Streamlining regulation of clinical trials - update on the Academy of Medical Sciences review and government's response

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History

- EU Clinical Trials Directive implemented in UK law May 2004
- Intention – to simplify and harmonise the regulation of clinical trials across the EU, thereby facilitation the internal market in medicinal products while protecting participants and public health

  "proportionality would answer many of the concerns raised about needless bureaucracy" *Woods BMJ 2004*
- Major concerns expressed prior to introduction
- Academy Medical Sciences Symposium 2003

  "will increase costs of non-commercial clinical research considerably"

  "imposes onerous responsibilities on the trial sponsor"

  "the position of the MHRA is that there is nothing in the Directive which the non-commercial sector cannot follow and the implementation in the UK will be done sensibly..... the history of regulation suggests that it will become more onerous as time passes."

History

- Research Governance Framework for Health and Social Care introduced April 2001
- A framework to ensure standards of quality are developed, continuously improved upon & monitored in all research activity that the minister for Health & Social Care has responsibility for.
- Introduced after high profile research misconduct cases
- David Southall, Griffiths report 2000

  Findings discredited.

History

- Alder Hey, Professor Van Velzen Redfern Report 2001

  We set out to discover how so many parents were induced into thinking that they were burying their children intact when in fact the large majority were buried without their vital organs. In our search we discovered the long-standing widespread practice of organ retention without consent. The practice arose from a sense of paternalism on the part of the medical profession.

- Not primarily about research practice

  Perhaps we should now all be asking ourselves what else we might be doing that seems routine and normal to us but might suddenly become the focus of public attention.

