (REBs) in Canada undertake all the ethical approvals required for studies with human participants, their data and tissue.

#### USA

In the USA, the federal Department of Health and Human Services oversees regulation on the Protection of Human Subjects, which includes a categorisation of projects according to the risk posed to the participant:

- Studies exempt from IRB review include research involving survey or interview procedures, observations of public behaviour, or diagnostic specimens where the subject cannot be identified.
- Studies are subject to expedited IRB review where 'the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests'. This category of minimal risk includes research on drugs for which an investigational new drug application is not required or the collection of biological specimens or data for research through non-invasive means.
- Research on human subjects that is deemed to present more than minimal risk is subject to full IRB review.

#### Canada

Proportionate review is a key feature of the Canadian tri-council policy statement (TCPS), which acknowledges that 'research involving humans covers the full spectrum from minimal to significant risks...A reduced level of scrutiny of a research project with minimal risks does not imply a lower level of adherence to the core principles. Rather, the intention is to reduce unnecessary impediments and facilitate the progress of ethical research.'

The TCPS sets out categories of research that are exempt from REB review. Minimal risk research is defined as 'research in which the probability and magnitude of possible harms implied by participation in the research is no greater than those encountered by the participant in those aspects of his or her everyday life that relate to the research' and is generally eligible for delegated review by an individual designated by a REB.

In 2009, in response to a review of the operation of NHS RECs by an *ad hoc* advisory group set up by Lord Warner,<sup>115</sup> NRES introduced a pilot scheme for proportionate review of studies that represent 'no material ethical issues'. The scheme is designed to increase the efficiency of the service and enable studies such as questionnaires for NHS staff, and research on anonymous tissue or data, to be reviewed within 10 days. The pilot started at four London RECs and has since been expanded. The average review

time in the pilot is currently 7.2 days from validation of the application to notification of opinion. The application is considered by a sub-committee of at least three members, including a lay member, either at a meeting or by correspondence. NRES expects that the number of RECs could be further decreased on full implementation of proportionate review.

Several respondents to the first call for evidence raised concerns about the lack of proportionality in the ethics review system,

115 Department of Health (2005). *Report of the ad hoc advisory group on the operation of NHS Research Ethics Committees*. [http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/@dh/@en/documents/digitalasset/dh\\_4112417.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4112417.pdf)



for example, questionnaires of healthcare practitioners requiring full ethics review. However, the proportionate review pilot is now available to all researchers in the UK, albeit only through a small selection of the RECs. We support the further roll out of this pilot, which will be important to address the existing lack of proportionality.

Although the proportionate review pilot has reduced the time taken to obtain an opinion for certain types of study, this evidence suggests that there would also be value in extending a proportionate approach to other study requirements. One respondent noted that even minor changes to the protocol that are required after approval are often deemed to be 'substantial' amendments. The application of a proportionate approach across health research is addressed further in Chapter 9.

#### **8.4.2 Consistent advice and guidance**

Consistency in the application of ethical principles is an important feature of an effective, transparent and reasonable ethics review. Some respondents raised the lack of consistency in decisions by RECs as a concern although no specific examples were provided. A small scale evaluation in 2007 did highlight some lack of consistency between REC decisions,<sup>116</sup> although it has been acknowledged that consistency of decision making across RECs is difficult to assess in a robust way. In addition, because each study involves the consideration of multiple factors, apparently different decisions do not necessarily imply inconsistency. The NRES submission to the Academy noted that further improvements to quality and consistency are the '*most important challenge*' facing the service and NRES plans to use training and quality assurance to address these issues.

Some of the evidence suggested that the current ethical guidance to researchers can be variable and inconsistent and respondents encouraged the further development of clear

advice. NRES has introduced a pilot scheme that has sought to improve the ethics review process by providing guidance to researchers before their application is sent to the REC. This should enable problems with the application to be identified and resolved before consideration by the REC. We encourage the wider implementation of this system in order to address these concerns.

High ethical standards are integral to successful research practice, but can only be partly achieved through regulation and governance. For example, it is important that researchers take responsibility to identify the ethical issues arising in their research. Chapter 3 notes the important role that culture plays in the conduct of research and this approach will require an appropriate research culture that considers the ethical dimensions of studies, and the development of the ethical skills of researchers, to be central to good practice. On a practical level, researchers need to be supported by advice and training that is available to them independently of obtaining a REC opinion. Recommendation 12 sets out an approach to achieve this.

#### **8.4.3 Specialist expertise**

A few responses to the call for evidence questioned the level of specialist expertise on some RECs, for example in paediatrics. They noted that ethics review is a far more constructive process with an informed committee with relevant expertise. In the current system, certain RECs are 'flagged' for their expertise in a particular area such as mental capacity, tissue banks and databases, medical devices, certain types of CTIMPs and low-risk gene therapy. Such a system could be extended to cover other areas where specific expertise is important and committee expertise may need to continue to develop in response to scientific advances in areas such as genomics.



**Recommendation**

*We welcome the progress that the National Research Ethics Service (NRES) has made in recent years. Under the new arrangements outlined in Chapter 9, NRES should maintain this momentum to ensure that further improvements are made, for example to increase consistency and specific committee expertise and reduce timescales. High ethical standards in research can only be partially achieved through regulation and governance and researchers need support to identify and address the ethical issues arising in their research, outside of applying for an ethics opinion. In addition to the need to embed a proportionate approach within the ethics system, including implementation of 'proportionate review' following the NRES pilot, we recommend that:*

**Recommendation 12:** NRES should lead on improving support and advice for researchers by providing centralised, coordinated guidance and training on ethical issues for health researchers. Institutions engaged in health research should also improve the local availability of ethics advice and the training of local support staff.



## 9 A new Health Research Agency

### 9.1 Introduction

In this Chapter we draw on submissions to the calls for evidence and the conclusions from the previous chapters, to introduce our recommendation for the establishment of a new Health Research Agency to oversee the regulation and governance of health research. In July 2010, the Department of Health in England published '*Liberating the NHS: report of the arm's-length bodies review*', which set out a plan to re-organise various Arm's-Length Bodies and included the proposal to create a single regulator of research.<sup>117</sup> The Health Research Agency (HRA) that we recommend and the roles and responsibilities we outline below are a development of the Government's proposal and address the major challenges and bottlenecks described in this report.

In this chapter we review each of the three main regulatory and governance assessments (ethical approvals and licences; clinical trial authorisation; and NHS R&D permissions) and consider the extent to which these functions should be brought within the remit of the HRA. We also consider the wider role that the HRA could play in transforming the regulatory and governance landscape and improving the culture and ethos of health research in the UK.

### 9.2 Reducing complexity across the regulation and governance pathway

Responses to the first call for evidence demonstrated that stakeholders find the current regulation and governance pathway extremely complex. Respondents described multiple layers of regulation and governance resulting in uncertainty of interpretation, a lack of trust in the system, duplication and overlap in roles

and responsibilities, and a lack of leadership and coordination. This evidence demonstrated a clear need to reduce complexity of the overall framework as well as improving individual elements of the pathway.

#### 9.2.1 The arm's-length body review

In July 2010 the Department of Health published '*Liberating the NHS: report of the arm's-length bodies review*' (ALB review). Specifically, the review set out proposals to:

- Create a single research regulator.
- Abolish the National Patient Safety Agency (NPSA) which has previously had responsibility for the National Research Ethics Service (NRES).
- Transfer the research regulatory functions of the Human Tissue Authority (HTA) and Human Fertilisation and Embryology Authority (HFEA) into the new single research regulator by the end of the Parliament. The ALB review proposes that the non-research functions of the HTA and HFEA are reassigned to the Care Quality Commission.

The Academy was invited by Government to consider the merits and potential scope and function of a single research regulator in the context of the current review.

#### 9.2.2 Opportunities and challenges of a single research regulator

In July 2010, the Academy issued a second call for evidence focusing on the potential functions of a single research regulator. We received over 100 responses. The recommendations made in this chapter are based on the evidence received to both the first and second calls for evidence, as well as subsequent discussions with key individuals and organisations.

<sup>117</sup> Department of Health (2010). *Liberating the NHS: report of the arm's-length bodies review*. [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_117691](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_117691)

Most respondents saw the creation of a single research regulator as an important opportunity to: simplify the system; more closely align the disparate elements of regulation; and increase

consistency. The views of the BioIndustry Association and the Wellcome Trust reflect those of many respondents:

#### **BioIndustry Association**

*'There is no evidence to support the view that multiple layers of regulatory review and governance checks required by several government agencies/committees and NHS Trusts would enhance the safety, rights and well-being of patients. On the contrary, these often duplicated administrative burdens have the potential to undermine public health by delaying important medicines being investigated in clinical trials and adding extra costs to product development unnecessarily.'*

#### **Wellcome Trust**

*'The multiple layers of bureaucracy, approvals processes and reporting requirements are introducing unnecessary delays and costs that hamper research. Rationalisation to streamline processes, provide efficiencies, and save money would provide real benefits. This could be achieved by reducing the number of layers involved in the oversight of various regulations.'*

In responses to the first call for evidence, the Netherlands was frequently cited as a country with a good record in research approvals. Its regulation and governance pathway is based

around a single research regulator, described in Box 9.1, which provides a useful example of how this approach can work in practice.

### **Box 9.1 Operation of a single research regulator in practice: regulation of health research in the Netherlands**

In the Netherlands, the Central Committee for Research Involving Human Subjects (CCMO) acts as a single research regulator.

Most studies on human participants, including most clinical trials of investigational medicinal products, apply for ethical approval from one of the 30 local Medical Research Ethics Committees (METCs). However, less routine studies, such as those involving gene therapy, RNA interference, antisense oligonucleotides, stem cell therapies, xenotransplantation, vaccines and non-therapeutic interventional studies on subjects without capacity and embryology, are considered by the CCMO. As part of CCMO or METC assessment the suitability of participating sites is considered, including review of a 'local feasibility declaration'.

The CCMO acts as a central ethics committee and a single approval from either an METC or the CCMO is required for multi-site studies. In addition to the CCMO's function in assessing specific studies, it also:

- Accredits and monitors the METCs.
- Keeps a register of, and analyses trends in, approved protocols.
- Acts as an appeals body.
- Provides guidance on the relevant legislation.

CCMO is also the National Competent Authority for clinical trial authorisation under the Clinical Trials Directive. The Netherlands is the only EU Member State to have implemented the Directive such that the ethical approvals and clinical trial authorisation are combined within a single organisation.

Respondents to the second call for evidence did not underestimate the challenges of setting up a single research regulator. They stressed that any reorganisation must avoid disrupting the parts of the system that currently deliver within reasonable timescales, including clinical trial authorisation by Medicines and Healthcare products Regulatory Agency (MHRA) and the provision of ethics opinions by NRES. Any model must be structured and managed in a way that streamlines the current process rather than, as some respondents feared, create another layer in the regulation and governance pathway. Participants at the PPI workshop also raised concerns that bringing all the regulation related to health research into one body could lead to a perception that '*researchers are regulating researchers*' thus losing the wider focus of the original bodies involved in this process. In sections 9.4.2 and 9.4.5 we outline ways in which confidence and trust can be built and maintained by the new body, including by public and patient involvement.