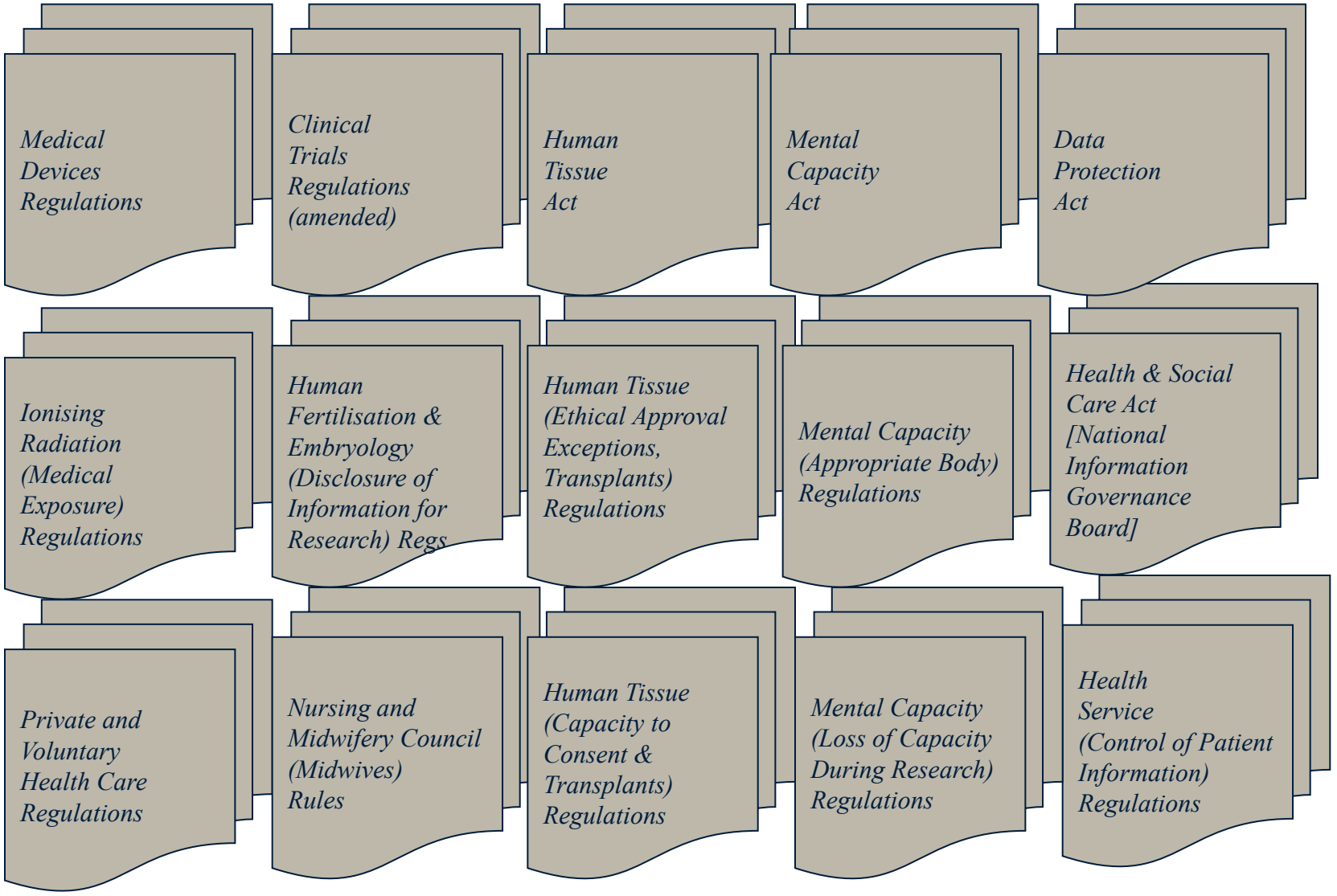
  Hall D, Arch Dis Child 2001

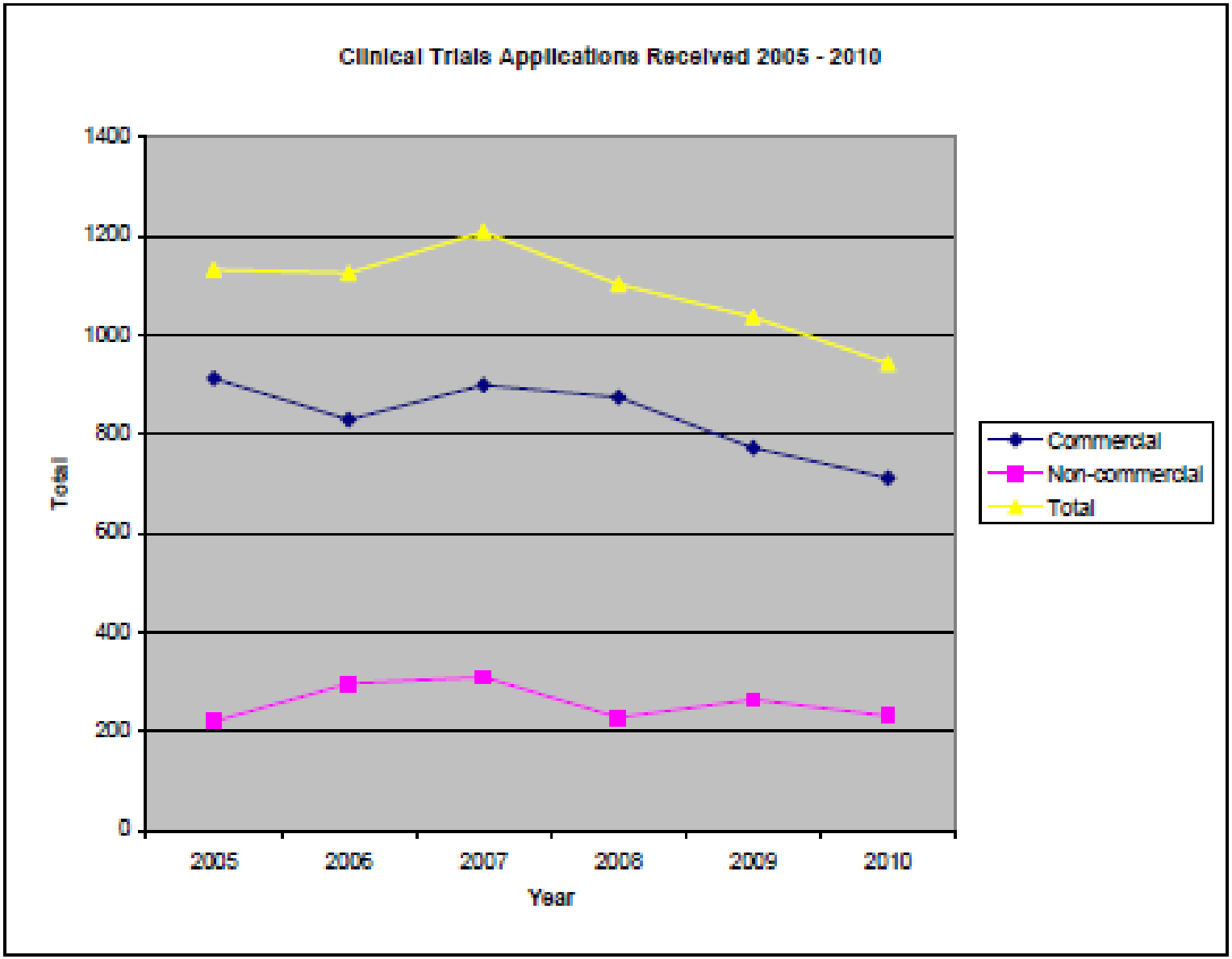
- Less comment from academic community on potential impact of Research Governance Framework