### **9.2.3 Vision for a single research regulator**

In general, respondents to the call for evidence considered that the challenges of establishing a single research regulator were not insurmountable and were outweighed by the benefits. Submissions to the calls for evidence and the principles for health research regulation and governance set out in Chapter 2 suggest the following potential roles for a single research regulator:

- Providing a single point of entry and exit for applications for the UK, as well as a single point of contact for each study.
- Overseeing all the approvals required for health research involving human participants, their tissue or data.
- Reducing inefficiencies and overall timescales for all regulatory and governance assessments by setting, and delivering to, a standard national timescale.
- Leading on the development of proportionate approaches to regulatory and governance processes.

- Horizon-scanning to consider developments with potential ethical or regulatory implications.

### **9.3 The creation of a Health Research Agency**

Based on the evidence received and subsequent engagement with stakeholders, we recommend the creation of a new Health Research Agency (HRA) with the following functions (Recommendations 13 and 14):

- To bring together the provision of ethics opinions and specialist approvals and licences to increase clarity, consistency and efficiency. NRES would become a key component of the HRA and continue to provide a single UK-wide ethics opinion through the established structure of RECs (see section 9.5.1). The HRA would provide a streamlined system for 'specialist approvals and licences' subsuming the research regulation functions of other organisations (see section 9.5.1).
- To include a new 'National Research Governance Service' (NRGS) for England, outlined in Chapter 4, which would perform all study-wide NHS governance checks and recommend research projects as suitable for undertaking within the NHS (see section 9.5.2).
- To work with the MHRA to ensure that regulatory processes are cohesive and assist in providing guidance on whether a requires clinical trial authorisation (see section 9.5.3).

The model proposed for the HRA is a genuine single regulator with NRES as a core component, combined with NHS governance functions. It was stressed in the evidence that the creation of a single research regulator that focused solely on ethical issues would not address the major barrier to health research that is posed by NHS permissions. We also considered, and rejected, two alternative models:

- **Façade model:** A single body could operate as a façade in which existing research regulatory components are brought together and housed in the single organisation without further streamlining. Submissions to the call for evidence raised fears that a façade model would simply add another layer of bureaucracy without reducing complexity. It was clear from the evidence received and from working group discussions that it would be necessary for the proposed body to have a core role as a genuine single regulator to fulfil the vision set out in Chapter 2 and section 9.2.3. The façade model was therefore rejected.
- **Transforming MHRA into the single research regulator:** A small number of stakeholders proposed that the ethics and specialist approvals and licences should be brought within the remit of MHRA. We did not support this suggestion because MHRA only has responsibility for clinical trials of investigational medicinal products rather than the full spectrum of health research that would need to be within the scope of the new body. In addition there are concerns about MHRA's ability to engage effectively with sponsors of non-commercial research including universities and the NHS; and there is a question whether public confidence about, for example, sensitive ethical issues could be maintained within an organisation primarily focused on the licensing of drugs for pharmaceutical companies.

The costs of regulatory and governance activities are currently covered by central funding, for example from the Department of Health (e.g. NRES), or by cost-recovery through fees (e.g. MHRA). Examining the financial implications of a new model was not part of our Terms of Reference but responses to the call for evidence stressed that the creation of a single research regulator should not introduce additional costs to researchers. However, if the HRA is implemented effectively we would expect any additional costs to be outweighed by

the overall financial benefits to the UK. These include economies of scale by centralising ethical and governance approvals, reductions in costly delays to public- and charity-funded research, and attracting and maintaining inward investment by the life sciences industry. In addition, as outlined in Chapter 1, outcomes of health research can reduce the burden on the NHS by identifying ineffective treatments, identifying disease at a stage where it can be treated at less cost (through screening) and improving public health.

## **9.4 The implementation and operation of a Health Research Agency**

For the HRA to be effective in fulfilling the principles set out in Chapter 2, several key factors must be considered from the outset.

### ***9.4.1 The need for prompt action and the rapid creation of the HRA***

The HRA needs to be created quickly to minimise further uncertainty and the potential disruption to regulatory and governance processes. This will also enable the HRA to start to make progress on solutions to current problems without delay, with a priority focus on the establishment of the NRGs. We therefore recommend that the HRA should be created as soon as possible as an interim Special Health Authority and established in primary legislation in due course (Recommendation 13).

### ***9.4.2 Building and maintaining the confidence of stakeholders***

The HRA will have stakeholders with whom it must earn and retain trust and confidence. They include patients and the public, the NHS, and other commercial and non-commercial research sponsors. For the NRGs component of the HRA to radically reduce timescales for NHS permissions, Trusts must have confidence in the Agency's processes and procedures, and patients and the public must feel reassured that the HRA will protect their interests.

Features of the HRA that will be essential to gain and maintain the confidence of these stakeholders are the following:

- *Independence.* The HRA must be created at arm's-length from the Department of Health. This will ensure that it has the neutrality to handle potentially difficult ethical issues yet retain public confidence.
- *Strong leadership and expertise.* These will be required on a day-to-day level to ensure that the HRA is equipped to manage the wide-range of studies and issues within its remit, and on a strategic level to drive forward the important changes for which the HRA will be responsible. This must include public and patient involvement to enable the interests of the lay public to be reflected as well as those of the research community (section 9.4.5).
- *Transparency.* The HRA should publish its underlying principles, policies and procedures (section 9.6).
- *Accountability.* The HRA should have mechanisms in place for appeal and review of decisions, and its performance should be assessed through regular review and published metrics.
- *Dialogue with other organisations.* The HRA must work closely with other bodies involved in health research, throughout the UK, to ensure a smooth transition and to bring about genuine improvements to the regulation and governance pathway.

#### **9.4.3 Taking a UK-wide approach**

Responses to the call for evidence made it clear that facilitating a streamlined UK-wide regulatory system was an important feature of the HRA. This would make it easier for researchers to set up studies across the whole of the UK and make the UK a more attractive international location for conducting research. However, there are potential difficulties in achieving this ideal because there are differences in current regulatory and governance arrangements between the four administrations. We consider this difficulty to be surmountable. We expect the HRA to work

by agreement with its counterparts in the devolved administrations and to streamline processes through shared standard operating procedures. The development of a single UK-wide ethics opinion demonstrates how such an arrangement can to work.

The HRA should collaborate with the devolved administrations to examine differences in practice and legislation, for example on issues of consent, and to develop supporting guidance or codes of practice that apply across the UK (Recommendation 15).

#### **9.4.4 Streamlined process**

The HRA should provide a single point of entry and exit for applications to undertake health research involving humans, their tissue or data in the UK. This same process should be used for all research studies including NIHR portfolio and non-portfolio studies. Applications would be submitted through IRAS and then triaged to determine which assessments are required for the study. A point of contact would be designated within the HRA from whom investigators can seek advice about issues arising during the assessment process. This point of contact should facilitate the assessment process by overseeing the application and liaise with regulatory and governance bodies that remain outside the HRA as well as with Trusts and sponsors. To achieve this, the HRA will need to work with external bodies involved in the regulation of health research, including the Ministry of Justice and Ministry of Defence.

#### **9.4.5 Leadership, expertise and patient and public involvement**

The vision that we have set out for the HRA is ambitious: we recognise the challenges presented by the creation of the HRA and the important changes for which it will be responsible. It is therefore essential that the HRA has strong leadership and a culture that upholds the four principles set out in Chapter 2.

The HRA will be responsible for the regulation and governance of a wide range of studies and issues. To fulfil these specialist functions effectively and maintain confidence in its ability to do so, the HRA will require appropriate medical, scientific and ethical expertise on specialist issues. This will be particularly important to build confidence in its ability to handle sensitive issues, such as embryo research.

Patients and the public play a vital role in health research and their interests must be recognised and represented in regulation and governance. It is important that the aim and purpose of patient and public involvement in the HRA is clearly articulated from the outset. We therefore recommend that the HRA has a leadership structure that reflects the interests of the lay public as well as the research community. It will be important for the HRA to learn from the experience of other organisations, such as the HTA and the HFEA, in involving patients and the public in ethically sensitive areas.

In addition to ensuring an appropriate balance in its leadership, the HRA will require well-trained staff to implement guidance and procedures in a consistent and constructive manner.

## 9.5 The core functions of the Health Research Agency

### 9.5.1 Functions in assessing approvals and licences

The current strengths and challenges around obtaining ethics opinion, approvals and licences to access human tissue and data, are outlined in Chapters 6, 7 and 8. Timescales are not perceived as rate-limiting and the current system for single UK-wide ethics opinion is seen as a considerable strength. However:

- The legislative framework supporting access to patient data is complex and there is a lack of consistency in the interpretation

of this legislation. The provision of guidance and processes to access data are highly fragmented.

- There is a multiplicity of organisations involved in ethics review and specialist review, which often involve consideration of ethical issues. For example, in embryonic stem-cell research licences from HTA and HFEA are required in addition to an ethics opinion.

We recommend bringing the research functions of the following organisations into the HRA (Recommendation 13a) as soon as possible:

- The National Research Ethics Service (NRES).
- The Appointing Authority for Phase I Ethics Committee (AAPEC).
- Ethics and Confidentiality Committee (ECC) of the National Information Governance Board.
- Gene Therapy Advisory Committee (GTAC).
- The Administration of Radioactive Substances Committee (ARSAC).

We recommend that NRES becomes a key component of the new HRA, continuing its existing function in coordinating a UK-wide ethics opinion across the RECs and retaining its identity within the new system. We envisage the Appointing Authority for Phase I Ethics Committees (AAPEC) being brought within the remit of the HRA, consolidating its strong relationship with NRES in order to maintain standard procedures across ethics opinions for all types of study. In addition, NRES should develop and implement a streamlined system for 'specialist' approvals and licences within the HRA around data, tissue and embryos, gene therapy and exposure to radiation.

NRES is well placed to fulfil this role owing to its culture of continuous improvement. For example it has taken a proactive approach in improving aspects of the wider regulatory environment in the UK by liaising with organisations involved in specialist ethics review to reduce bureaucracy and streamline processes within the current



framework. In addition, NRES works well with its counterparts in the devolved nations to deliver a single UK-wide ethics opinion, and these relationships will be important in ensuring the success of the HRA.

There is an urgent need to address the lack of consistent guidance on the interpretation of the complex legal framework around access to patient data for research. In addition to bringing the ECC within the HRA, the HRA should take the lead in providing consistent guidance on the interpretation of legislation and promote the use of data in research while maintaining appropriate safeguards for the public. To achieve this, the HRA will need to work closely with the Information

Commissioner's Office, the NHS Health and Social Care Information Centre, the remaining functions of the National Information Governance Board and other key stakeholders.

Our vision for the HRA is a 'one-stop-shop' for specialist approvals and accompanying guidance. We see significant advantages in providing a single authoritative and trusted body to oversee the processes and guidance for health research, which provides a clear focal point for patients, researchers and NHS Trusts in relation to research. This model was supported by the responses received to the second call for evidence, typified by the quote from the Christie NHS Foundation Trust.

#### **The Christie NHS Foundation Trust**

*'We believe that the ethics and research governance systems in the UK for medical research based upon EU directives needs to be less risk-averse and made more streamlined. The safety of the patient is fundamental to medical research and therefore a single substantive peer review of a study proposal via an accountable/competent review body should be of paramount importance.'*

Therefore, in addition to the bodies listed above, we also recommend transferring the research regulation functions of the HTA into this arm of the HRA.