Consequences of EU CTD and Research Governance Framework

- Establishment of R&D governance officers in NHS Trusts
- Absence of clinical research leadership in many Trusts led to risk averse culture
- No additional resources from funders or Trusts to support researchers
- Lack of clear guidance for implementation of the Research Governance Framework
- Commencement of MHRA Audits in NHS Trusts
- Research community belief that implementation of EU CTD disproportionate and gold plated
- Substantial increase in time to initiate clinical research studies

Complex legislation governing research



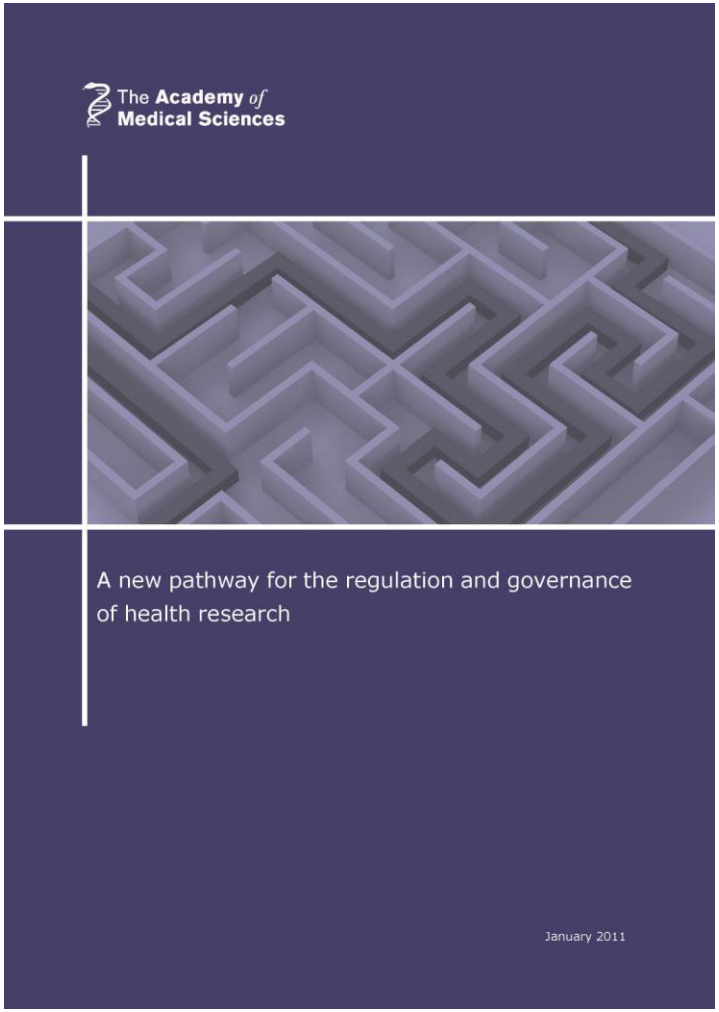

Clinical Trials Applications Received 2005 - 2010
1400
1200
1000
800
600
400
200
0
Total
2005
2006
2007
2008
2009
2010
Year
Commercial
Non-commercial
Total

Reviewing the regulation and governance of health research

- Building on UK strengths and recent investment.
- Government commission to review the landscape and make recommendations to increase the speed of decision-making, reduce complexity and eliminate unnecessary bureaucracy and cost.

Process:

- Academy working group.
- Two calls for evidence – over 300 submissions.
- Acknowledgements



Key bottlenecks

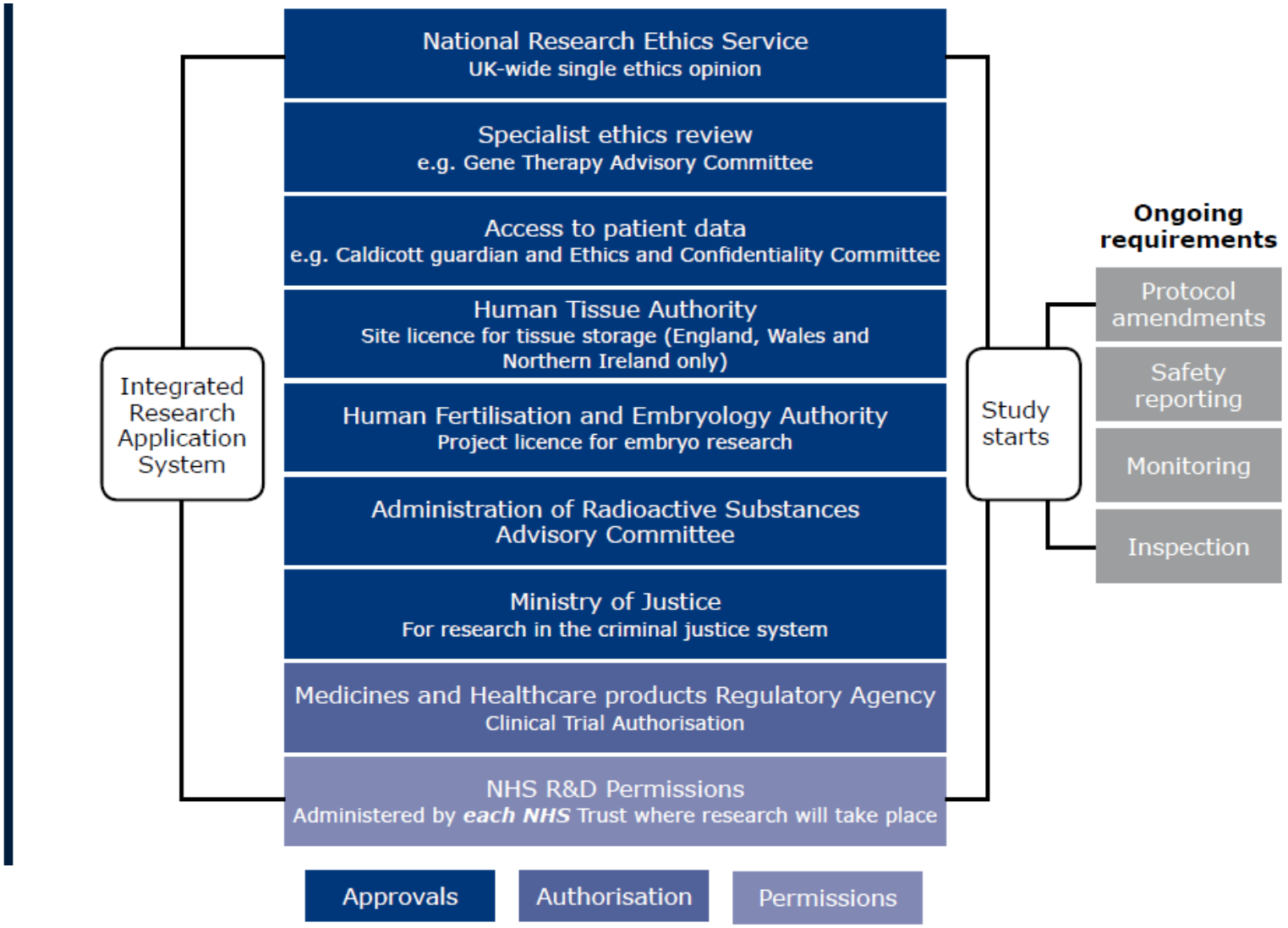
- Delays and duplication in obtaining research permission from **NHS R&D Trusts**. Obtaining **NHS permissions** single greatest barrier and rate-limiting step in most cases.
- **Complexity and inconsistency bureaucracy across the regulatory pathway** e.g. access to patient data.
- A lack of proportionality in the **regulation of clinical trials**.
- A **healthcare culture** that fails to fully support the value and benefits of health research.
- No evidence current measures have enhanced safety and well being of patients

$\Rightarrow$ Cancer Research UK: An average of 621 days from confirming funding to recruitment of the first patient.