Similarly, while we acknowledge the good practice undertaken by the HFEA (section 7.3), and the specific legislative and ethical issues related to research involving human embryos, if the Government's aim is to transfer the research regulatory functions from the HFEA by the end of the current parliament, we recommend that these functions are transferred via an appropriate mechanism into the HRA. It is important to ensure that if the research regulatory functions of the HFEA and HTA were to be transferred into the Health Research Agency that there is sufficient representation of appropriate medical and scientific expertise for the new body to be knowledgeable and effective.

#### **9.5.2 Functions relating to clinical trials of investigational medicinal products**

The challenges around the regulation of clinical trials of investigational medicinal products (CTIMPs) are described in Chapter 5. Central to addressing these is the need to fully revise the European Clinical Trials Directive (Recommendation 5).

However, several concerns can be addressed without changes to the legislation:

- A more proportionate approach to clinical trials regulation can be introduced.
- The quality, consistency and timeliness of advice on clinical trial authorisations can be increased.
- Good Clinical Practice (GCP) inspections can be improved so as not to exacerbate the risk-averse culture of NHS Trusts and discourage them from undertaking research.

- MHRA can engage more effectively with its stakeholders, particularly non-commercial organisations, in promoting mutual understanding and provide more suitable guidance and support.

Given the concerns around the clinical trial functions of MHRA, we gave serious consideration to transferring these functions to the HRA. Some respondents considered that moving GCP inspections into the HRA was the only way to bring about a sufficiently significant cultural change to address the problems that exist. However clinical trial authorisation is not rate-limiting and it is important not to disrupt the UK policy interface with the European Commission at a critical stage of discussions on the future of the European Clinical Trials Directive. In addition, we appreciate the concern, particularly from industry, that transferring clinical trial functions away from the MHRA risks breaking the continuum of regulation through clinical trials to market authorisation and long-term pharmacovigilance. Therefore, on balance, we propose that these functions should currently be retained within the MHRA.

We recommend that the MHRA works in consultation with the HRA, reinforced if necessary by a legal duty, to address the challenges around the regulation of CTIMPs and enable the HRA to act as a one-stop-shop for researchers (Recommendation 14) by:

- Providing consistent and clear direction on the interpretation of the Medicines for Human Use (Clinical Trial) Regulations (2004), including guidance on which studies should be classified as CTIMPs. In addition to being invaluable to researchers and sponsors, this will enable the HRA to correctly triage applications that fall within the scope of the EU Clinical Trials Directive (CTD).
- Improving the approach taken to GCP audit by ensuring that inspections are a proportionate and constructive part of the regulatory process.

The HRA should undertake an initial, independent, review of GCP inspections and the Clinical Trials Unit. This review should include: sponsors' views on the time and resource implications of processes; the quality of advice received; and the behaviour of inspectors. We are concerned that currently investigators are reluctant to complain to the MHRA for fear of a negative impact on future inspections. There may be a need for the HRA to have a continuing role in this area so as to provide sponsors and investigators with the opportunity to provide feedback on inspections.

The progress made by the MHRA, in adopting this report's recommendations (Chapter 6) should be reviewed after two years and if insufficient progress has been made, consideration should be given to incorporating the MHRA's functions in relation to clinical trial authorisation and inspection into the HRA.

### **9.5.3 NHS R&D permission**

The challenges currently raised by the NHS R&D permission process are summarised in Chapter 4 and include the following:

- Inconsistency in advice and interpretation of checks from Trust R&D.
- Variation in performance.
- Inconsistency in the permissions process.
- Duplication of checks across and between Trusts and with external regulators (e.g. MHRA or NRES).
- Major delays and a lack of timelines in acquiring Trust R&D permissions.
- Difficulties in the local negotiation of contracts and costs.

Obtaining NHS permission is the single greatest barrier to health research and is perceived to be the rate-limiting step by most sponsors and investigators. Removing this barrier as quickly as possible is an essential part of our new pathway. In Chapter 4 we recommend the creation of a National Research Governance Service (NRGS) which would ensure consistent national standards and clear and consistent interpretation of requirements for compliance.

The NRGs could be formed as a standalone body, or as a component of the HRA. Provided that the HRA can be created quickly we would see NRGs forming a core part of this organisation from the outset (Recommendations 3 and 13b). This would avoid the disruption, cost and uncertainty involved in creating a standalone NRGs. Establishing the NRGs as part of the HRA would facilitate the seamless approach to regulation and governance we seek, and ensure that the HRA is well connected with the NHS from its inception. To promote a mutual understanding between Trusts and the new body, and to build confidence in the new NRGs, we recommend that the NRGs, like NRES, is a recognisable entity within the HRA. A priority for the HRA will be engaging NHS Trust Chief Executive Officers (CEOs) in the development and implementation of the NRGs.

## 9.6 Delivering our vision for the HRA

The creation of the HRA will clearly separate regulatory and governance assessments from funding and infrastructure provided by organisations such as NIHR, MRC and health research charities, and from the delivery of research provided by NHS Trusts, commercial and non-commercial organisations. In addition to the key regulatory functions set out above, the HRA should also have an important role in the following:

- **Monitoring performance.** The HRA should establish and monitor timelines for NHS Trusts to assess the feasibility of studies and for specialist approvals processes (Recommendation 19). It should also develop metrics and indicators for the performance of the UK regulation and governance pathway as a whole. Within these wider measures the HRA should assess, and report, on its own performance such as, for example, the time taken from a study to be submitted through IRAS to a final decision being given on whether it can proceed. Metrics should be developed
- **Proportionate approach.** One of the main criticisms of the current regulation pathway is the failure to adopt an approach to regulation that is proportionate to risk (for example, see Chapter 5). The HRA should lead on the development of proportionate approaches to regulation and governance that take into account the benefits and risks of a research study, rather than applying a 'one-size-fits-all' model. This should be embedded through a new edition of the Research Governance Framework (Recommendation 17).
- **Guidance, education and training.** We see advantages in the HRA providing a single location to approach for guidance, for example, maintaining the Clinical Trials Toolkit<sup>118</sup> and similar tools and providing advice on the consistent interpretation of legislation including the use of patient data (Recommendation 16). The HRA should consider taking a proactive role in supporting the regulatory environment through education and training for researchers and local regulation or governance organisations.
- **Communications.** Clear communication will be important to engender trust in the HRA. The Science Media Centre highlighted the critical role played in the past by the press offices of regulators such as the HTA and HFEA who have helped the UK media to report accurately on issues including stem cell research and hybrid embryos. It is important to retain this expertise in communication at the HRA, particularly in relation to sensitive ethical issues.
- **Public engagement.** Many existing bodies within and beyond government aim to increase public engagement in health research and the HRA will need to be aware of these. The HRA may also need to commission public dialogue on emerging or sensitive areas to better understand patient

and public views and to inform decisions - as the HFEA and the Academy have done in relation to the use of human admixed embryos, and the regulation of research using animals containing human material respectively.<sup>119,120</sup>

- **Future-proofing the HRA.** The HRA will need the flexibility to respond to emerging areas of health research that raise ethical concerns or that will impact on regulatory processes. In addition, it should be able to take advantage of emerging

techniques that could improve regulation and governance such as a greater use of statistics in monitoring clinical trials. The HRA should have within it or be able to access, for example through the Academy or similar bodies, a horizon-scanning capacity. This would enable the agency to be prepared for, and respond to, emerging challenges and opportunities. In addition, the HRA must also be able to engage with relevant developments internationally.

## Recommendations

*The creation of a Health Research Agency will provide the necessary oversight and impetus to introduce recommendations made throughout this report, as well as removing complexity and streamlining the pathway as a whole. It also provides a home for some aspects of regulation and governance that urgently require better coordination and clearer governance - a good example being research involving patient data.*

*We have made the following recommendations in relation to our vision for a Health Research Agency. The success of the creation of such a body is highly dependent on cultural changes, such as those outlined in Chapter 3. In addition, as we have addressed in Chapter 4, the most highly criticised stage of the pathway is NHS permissions. The creation of a new National Research Governance Service (see Chapter 4) within the Health Research Agency will create the 'one-stop-shop' that is desired by so many research stakeholders.*

**Recommendation 13:** We recommend that a 'Health Research Agency' is established as an arm's-length body to oversee the regulation and governance of health research. To ensure that the current problems are addressed quickly, the HRA should be created as soon as possible as an interim Special Health Authority and then established in primary legislation, as a non-departmental body, in due course. The HRA would:

- a. Increase clarity, consistency and efficiency by bringing together the provision of ethics opinion and 'specialist approvals and licences' to:
  - Provide a single ethics opinion.
  - Provide 'specialist approvals and licences', (e.g. for studies involving patient data, human tissue, gene therapies or human stem cells).
- b. Include a new National Research Governance Service. The NRGs would be established as a recognisable entity within the HRA as soon as possible and priority should be given to gaining the confidence of NHS Trusts and implementing timelines for NHS R&D permission.

<sup>119</sup> Human Fertilisation and Embryology Authority (2007). *Hybrids & chimeras: a report on the findings of the consultation.* [http://www.hfea.gov.uk/docs/Hybrids\\_Report.pdf](http://www.hfea.gov.uk/docs/Hybrids_Report.pdf)

<sup>120</sup> Ipsos MORI/Academy of Medical Sciences (2010). *Exploring the boundaries: report on a public dialogue into animals containing human material.* <http://www.acmedsci.ac.uk/download.php?file=/images/page/128619890736.pdf>

**Recommendation 14:** The Health Research Agency should work in consultation with the MHRA to become a 'one-stop-shop' for health research regulation and support a shift in the MHRA's approach to clinical trial regulation:

- a. The HRA should undertake an independent assessment of the Clinical Trials Unit of the Medicines and Healthcare products Regulatory Agency (MHRA) and Good Clinical Practice (GCP) monitoring inspections. This should include sponsors' and investigators' views on: the time and resource implications of the processes; the quality of advice received; and the approach of inspectors. The findings of this assessment should be used as a benchmark to formally review the progress made by the MHRA in adopting recommendations from this report (see Chapter 6) after two years.
- b. The Clinical Trials Unit of MHRA should work with the HRA to develop clear guidance on the interpretation of the scope and requirements of the Clinical Trials Directive (CTD) to provide consistent advice on studies.
- c. With respect to GCP inspections, the MHRA should work in consultation with the HRA to set standards and best practice.

**Recommendation 15:** The Health Research Agency and the regulatory and governance organisations in the devolved nations should work to develop a seamless regulatory system for the UK, for all aspects of its remit. To inform a more 'joined-up' approach across the UK, we recommend that the HRA undertakes an evaluation of the differences in law and practice across the UK for example in the use of human tissue and access to patient data.

**Recommendation 16:** The Health Research Agency should support researchers and raise research standards by providing consistent advice and interpretation of legislation and a single point of contact to ensure better communication in navigating the regulation and governance pathway. As a priority the Health Research Agency, with advice from other bodies, should coordinate and develop guidance for healthcare professionals and researchers relating to the use of data in research.

**Recommendation 17:** The Health Research Agency, and the regulation and governance pathway which it oversees, should operate in accordance with the four principles outlined in Chapter 2. To this end, the HRA should:

- Have the necessary authority to oversee the required structural and cultural changes to the regulatory and governance environment.
- Devise, in consultation with stakeholders, published metrics through which its impact on research in the UK and performance in meeting the four principles can be judged.
- Lead on the development of proportionate approaches to regulation and governance. This should include the production of a revised Research Governance Framework which establishes a proportionate governance pathway and communicates changes in the responsibilities of different stakeholders following recommendations made in this report.
- Draw on appropriate expertise, including from patients and the public.



## 10 A new regulation and governance pathway

### 10.1 Introduction

The UK has a long and established tradition of undertaking groundbreaking health research with benefits to citizens – not just in the UK, but also globally. The future, however, is jeopardised by the UK's regulatory and governance environment which threatens the ability of researchers to meet the expectations and aspirations of patients and the public.

The existing regulation and governance pathway has developed in a piecemeal manner and is characterised by a plethora of regulatory bodies, overlapping legislation and guidance at the international, national and local levels, and a fragmented process that can result in elements of a research proposal being reassessed at multiple stages. The recommendations in this report are designed to dramatically improve the UK environment for health research and streamline regulation and governance, without undermining its effectiveness.

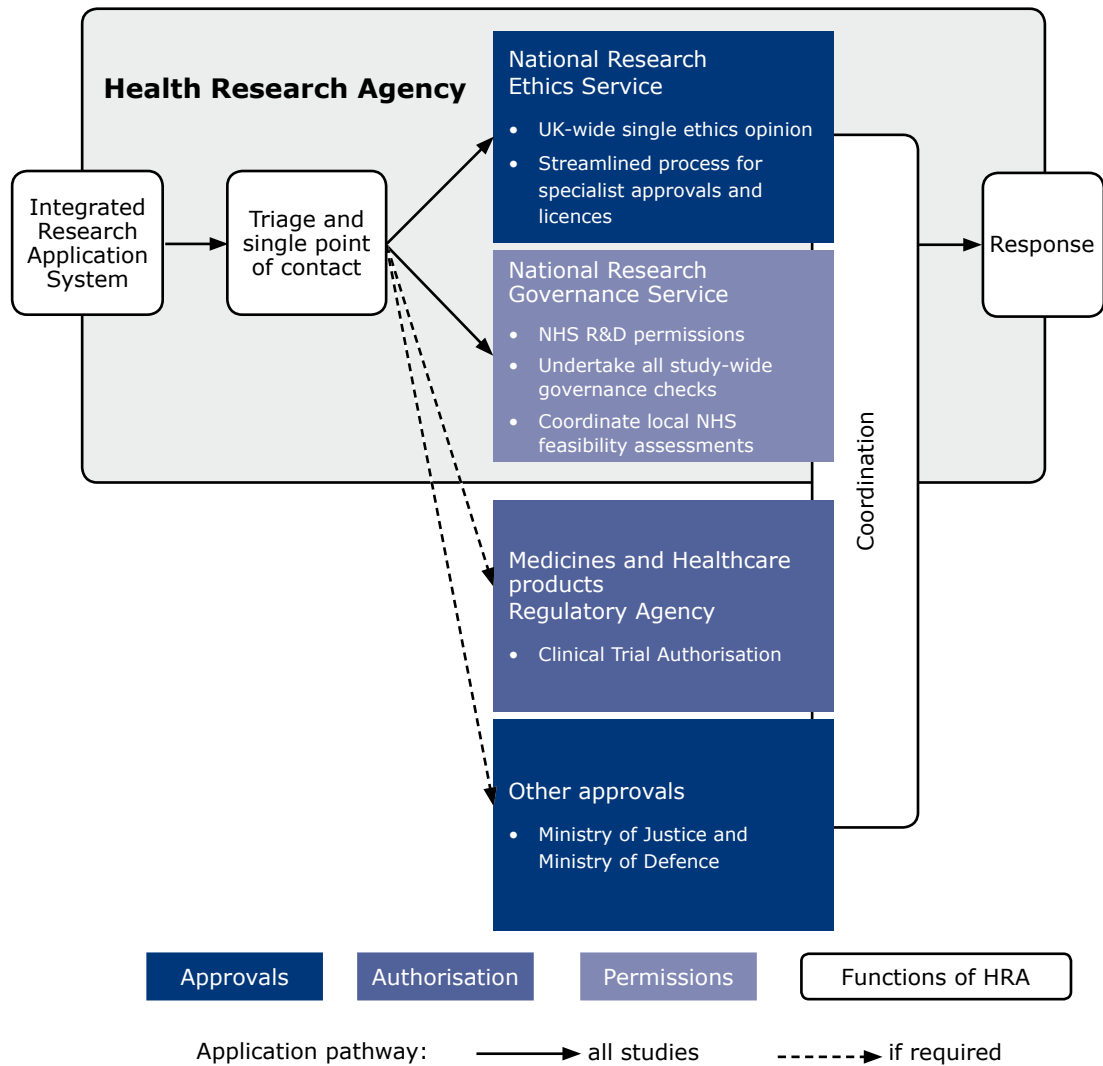
As well as examining individual components of the process a key objective of this review was to assess the regulation and governance pathway as a whole and identify opportunities to increase the speed of decision-making, reduce complexity, and eliminate unnecessary bureaucracy and cost. In this final chapter we briefly compare the performance of the existing model of regulation and governance with the new pathway that we have proposed in preceding chapters.

### 10.2 Overview of report recommendations

Those contributing to our review highlighted the following:

- Duplication of checks within and between different levels of the system.
  - The need for greater clarity and authority of advice.
  - Benefits that could be gained from better leadership, ownership and oversight of the regulation and governance pathway as a whole.
  - Opportunities to reduce timelines, costs and inefficiencies.
- In recent years individual regulators, the National Institute for Health Research (NIHR), NHS Research Scotland, various NHS Trust collaborations such as the North West Exemplar and others have made progress in improving the process. Our recommendations seek to build on the progress already made to produce a step-change improvement. The recommendations aim to:
- Safeguard public safety by removing unnecessary complexity and facilitating a proportionate approach that allows researchers and regulators to focus on the specific benefits and risks of a given study.
  - Achieve greater consistency and provide clearer guidance by streamlining the number of separate regulatory and governance bodies and the assessment processes.
  - Eliminate unnecessary bureaucracy and increase the speed of decision making to ensure that patients and the public can reap the benefits of research and increase the attractiveness of the UK for commercial and non-commercial research.
  - Provide greater leadership and oversight of the regulatory and governance pathway, including the introduction of agreed timelines and national standards.
  - Build trust and confidence in the regulatory process through greater clarity and transparency, achieved in part through the publication of metrics on research activity and approval timelines.

**Figure 10.1 A new regulation and governance pathway**



**10.3 Comparing the current and proposed regulation and governance pathways**

Throughout this report we have highlighted examples of where the current framework does not meet the principles set out in Chapter 2. Below we demonstrate how our proposed framework better meets these principles and will safeguard participants and promote high quality health research.

***Principle 1: safeguard the well-being of research participants***

There is no indication that the current regulation and governance pathway has failed to adequately safeguard the well-being of research participants. However, the focus on bureaucracy and administration in the current system (e.g. unselective and over-reporting of possible safety incidents) has led to a focus on *process* rather than *outcomes*. By reducing unnecessary complexity in regulation and governance our proposals will ensure that those responsible for the safety of participants can concentrate on managing genuine risks (e.g. Recommendations 5c and 13).



***Principle 2: facilitate high-quality health research to the public benefit***

Our review has highlighted many examples where the current regulation and governance pathway has significantly delayed or completely prevented health research that would have benefitted the UK public. This particularly applies to delays in obtaining NHS permissions. We consider this a major failure of the current pathway. Clearer mechanisms for researchers to identify eligible patients to invite to participate in research studies are key to delivering this principle (Recommendation 10). The introduction of the National Research Governance Service (NRGS) and new timelines for NHS R&D permissions (Recommendation 3) will enable the regulation and governance pathway to better meet this principle. To facilitate the assessment process, we propose that within the Health Research Agency (HRA) there is single point of contact for sponsors and researchers to oversee research applications (Recommendation 16).

***Principle 3: be proportionate, efficient and coordinated***

Many aspects of the current regulation and governance pathway are not proportionate to the risks and benefits of research and proportionality is not built into key legislation and guidance. Key components of the current system lack efficiency and coordination. This is particularly true for the process of gaining NHS R&D permission which often replicates governance checks and regulatory assessments that have already been undertaken.

The establishment of a single coordinating body for the regulation and governance of health research will enhance efficiency. The HRA (and the mechanism provided by the NRGS) will provide a single, streamlined system for regulating health research and eliminate the need for repeated checks of the same information.

The new Agency, in consultation with others such as the MHRA and organisations from the devolved nations, will lead on the development of proportionate approaches to regulation and governance of health research studies (Recommendation 17). Revision of the European Clinical Trials Directive, and the approach taken to regulation of human tissue in research, will be central to achieving this objective (Recommendations 5 and 11).

***Principle 4: maintain and build confidence in the conduct and value of health research through independence, transparency, accountability and consistency***

Although, broadly speaking, the public is supportive of health research, this support will always be conditional and is threatened by a lack of clarity, consistency and accountability in the existing system of regulation and governance.

The HRA will be independent from government and research sponsors and will seek to earn and retain the confidence and trust of all stakeholders, including patients and the public. The HRA will develop and publish metrics for monitoring both its own activities and the performance of NHS Trusts in facilitating research (Recommendation 17). The new body will seek to ensure consistency in its advice and regulatory decisions; establishing a single body will provide clarity in both its accountability and channels of communication.

The views of patients and the public will be important in informing the operation of the HRA (Recommendation 17). The new body should be assisted by efforts to enhance the culture of research through: better communication about the benefits of research among NHS staff, patients and the public (Recommendation 1); and initiatives to embed research in NHS governance and leadership processes (Recommendation 2).

#### 10.4 A time for action

The evidence submitted to the Academy identified the key problems in the existing regulation and governance pathway for health research including unnecessary process steps, delays and complexity. Recommendations addressing individual components of the existing system are made in Chapters 3 to 8 that – if implemented – would deliver considerable improvement to the regulation and governance pathway in the UK. However, these individual recommendations should not be considered in isolation because the piecemeal approach of the past has not delivered an environment in which health research is able to flourish. We therefore believe that the establishment of the HRA, described in Chapter 9, is the most efficient and effective way to deliver the improvements required, by providing coordination and oversight across the whole regulation and governance pathway.

We know that the Government, particularly the Department of Health, will want to consult widely with a range of internal and external stakeholders as it considers the implementation of our recommendations. We look forward to continuing to engage with them throughout this process.

It is important that the recommendations in this report are taken forward promptly to build on the existing momentum for improvement, to make effective use of Government's support for health research indicated by the 2010 Comprehensive Spending Review, and to capitalise on the public's support for research.

We welcome the Government's support for health research and its commitment, in the 2010 Health White Paper to '*consider the bureaucracy affecting research... and bring forward plans for radical simplification*' in light of the Academy's review. We hope the recommendations in this report will deliver a level of change that substantially improves the environment in the UK, within which the highest quality health research can work for us all. Patients and the public deserve no less.