AMS four principles should underpin health research regulation and governance

- Safeguard the well-being of research participants
- Facilitate high-quality health research to the public benefit
- Be proportionate, efficient and coordinated
- Maintain and build confidence in the conduct and value of health research through independence, transparency, accountability and consistency

The current regulation and governance pathway



Main recommendations

- The creation of a new **National Research Governance Service**

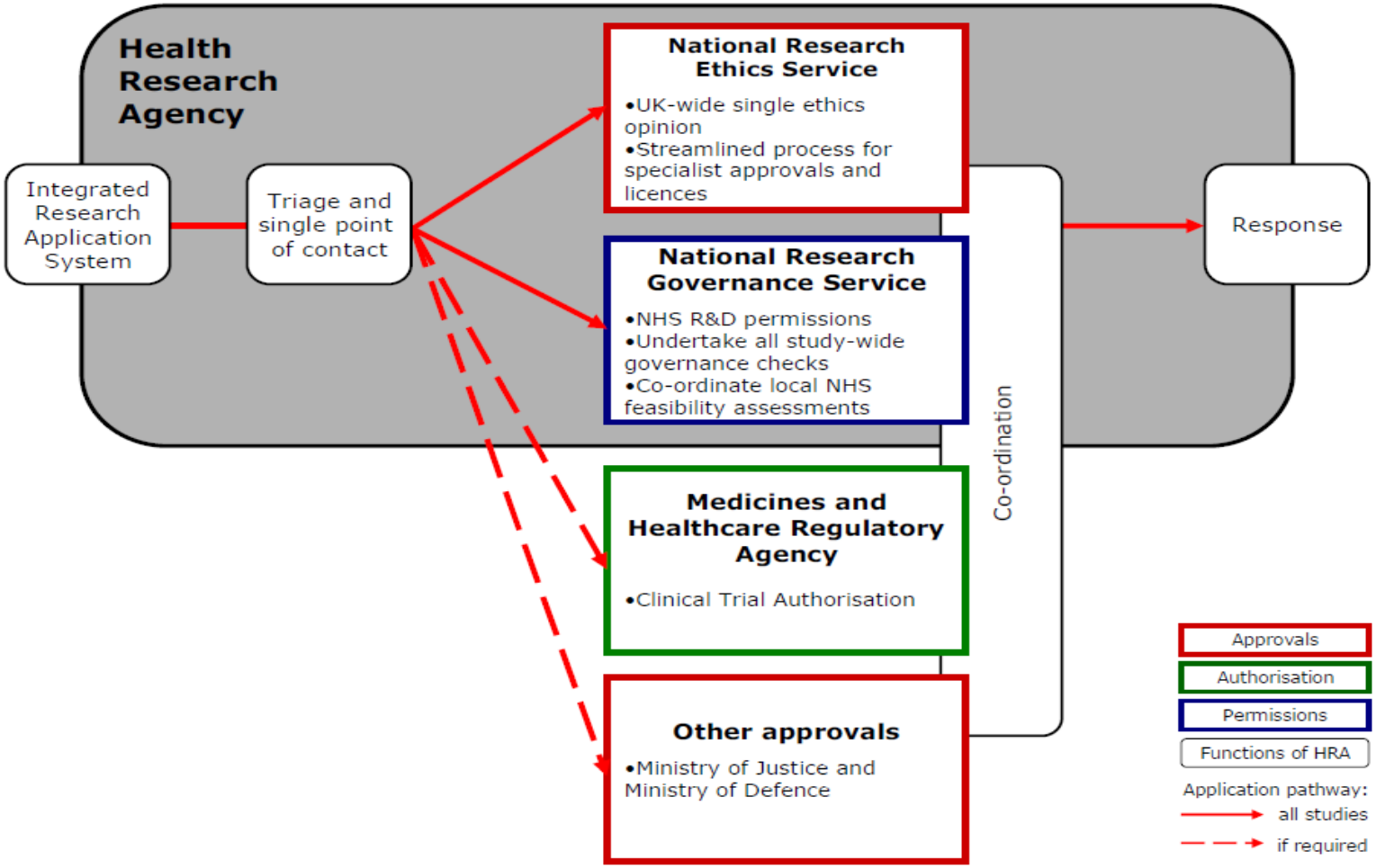
- As one core component within a new **Health Research Regulatory Agency** that would also undertake ethics and required specialist approvals.