## Recommendations

### Culture around health research (Chapter 3)

*To support recommendations made throughout this report to improve the regulatory and governance pathway, cultural change is required within the NHS to embed health research as a core function, to foster a more facilitative approach to research governance and to promote public and patient engagement in research. All those involved in health research and its regulation have a role to play in supporting this culture change and in enabling the UK to realise its potential as a world leader in health research.*

**Recommendation 1:** The UK health departments, with the support of other government departments, should communicate the core role of health research to all NHS staff, and continue to work with organisations such as INVOLVE and AMRC to provide coordinated information for patients and the public about the role and benefits of health research.

**Recommendation 2:** To embed research as a core function in the NHS we recommend that:

- a. The Director General of NHS R&D should serve as a member of the proposed NHS Commissioning Board in England.
- b. Key metrics and indicators of research activity should be developed by the proposed new Health Research Agency (HRA) (Recommendation 13), in consultation with stakeholders, and included in the next NHS Operating Framework. These metrics should include timelines for assessment of local feasibility, delivery and recruitment under the new National Research Governance Service (NRGS) model (Recommendation 3). The use and publication of these metrics should allow the research performance of Trusts to be compared and scrutinised by the Trust Board, research funders and the public.

- c. An executive director of each NHS Trust should be responsible for promoting research within the organisation and report on current research activity (including metrics) at each Board meeting.
- d. Challenges around the definition and allocation of research costs remain a major disincentive for Trusts to engage in research. The forthcoming re-organisation of NHS commissioning arrangements provides an important opportunity to improve the provision of Excess Treatment Costs and remove the current difficulties this creates for non-commercial research.
- e. All those involved in training healthcare professionals, including the General Medical Council, the Nursing and Midwifery Council, the General Pharmaceutical Council, medical schools and the medical Royal Colleges, should ensure that the NHS workforce is aware of the important role of health research and equipped to engage with studies taking place in their Trust. This should include providing support to patients who are considering whether or not to participate in research.

### NHS research and development (Chapter 4)

*Obtaining NHS permissions was identified as the single greatest barrier to health research and the rate-limiting step in most studies. Changes are needed to reduce bureaucracy and increase the speed of NHS R&D permissions by replacing multiple, inconsistent, slow checks by individual NHS Trusts, with a single, consistent, efficient process for the NHS as a whole. We therefore recommend that:*

**Recommendation 3:** A new National Research Governance Service (NRGS) should be established as a core component of the new Health Research Agency outlined in Chapter 9. The NRGS should be created as a matter of

urgency, to oversee a streamlined, common process for NHS R&D permission for all single and multi-site studies in the NHS in England. The NRGS should provide clear guidance and leadership on a new permission process, including clarity on different aspects of research indemnity. The NRGS would:

- Undertake all study-wide NHS governance checks, ensuring consistent national standards and interpretation of requirements for compliance.
- Recommend research projects as suitable for undertaking within the NHS subject to local assessment of feasibility and delivery.
- Facilitate new R&D timelines that would require participating Trusts to determine local feasibility within 20 working days.
- Maintain up-to-date records on NHS staff to confirm their competence to conduct research, and that, for example, they have the expertise and accreditation relevant to their role in the study and have passed Criminal Records Bureau (CRB) checks.
- Issue model agreements and provide clarity on research costs and payment.

**Recommendation 4:** The National Institute for Health Research should develop a transparent system to formally assess the performance of Trusts in approving and undertaking research and use this to inform its funding allocations.

### Clinical trials of investigational medicinal products (Chapter 5)

*The broad scope and lack of proportionality in the European Clinical Trials Directive have created a major barrier to undertaking studies of established products, without providing greater levels of protection to study participants. Within the UK, despite punctual administration of Clinical Trial Authorisations (CTA), there are concerns about: the way in which Medicines and Healthcare products Regulatory Agency (MHRA) engages with*

*stakeholders; the provision of timely and consistent advice before a CTA is submitted; a lack of proportionality in the MHRA's approach to regulation; and the approach to some Good Clinical Practice (GCP) inspections. In addition to recommendations in Chapter 9, where we outline our proposal for a Health Research Agency, we recommend that:*

**Recommendation 5:** The Government, supported by the MHRA, should seek to influence the European Commission to act quickly to revise the EU Clinical Trials Directive. The Directive should be amended to:

- Reduce the scope of the Directive through the revision of the definitions set out in Article 2.
- Ensure that approval and monitoring requirements are proportionate to risk.
- Simplify the requirements for the reporting of adverse events.

**Recommendation 6:** Before revision of the Clinical Trials Directive the MHRA should adopt a more proportionate approach to clinical trials regulation without delay. This should include implementing the recommendations of their current project on risk stratification and developing alternative and appropriate systems for the audit of GCP. In addition, the MHRA should ensure that GCP inspections are consistent, assessing against relevant standards, and conducted objectively, professionally and constructively at all times.

**Recommendation 7:** The MHRA should increase the quality, consistency and timeliness of advice from its Clinical Trials Unit. The MHRA should designate a clear single point of contact for every CTA application with which applicants can work to overcome problems. The Clinical Trials Unit and GCP Inspectorate must engage more effectively across the full range of stakeholders to promote mutual understanding and provide support that is tailored to the needs of different sectors.

## Use of patient data in health research (Chapter 6)

*The legal framework around access to patient data is complicated involving UK legislation, case decisions, and an EU Directive. There are also a wide range of bodies involved in producing advice, each of which differs slightly in their focus, context and jurisdiction. This has resulted in conflicting interpretations of the regulation among stakeholders and a lack of clarity for patients and the public. Aspects of these problems are dealt with in our recommendations in Chapter 9, where we outline our proposal for a Health Research Agency. We urge the Government to evaluate progress on taking forward the recommendations from the Data Sharing Review (2008) and to ensure that the fundamental changes outlined within it are taken forward at pace, alongside the recommendations below. We recommend that:*

**Recommendation 8:** The Ministry of Justice should undertake a thorough review of the UK Data Protection Act to identify aspects that require clarification in relation to health research so as to inform the planned revisions to the EU Data Directive and subsequent amendments to the UK Data Protection Act. As a priority, clear guidance on interpretation of these aspects of the Act should be provided for researchers and healthcare professionals by the Information Commissioner in conjunction with the proposed new Health Research Agency.

**Recommendation 9:** The role of Caldicott Guardians should not include the approval of research studies. Instead it should focus on facilitating the delivery of research studies for which approvals relating to data have already been granted by other bodies.

**Recommendation 10:** As recommended in the Data Sharing Review, a system should

be developed to allow approved researchers to work with healthcare providers to identify potential patients to be contacted about research studies in which they might wish to participate. The Information Commissioner's Office and the new Health Research Agency should work with the health departments and other stakeholders to provide definitive guidance on this issue. This should state that researchers, or appropriate members of a research team such as research nurses, working on an ethically approved study should be considered part of a clinical care team for the purposes of accessing data to identify patients eligible to be contacted about research studies. The initial contact with these patients about a research study would be by a member of the patient's clinical care team (i.e. not a researcher).

## Use of tissue and embryos in research (Chapter 7)

*There has been much progress in the approach to regulation of human tissue in research across the UK, with stakeholders indicating that they are largely clear on the requirements. However, the regulatory approach taken in England is seen to be disproportionate, whereby the broad definition of 'relevant materials' in the Human Tissue Act does not appear to have been determined against any specific categories of risk, and there is a lack of consistency in approach to the materials listed as exemptions. We therefore recommend that:*

**Recommendation 11:** Hair and nails from living subjects are already excluded from the materials covered by the Human Tissue Act. To ensure a proportionate approach to the regulation and governance of the use of tissue from living subjects, the following exclusions should be introduced: plasma, serum, urine, faeces, and saliva.

## Ethics (Chapter 8)

*We welcome the progress that the National Research Ethics Service (NRES) has made in recent years. Under the new arrangements outlined in Chapter 9, NRES should maintain this momentum to ensure that further improvements are made, for example to increase consistency and specific committee expertise and reduce timescales. High ethical standards in research can only be partially achieved through regulation and governance and researchers need support to identify and address the ethical issues arising in their research, outside of applying for an ethics opinion. In addition to the need to embed a proportionate approach within the ethics system, including implementation of 'proportionate review' following the NRES pilot, we recommend that:*

**Recommendation 12:** NRES should lead on improving support and advice for researchers by providing centralised, coordinated guidance and training on ethical issues for health researchers. Institutions engaged in health research should also improve the local availability of ethics advice and the training of local support staff.

## A new Health Research Agency (Chapter 9)

*The creation of a Health Research Agency will provide the necessary oversight and impetus to introduce recommendations made throughout this report, as well as removing complexity and streamlining the pathway as a whole. It also provides a home for some aspects of regulation and governance that urgently require better coordination and clearer governance - a good example being research involving patient data.*

*We have made the following recommendations in relation to our vision for a Health Research Agency. The success of the creation of such a body is highly dependent on cultural changes,*

*such as those outlined in Chapter 3. In addition, as we have addressed in Chapter 4, the most highly criticised stage of the pathway is NHS permissions. The creation of a new National Research Governance Service (see Chapter 4) within the Health Research Agency will create the 'one-stop-shop' that is desired by so many research stakeholders.*

**Recommendation 13:** We recommend that a 'Health Research Agency' is established as an arm's-length body to oversee the regulation and governance of health research. To ensure that the current problems are addressed quickly, the HRA should be created as soon as possible as an interim Special Health Authority and then established in primary legislation, as a non-departmental body, in due course. The HRA would:

- a. Increase clarity, consistency and efficiency by bringing together the provision of ethics opinion and 'specialist approvals and licences' to:
  - Provide a single ethics opinion.
  - Provide 'specialist approvals and licences', (e.g. for studies involving patient data, human tissue, gene therapies or human stem cells).
- b. Include a new National Research Governance Service. The NRGGS would be established as a recognisable entity within the HRA as soon as possible and priority should be given to gaining the confidence of NHS Trusts and implementing timelines for NHS R&D permission.

**Recommendation 14:** The Health Research Agency should work in consultation with the MHRA to become a 'one-stop-shop' for health research regulation and support a shift in the MHRA's approach to clinical trial regulation:

- a. The HRA should undertake an independent assessment of the Clinical Trials Unit of the Medicines and Healthcare products Regulatory Agency (MHRA) and Good Clinical Practice (GCP) monitoring inspections. This should include sponsors' and investigators' views on: the time and

resource implications of the processes; the quality of advice received; and the approach of inspectors. The findings of this assessment should be used as a benchmark to formally review the progress made by the MHRA in adopting recommendations from this report (see Chapter 6) after two years.

- b. The Clinical Trials Unit of MHRA should work with the HRA to develop clear guidance on the interpretation of the scope and requirements of the Clinical Trials Directive (CTD) to provide consistent advice on studies.
- c. With respect to GCP inspections, the MHRA should work in consultation with the HRA to set standards and best practice.

**Recommendation 15:** The Health Research Agency and the regulatory and governance organisations in the devolved nations should work to develop a seamless regulatory system for the UK, for all aspects of its remit. To inform a more 'joined-up' approach across the UK, we recommend that the HRA undertakes an evaluation of the differences in law and practice across the UK for example in the use of human tissue and access to patient data.

**Recommendation 16:** The Health Research Agency should support researchers and raise research standards by providing consistent advice and interpretation of legislation and a single point of contact to ensure better communication in navigating the regulation and governance pathway. As a priority the Health Research Agency, with advice from other bodies, should coordinate and develop guidance for healthcare professionals and researchers relating to the use of data in research.

**Recommendation 17:** The Health Research Agency, and the regulation and governance pathway which it oversees, should operate in accordance with the four principles outlined in Chapter 2. To this end, the HRA should:

- Have the necessary authority to oversee the required structural and cultural changes to the regulatory and governance environment.
- Devise, in consultation with stakeholders, published metrics through which its impact on research in the UK and performance in meeting the four principles can be judged.
- Lead on the development of proportionate approaches to regulation and governance. This should include the production of a revised Research Governance Framework which establishes a proportionate governance pathway and communicates changes in the responsibilities of different stakeholders following recommendations made in this report.
- Draw on appropriate expertise, including from patients and the public.





## Annex I: The current UK regulatory and governance pathway

### Introduction

The UK regulation and governance pathway around health research is shaped by primary and secondary legislation, local governance arrangements, and the actions and oversight of a wide range of organisations. The breadth of regulation and governance checks reflect the multiple considerations that relate to health research including assessment of: scientific purpose and quality; ethical issues including consent and confidentiality; participant safety; effective use of public money; and capacity and local feasibility. In addition, further complexity is created by the fact that some health research legislation is UK-wide, while other legislation is specific to a subset of the four administrations.

This chapter provides an overview of the current regulatory pathway and introduces terminology that is used throughout the report.

It is not intended as an exhaustive guide to using the system, but to provide the necessary context and background for the report's findings and recommendations. Further detail on specific areas is provided in the relevant chapters.

During the process of the Academy's review, the Department of Health set out proposals to reorganise and abolish some of the bodies described in this chapter and to establish a single research regulator.<sup>121</sup> The working group was asked by Government to consider the possible scope and function of a single research regulator, as well as the future of a number of individual bodies (see Box I). The Academy launched a second call for evidence on this subject and Chapter 9 assesses the submissions received and contains conclusions and recommendations for a new regulation and governance pathway.

### Box I Department of Health arm's-length bodies review

In July 2010, the Department of Health published 'Liberating the NHS: Report of the arm's-length bodies (ALB review)', which set out steps to abolish and re-organise various arm's-length bodies in an attempt to: 'create a more streamlined sector'; ensure 'less bureaucracy'; 'reduce intervention'; and enable 'greater efficiency through contestability'.<sup>122</sup> The ALB review was identified by Government as an integral component of their wider plans for rationalisation set out in the NHS White Paper, 'Equity and excellence: Liberating the NHS'.<sup>123</sup> Specifically, the report set out proposals to:

- Create a single research regulator.
- Abolish the National Patient Safety Agency (NPSA) which has previously had responsibility for the National Research Ethics Service (NRES).
- Transfer the research regulatory functions of the Human Tissue Authority (HTA) and Human Fertilisation and Embryology Authority (HFEA) into the new single research regulator by the end of the Parliament. The ALB review proposes that the non-research functions of the HTA and HFEA are reassigned to the Care Quality Commission.

In the context of its wider ongoing review of the regulation and governance pathway, the Academy was asked by the Government to consider the possibility of a single research regulator, as well as the future of NRES and the research-related activities of the HFEA and HTA.

121 Department of Health (2010). *Liberating the NHS: report of the arms-length bodies review*. [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_117691](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_117691)

122 Department of Health (2010). *Liberating the NHS: report of the arms-length bodies review*. [http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_117691](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_117691)

123 Department of Health (2010). *Equity and excellence: liberating the NHS*. [http://www.dh.gov.uk/prod\\_consum\\_dh/groups/dh\\_digitalassets/@dh/@en/@ps/documents/digitalasset/dh\\_117794.pdf](http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/@ps/documents/digitalasset/dh_117794.pdf)

## The current pathway: overview and terminology

The focus of this report is on health research involving human participants, their tissue or data. As explained in Chapter 1, the remit includes experimental medicines, clinical trials and epidemiological research. Studies in these areas are captured within a broader definition of what is considered to be 'research' in the Research Governance Framework for Health and Social Care (RGF) that applies to all research within the remit of the Secretary of State for Health.<sup>124</sup> The RGF defines 'research' as the 'attempt to derive generalisable new knowledge by addressing clearly defined questions with systematic and rigorous methods', an activity that is distinct from audit or service evaluation. The RGF sets out the broad principles of good research governance (see Chapter 4) for health and social care research, covering some disciplines that are outside the scope of this review.

The regulation and governance pathway includes study-specific assessments that must be undertaken before the research starts and

continuing requirements once the study has started. In addition there are site-specific assessments and monitoring requirements for some types of research. A schematic overview of the regulatory and governance requirements for different types of health research is given in Figure I and further information (such as whether they have a statutory basis and which organisations are involved) is provided below. It is important to note that many of these different assessments and requirements do not occur in parallel, but in series. This therefore extends the overall timeline.

The type and number of study-specific regulatory and governance assessments depend on the nature of the study being undertaken and therefore vary on a case by case basis. As a minimum these studies require approval from an NHS Research Ethics Committee (REC) and NHS R&D permission. Additional authorisation, approvals or licences may be required for certain types of studies, for example, Clinical Trials of Investigational Medicinal Product (CTIMP) require clinical trial authorisation and a separate approval is needed to access identifiable patient data. The terminology used throughout the report is outlined in Box II.

### Box II Terminology

The term 'assessments' is used as an umbrella term for the full range of regulatory and governance requirements covered in this report that must be undertaken before a study starts. These key assessments can be categorised as follows:

#### **Approvals (and licences)**

The term 'approvals' is used to include positive ethics opinion from a NHS Research Ethics Committee (REC) and a selection of more specialist approvals that are required before certain types of research can begin. These specialist approvals include: access to use identifiable patient data without consent (Ethics and Confidentiality Committee); research on embryos (Human Fertilisation and Embryology Authority); and the use of human tissue in research (Human Tissue Authority). These approvals cover both study-specific (e.g. HFEA) and site licenses (e.g. HTA). Various approvals and licences are the focus of Chapters 5, 7 and 8.

#### **Authorisations**

The term 'authorisation' is used to refer to clinical trial authorisation (CTA). A CTA is required for any clinical trial of an investigational medicinal product (CTIMP) and is assessed in the UK by the designated National Competent Authority (NCA), the Medicines and Healthcare products Regulatory Agency (MHRA). Authorisation of CTIMPs is the focus of Chapter 6.

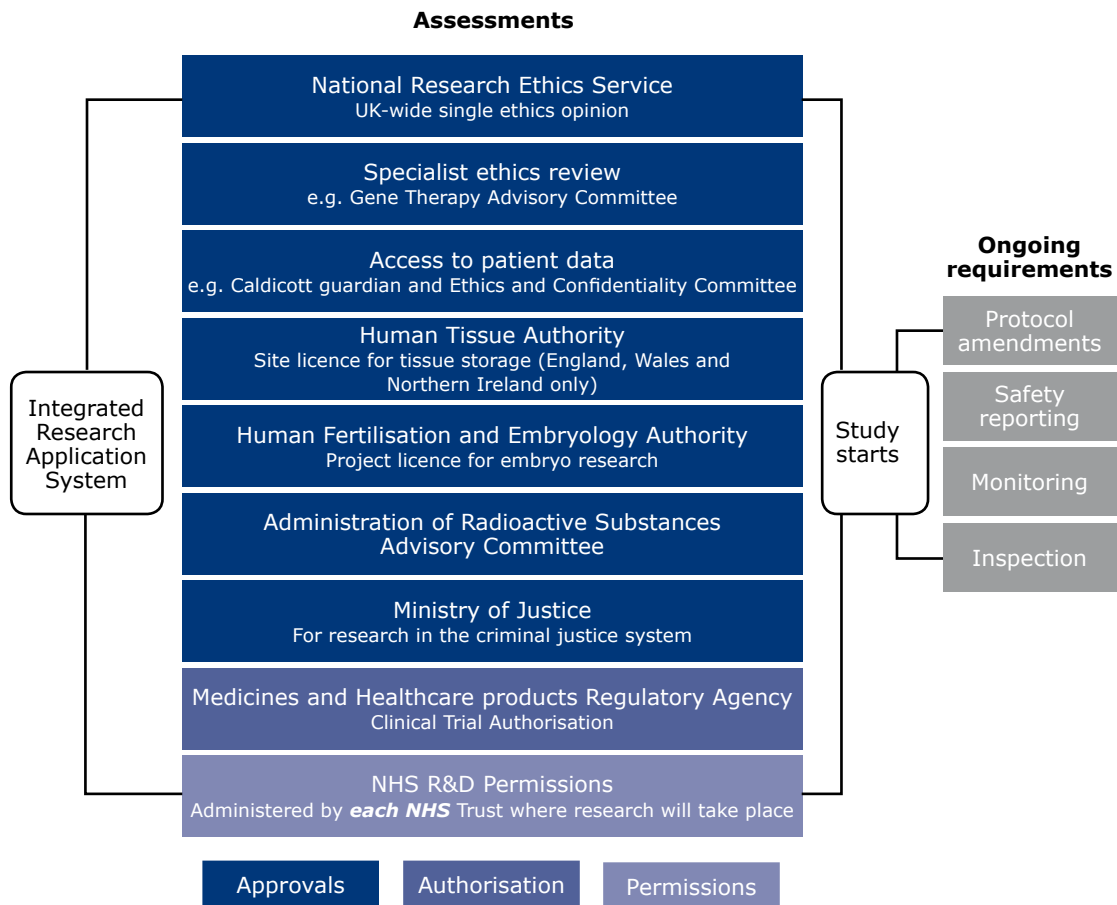
**Permissions**

Before health research and development (R&D) involving NHS patients can begin, permission is required from all NHS Trusts involved in the research. The current permissions process involves checking that a range of quality assurance and statutory requirements are in place, including that appropriate approvals and authorisations have been granted where relevant. NHS R&D permissions are the focus of Chapter 9.

To pass through the range of regulatory and governance assessments, amendments may be required to the protocol or other key documents to satisfy the requirements of assessing bodies.

If approvals from multiple organisations are undertaken in parallel then amendments must be reported to the other relevant agencies to inform their decision.

**Figure I: The current regulatory & governance pathway**



The following sections briefly introduce the regulatory and governance assessments covered in Figure I. Details on how these approvals, authorisations and permissions are granted and

the associated issues raised in the evidence submitted to the Academy are provided in Chapters 5 to 9.

## Approvals

### **Research Ethics Committee opinion**

A positive opinion from an NHS REC is required for research on human participants, their tissue or data to take place in the NHS. For CTIMPs this positive ethics opinion is a legal requirement, set out in the Medicines for Human Use (Clinical Trials) Regulations (2004).<sup>125</sup> The National Research Ethics Service (NRES) is the overarching body for RECs in England.<sup>126</sup> RECs consider a broad range of underlying regulation when reviewing the ethical aspects of research, including the Human Tissue Act (2004)<sup>127</sup> and the Mental Capacity Act (2005)<sup>128</sup> (with some variation in this legislation across the devolved countries). Most RECs are generalist and handle a range of studies. However, some RECs have specialist expertise, for example to review phase I trials, and the Social Care Research Ethics Committee reviews studies from the social care sector that would not otherwise have access to ethics review.<sup>129</sup>

Responses to the call for evidence noted the substantial improvement that single UK-wide opinion and timescales had made to ethics approval since its introduction and further details on this are included in Chapter 8.

### **Specialist ethics approval**

Specialist ethics approval is required for research in certain areas:

- The Gene Therapy Advisory Committee (GTAC)<sup>130</sup> is an advisory non-departmental public body of the DH and is a recognised REC that handles applications specifically for research on products based on gene or stem cell therapies.
- The Ministry of Defence (MoD) has two research ethics committees, known collectively as MoDREC<sup>131</sup>, to approve research on human participants that is

undertaken, funded or sponsored by MoD. MoDREC operates to standards recognised by the UK Health Departments as equivalent to those of RECs.

- Seven Independent Ethics Committees (IECs), designated by the Appointing Authority for Phase I Ethics Committees (AAPEC)<sup>132</sup>, to give an opinion on trials on healthy volunteers taking place outside of the NHS.

### **Access to patient data**

This report considers the use of both identifiable and anonymous patient data (Chapter 6).

#### *Identifiable patient data*

A number of approvals are required to access identifiable patient data. Regardless of whether or not consent is to be obtained, studies that propose to make use of existing patient-identifiable data sets must follow the Caldicott principles:

- Justify the purpose(s) of every proposed use or transfer of data.
- Do not use data unless it is absolutely necessary.
- Use the minimum data necessary.
- Access to data should be on a strict need-to-know basis.
- Everyone with access to data should be aware of their responsibilities and understand and comply with the law.

The use of patient-identifiable information, including research, is overseen by the Caldicott Guardian within each NHS organisation.<sup>133</sup>

The underpinning legislation and approvals processes for the use of identifiable patient information without consent varies among the devolved nations. Approvals are handled by the National Information Governance Board for Health and Social Care (NIGB)<sup>134</sup> in England and

125 For further information see <http://www.legislation.gov.uk/uksi/2004/1031/contents/made>

126 For further information see <http://www.nres.npsa.nhs.uk>

127 For further information see <http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/legislation/humantissueact.cfm>

128 For further information see <http://www.legislation.gov.uk/ukpga/2005/9/contents>

129 For further information see <http://www.srec.org.uk/>

130 For further information see <http://www.nres.npsa.nhs.uk/>

131 For further information see <http://www.science.mod.uk/engagement/modrec/modrec.aspx>

132 For further information see <http://www.aapec.org.uk/index.html>

133 For further information see <http://www.connectingforhealth.nhs.uk/systemsandservices/infogov/caldicott>

134 For further information see <http://www.nigb.nhs.uk/>

Wales and by the Privacy Advisory Committees (PAC) of Scotland<sup>135</sup> and Northern Ireland. In England and Wales, the Ethics and Confidentiality Committee (ECC)<sup>136</sup> of NIGB administers applications under section 251 of the NHS Act (2006), which allows the common law of confidentiality to be waived for research under certain conditions. The ECC requires approval from the local Caldicott Guardian before section 251 exemptions are granted. The NIGB is an advisory non-departmental public body of the DH and as such advises the Secretary of State on each application, rather than having the authority to grant exemptions directly.

In Scotland, applications are made to the PAC for the release of identifiable information from the Information Services Division of the NHS, which holds health data for Scotland, or by the General Register Office for Scotland.<sup>137</sup>

#### *Anonymised patient data*

Databases of anonymised patient data include the General Practice Research Database (GPRD) that contains medical records from primary care and the Yellow Card scheme that records suspected adverse drug reactions. The Independent Scientific Advisory Committee for MHRA database research (ISAC)<sup>138</sup> advises MHRA on the authorisation of research related requests to access data from both the Yellow Card Scheme and the GPRD.

The call for evidence raised concerns about the legislation and mechanisms in place for accessing patient data and these issues are addressed in more detail in Chapter 6.

#### **Use of human tissue and embryos in research**

Approval to use human tissue or embryos in research is provided by:

- The *Human Tissue Authority* (HTA)<sup>139</sup> licenses sites in England and Wales and Northern Ireland that store human tissue for research, as required by the Human Tissue Act (2004). A continuous licensing system is used and a licence is not required for the storage of tissue for a specific research study that has been approved by a recognised REC. The HTA inspects licensed sites to ensure that the premises, practices and individuals involved are fit for their licensed purpose. Human tissue legislation differs in Scotland, where a licence is not required to store tissue from living donors.
- The *Human Fertilisation and Embryology Authority* (HFEA)<sup>140</sup> grants licences for research using human embryos for up to three years for individual research projects, as required by the Human Fertilisation and Embryology Act (2008). Inspection and peer review form part of the licensing process and the HFEA aims to approve 90% of licence applications within three months. REC approval is also required for these studies.

The main problem identified relating to this issue in the call for evidence was the inclusion of certain types of tissue as defined by the Human Tissue Act (2004). The use of tissue and embryos in research is considered further in Chapter 7.

#### **Other approvals**

Other specialist approvals include the following:

- Various approvals may be required for health research in the criminal justice system. These depend on the type of research and include National Offender Management Service approval for research in prisons or the probation service and Ministry of Justice Research Quality Assurance. A positive opinion from a REC is also required in certain cases.<sup>141</sup>

135 For further information see [http://www.nhsnss.org/pages/about/pac\\_privacy\\_advisory\\_committee.php](http://www.nhsnss.org/pages/about/pac_privacy_advisory_committee.php)

136 For further information see <http://www.nigb.nhs.uk/ecc>

137 For further information see [http://www.nhsnss.org/pages/about/pac\\_privacy\\_advisory\\_committee.php](http://www.nhsnss.org/pages/about/pac_privacy_advisory_committee.php)

138 For further information see <http://www.mhra.gov.uk/Committees/IndependentScientificAdvisoryCommitteeForMHRADatabaseResearch/index.htm>

139 For further information see <http://www.hta.gov.uk/>

140 For further information see <http://www.hfea.gov.uk/>

141 Hayes A, Lennox L & Senior J (2010). *OHRN toolkit*. <http://www.ohrn.nhs.uk/toolkit/Toolkit4thEdition.pdf>

- In the UK, Administration of Radioactive Substances Advisory Committee (ARSAC)<sup>142</sup> research certification is required where the research involves exposures to radioactive substances in addition to normal clinical care, in accordance with the Medicines (Administration of Radioactive Substances) Regulations (1978). In England, Scotland and Wales exposure to radiation in research must also comply with the Ionising Radiation (Medical Exposure) Regulations (2000) (IRMER). Trusts are responsible for ensuring that this legislation is appropriately implemented and the Care Quality Commission ensures compliance with IRMER through inspections.

### **Clinical trial authorisation**

Clinical trial authorisation (CTA) is required for any clinical trial of an investigational medicinal product (CTIMP) to be conducted, according to the Clinical Trials Directive, which is implemented in the UK as the Medicines for Human Use (Clinical Trials) Regulations (2004). For certain types of first-in-human trials, including those on compounds affecting the immune system, the MHRA seeks advice from its Clinical Trials Expert Advisory Group (EAG) of the Commission on Human Medicine (CHM)<sup>143</sup> before giving approval. The MHRA also regulates devices according to the Medical Device Regulations, which transposed the EU Medical Devices Directive into UK law.

The call for evidence raised major concerns about the scope and requirements set out by the Clinical Trials Directive and the interpretation and implementation of the UK regulations by the MHRA. These issues are considered further in Chapter 5.

### **NHS Research and Development (R&D) permissions**

NHS Trusts (England and Northern Ireland) and Health Boards (Scotland and Wales) review research projects that are proposed to take place within the NHS. Permissions must be obtained at all NHS sites where the research is taking place and is administered by the Trust or Health Board R&D office. Although there are target timeframes in some cases, there is no legal requirement for a response to applications to be made within a certain timeframe.

R&D permissions were highlighted by those responding to the call for evidence as posing the greatest burden of health research regulation and governance. These issues are considered in further detail in Chapter 4.

### **Ongoing study requirements**

Once a project is underway there are additional regulation and governance processes that must be observed. These requirements depend on the type of study, for example CTIMPs are subject to protocol set out in the Clinical Trials Directive and the corresponding UK regulations.

#### ***Reports to ethics committees***

For all types of study the main REC requires an annual report, which includes information on sites such as recruitment, participant safety, amendments and breaches of the protocol. The actual requirements vary depending on whether or not the study is a CTIMP.

#### ***Amendments to the protocol***

The process for notification of amendments to the study protocol varies depending on whether the study is a CTIMP or not. For non-CTIMP studies, the main REC must be informed of all substantial amendments. For CTIMPs 'substantial amendments', as defined by the Clinical Trials Directive, must be authorised by the MHRA and/or a favourable opinion given

<sup>142</sup> For further information see <http://www.arsac.org.uk/>

<sup>143</sup> For further information <http://www.mhra.gov.uk/Committees/Medicinesadvisorybodies/CommissiononHumanMedicines/ExpertAdvisoryGroups/ClinicalTrials/index.htm>

by the main REC depending on whether the amendment affects the terms of the original clinical trial authorisation or REC opinion. No notification is required of 'non-substantial amendments', but a record of these must be kept.

### ***Safety reporting for CTIMPs***

The UK Medicines for Human Use (Clinical Trials) Regulations (2004) set out the responsibilities of investigators and sponsors to report adverse events in the context of a CTIMP, with timescales for reporting that are dependent on the severity of the reaction. In addition, annual safety reports are made to the MHRA and the main REC. These safety reporting requirements are described in Chapter 5.

The call for evidence identified some aspects of safety reporting to be burdensome for sponsors, ethics committees and investigators, without improving patient safety, as discussed in Chapter 5.

### ***Inspections***

The MHRA undertakes Good Clinical Practice (GCP) inspections of sites involved in CTIMPs to ensure that they are carried out to appropriate standards. GCP inspections assess compliance with the regulatory requirements and GCP

guidelines, as well as Good Manufacturing Practice (GMP) inspections to assess whether medicinal products, including investigational medicinal products used in a clinical trial, are consistently produced and controlled to appropriate quality standards.

The call for evidence identified major concerns around how some GCP inspections have been conducted, which impacts on the researchers and sites involved and is also believed to contribute to a risk-averse attitude to research amongst NHS Trusts (this is discussed further in Chapters 3 and 5).

### ***NHS R&D permissions***

The Research Governance Framework notes that those involved in research may be liable under common law if they are negligent and that it is an offence not to comply with the law for clinical trials involving medicines. The RGF also suggests a framework for mechanisms that could be used to monitor the quality of health research, including audit and appraisal.

In addition to these standard processes, further reports may also be required to other stakeholders with an interest in the research, for example funders, Clinical Research Networks and Trust R&D offices.





## Annex II: Working group membership

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Working group members participated in a personal capacity, not as representatives of the organisations listed.

### Chair

**Professor Sir Michael Rawlins FMedSci**, Emeritus Professor, University of Newcastle

### Members

**Professor Deborah Ashby OBE**, Professor of Medical Statistics and Clinical Trials and Co-Director, Imperial Clinical Trials Unit, School of Public Health, Imperial College London

**Dr Mary Baker MBE**, President, European Federation of Neurological Associations

**Professor Sir Rory Collins FMedSci**, BHF Professor of Medicine & Epidemiology, Clinical Trial Service Unit & Epidemiological Studies Unit, University of Oxford

**Professor Janet Darbyshire CBE FMedSci**, Emeritus Professor of Epidemiology, University College London

**Professor Carol Dezateux CBE FMedSci**, Professor of Paediatric Epidemiology and Director of MRC Centre of Epidemiology for Child Health, Institute for Child Health

**Professor Stephen Evans**, Professor of Pharmacoepidemiology, London School of Hygiene and Tropical Medicine

**Mr Mike Farrar CBE**, Chief Executive of NHS North West

**Professor Gary Ford**, Jacobson Chair of Clinical Pharmacology, University of Newcastle

**Dr David Gillen**, Senior Director and Head of International Medical Affairs, Gilead Sciences

**Professor Peter Johnson**, Cancer Research UK's Chief Clinician and, Chair of Medical Oncology, University of Southampton

**Professor Shitij Kapur FMedSci**, Vice Dean and Head of School, Institute of Psychiatry

**Sir Ron Kerr**, Chief Executive of Guy's and St Thomas' NHS Foundation Trust

**Professor Jonathan Knowles**, Vice Chairman, Caris Life Sciences

**Professor Mike Parker**, Professor of Bioethics and Director of the Ethox Centre, University of Oxford

**Professor Genevra Richardson CBE FBA**, Professor of Law, King's College London

**Mr Paddy Storrie**, Deputy Head, St George's VA School, Harpenden

**Professor Patrick Vallance FMedSci**, Senior Vice President, Drug Discovery, GlaxoSmithKline

**Professor David Webb FMedSci**, Christison Professor of Therapeutics and Clinical Pharmacology, University of Edinburgh

## Observers

Observers joined the initial working group meetings to clarify factual points but were not present for discussion of the conclusions and recommendations of the study.

**Mr Marc Taylor**, Deputy Director of Research & Development, Head of Research & Development Systems and Governance, Department of Health

**Dr David Griffiths-Johnson**, Head of Innovation, Office for Life Sciences, Department for Business, Innovation & Skills

**Professor Kent Woods FMedSci**, Chief Executive, Medicines and Healthcare products Regulatory Agency; substituted by:

**Miss Margaret Jackman**, Head of Strategy and European Medicines Policy, Medicines and Healthcare products Regulatory Agency

**Dr Martyn Ward**, Head of Clinical Trials Unit, Medicines and Healthcare products Regulatory Agency

## Secretariat

**Dr Robert Frost (Lead Secretariat)**, Policy Manager, Academy of Medical Sciences

**Miss Emma Greenwood**, Policy Researcher, Cancer Research UK

**Dr Rachel Quinn**, Director, Medical Science Policy, Academy of Medical Sciences

**Dr Beth Thompson**, Policy Officer, Wellcome Trust

## Annex III: Review group membership

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This report was reviewed by an external panel appointed by the Council of the Academy of Medical Sciences. Reviewers were asked to consider whether the report met the terms of reference and whether the evidence and arguments presented in the report were sound and supported the conclusions. Reviewers were not asked to endorse the report or its findings.

**Professor Patrick Sissons FMedSci** (Chair)

Regius Professor of Physic, University of Cambridge

**Professor Jeffrey Almond FMedSci**

Vice President, Discovery Research and External Research and Development, Sanofi Pasteur

**Professor Robert Califf**

Vice Chancellor for Clinical Research and Director of the Duke Translational Medicine Institute, Duke University

**Professor Andrew Morris FRSE FMedSci**

Professor of Diabetic Medicine and Director of Biomedical Research Institute, University of Dundee

**Sir Nick Partridge OBE**

Chairman, INVOLVE and Chief Executive, Terrence Higgins Trust

**Sir John Pattison FMedSci**

Former Director of Research and Development, Department of Health

**Baron Warner of Brockley**

Former Minister of State, Department of Health

**Professor Simon Wessely FMedSci**

Vice Dean, Institute of Psychiatry and Professor of Psychological Medicine, King's College London



## Annex IV: Respondents to the calls for evidence

Two calls for evidence were issued to inform the review. The project was launched with an initial call for evidence in May 2010 to determine the priorities for the study and a second call was launched in July 2010 to seek responses to the Department of Health's announcement that it was considering the creation of a new arm's length body to regulate research (see <http://www.acmedsci.ac.uk/p47prid80.html>).

Those who submitted written evidence are listed below. We apologise to anyone that we have inadvertently omitted from the list.

### **Organisations**

Academy of Social Sciences	Childhood Cancer & Leukaemia Group
Alder Hey Children's NHS Foundation Trust	Clinical Contract Research Association
Amgen	Clinical Trials Research Unit, University of Leeds College of
Appointing Authority for Phase I Ethics Committees	Emergency Medicine
Administration of Radioactive Substances	Cook Medical
Advisory Committee	Council for Healthcare Regulatory Excellence
Association of Clinical Research Organizations	DeNDRoN Huntington's Disease Clinical Studies Group, University of Cardiff
Association of Medical Research Charities	Dental Schools Council
Association of Research Ethics Committees and National Research Ethics Advisory Panel	ESRC Centre for the Economic and Social Aspects of Genomics, University of Cardiff.
Association of the British Pharmaceutical Industry	Essex & Hertfordshire CLRN
Association of UK University Hospitals	Faculty of Health and Life Sciences, University of Liverpool
Asterand UK Ltd	Faculty of Health Sports and Science, Glamorgan
AstraZeneca	Faculty of Pharmaceutical Medicine
Athenaeum Group	FMRIB Centre, University of Oxford
Barts and The London School of Medicine and Dentistry and The London NHS Trust	Gene Therapy and Advisory Committee
Belfast Health and Social Care Trust	Genetic Alliance UK and Rare Disease UK
Berkshire Healthcare NHS Foundation Trust	Genewatch UK
BioIndustry Association	Genzyme Therapeutics Ltd
Breast Cancer Campaign	GlaxoSmithKline
British Association for Psychopharmacology	Greater Manchester Primary Care Research Governance Partnership
British Heart Foundation	Gregory Fryer Associates Ltd
British Medical Association	Health and Safety Executive
British Pharmacological Society	Health Ethics and Law Network, University of Southampton
British Society for Oral and Dental Research	Health Protection Agency
Cancer Research UK	Health Services Research Network, The NHS Confederation, London
Cardiff University School of Medicine & Cardiff and Vale University	Human Fertilisation and Embryology Authority
Care Quality Commission	Human Genetics Commission
Central Manchester University Hospitals NHS Foundation Trust	Human Tissue Authority
Centre for Health Services Studies, University of Kent	Human Tissues Working Party

ICR Cancer Research Clinical Trials & Statistics Unit  
 Imperial Clinical Trials Unit  
 Imperial College  
 Imperial College Academic Health Science Centre  
 Independent Cancer Patients' Voice  
 Institute of Cancer Research  
 Institute of Clinical Research  
 Integrated Research Application System  
 INVOLVE Coordinating Centre  
 Kent and Medway Comprehensive Local Research Network  
 Kidney Research UK  
 Lawford Davies Denoon  
 Leicestershire, Northamptonshire, Rutland Comprehensive Local Research Network  
 Liverpool Women's Health NHS Trust  
 London School of Hygiene and Tropical Medicine  
 Manchester Academic Health Sciences Centre  
 Medical Schools Council  
 Medicines and Healthcare products Regulatory Agency  
 Meditronic  
 MRC Centre for Transplantation  
 Napp Pharmaceuticals Ltd  
 National Cancer Research Network  
 Consumer Liaison Group  
 National Information Governance Board  
 National Institute for Social Care and Health Research  
 National Research Ethics Advisors' Panel and Association of Research Ethics Committees  
 National Research Ethics Service  
 NCRI Palliative Care Clinical studies group; Association for Palliative medicine of Great Britain and Ireland; Help the Hospices  
 NCRI PET Research Network  
 Newcastle University and the Newcastle upon Tyne Hospitals NHS Foundation Trust  
 NHS Derbyshire County and Derbyshire Community Healthcare Services  
 NHS East of England  
 NHS North of Tyne  
 NHS Research Scotland  
 NIHR Clinical Research Coordinating Centre  
 NIHR Medicines for Children Research Network  
 North Tyneside Primary Care Trust  
 Northumberland Tyne and Wear Clinical Genetics Specialty Group  
 Novartis  
 Novo Nordisk  
 Nuffield Council on Bioethics  
 Offender Health Research Network  
 onCore UK  
 Parkinson's UK  
 Pathological Society  
 Peninsula R&D Community  
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 Royal College of Pathologists  
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 Royal College of Physicians  
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 School of Medicine, Dentistry and Biomedical Sciences at Queen's University Belfast  
 School of Nursing, Midwifery & Social Work, University of Manchester  
 Science Media Centre  
 Scottish Health Informatics Programme  
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 Southern Health and Social Care Trust  
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 The Health Services Research Network  
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## Annex V: Abbreviations and acronyms

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AAPEC	Appointing Authority for Phase I Ethics Committees
ABPI	Association of the British Pharmaceutical Industry
AIDS	Acquired Immune Deficiency Syndrome
AMRC	Association of Medical Research Charities
ASR	Annual Safety Report
ARSAC	Administration of Radioactive Substances Advisory Committee
BIA	Bioindustry Association
CCMO	Central Committee for Research Involving Human Subjects (the Netherlands)
CLRN	Comprehensive Local Research Network
CRB	Criminal Records Bureau
CRN	Clinical Research Network
CSP	NIHR Coordinated System for gaining NHS Permissions
CSPU	NIHR Coordinated System for gaining NHS Permissions Unit
CTA	Clinical Trial Authorisation
CTD	Clinical Trials Directive
CTFG	Clinical Trials Facilitation Group
CTIMP	Clinical Trial of Investigational Medicinal Product
ECC	Ethics and Confidentiality Committee
EMIG	Ethical Medicines Industry Group
ETC	Excess Treatment Cost
EU	European Union
FDA	Food and Drug Administration (USA)
GAfREC	Governance Arrangements for Research Ethics Committees
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GTAC	Gene Therapy Advisory Committee
HFEA	Human Fertilisation and Embryology Authority
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
HTA	Human Tissue Authority/Human Tissue Act
ICH	International Conference on Harmonisation
ICREL	Impact on Clinical Research of European Legislation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRAS	Integrated Research Application System
IRB	Institutional Review Board
LRN	Local Research Network
MHRA	Medicines and Healthcare products Regulatory Agency
METC	Medical Research Ethics Committee (the Netherlands)
MRC	Medical Research Council
NCA	National Competent Authority
NHS	National Health Service
NIHR	National Institute for Health Research
NIGB	National Information Governance Board

NPSA	National Patient Safety Agency
NREAP	National Research Ethics Advisory Panel
NRES	National Research Ethics Service
PPI	Patient and Public Involvement
R&D	Research and Development
REB	Research Ethics Board
REC	Research Ethics Committee
RGF	Research Governance Framework
RSS	Research Support Services
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
UKCRC	UK Clinical Research Collaboration
VHP	Voluntary Harmonisation Procedure





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