- **Revision of the European Clinical Trials Directive and a more proportionate approach by the MHRA** to clinical trials regulation and monitoring.

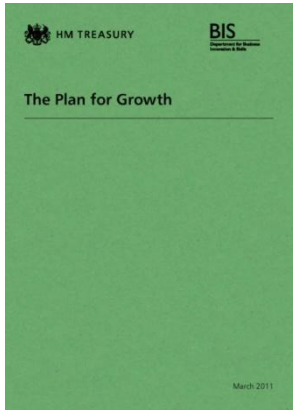
- **Health research** formally and irreversibly **embedded into NHS** leadership and governance processes.

⇒ Broad support from across the political parties and the commercial and non-commercial research community.

Academy of Medical Sciences report – proposed solution



Plan for Growth



- **Focus on 'healthcare and life sciences' as a key sector for long-term growth.**
- **Accepted AMS review findings**
- **Simpler regulation of health research at national level**

Combine and streamline approvals under a Health Research Regulatory Agency.
Agency established as a Special Health Authority, with the National Research Ethics Service as its core, in 2011.

- **Consistent national system of research governance**

The agency will work with the MHRA to create a unified approval process for clinical trials.
The agency and the MHRA will promote proportionate standards for compliance and inspection, including EU law on clinical trials.

Greater efficiency in NHS R&D approval

- *"Link NHS research funding to hospital performance on R&D approval and patient recruitment" (Plan for Growth)*
- Future NIHR funding will become conditional on Trusts adopting new Research Support Services: a 'bottom-up' approach to standardising good practice.
- Funding conditional on meeting benchmarks in the R&D approval process, including a 70 day benchmark from funding being agreed to the recruitment of the first patients into trials.
- Trusts will publish metrics on their performance.

Causes R&D approval delays in Newcastle Hospitals NHS Foundation Trust

- 195 NIHR Portfolio studies processed though Comprehensive System of Permissions
- Median 82 days (no clock stopping)
  31% < 60 days
- Studies > 60 days

Agreements	32%
Delayed submission	15%
Other approvals (REC/MHRA)	14%
Trust (R&D)	13%
Delays in PI/Sponsor response	8%
Trust (support departments)	7%
Peer review	2%
Other	9%

A new Health Research Regulatory Agency

- *"Set up a new health research regulatory agency (HRRA) this year to combine and streamline approvals for health research" (Plan for Growth)*

- Initially established as Special Health Authority – comes into force 1 Dec 2011
- Functions:
  - The facilitation and promotion of research
  - The establishment of Research Ethics Committees, and the appointment and indemnification of REC members
  - Such other functions as the Secretary of State may direct
- Chief Executive and Senior Responsible Officer recently appointed.
- New agency will be established in primary legislation

Possible model for Health Research Regulatory Agency

Body	Research remit	Advise	Review	Approve	License	Monitor	Inspect	Enforce
	Regulation							
MHRA	**Medicines**	**Medicines & Healthcare products Regulatory Agency**						
MHRA	**Devices**							
HFEA	**Embryology**	**Health Research Regulatory Agency** For research approvals					**Care Quality Commission**	
HTA	**Tissue**							
ARSAC	**Radiation**							
NRES	**Ethical review**							
GTAC	**Gene therapy**							
NIGB	**Patient information**							
CQC	**Quality of care**							
NOMS, MOJ	**Prisons**		MOJ					
GMC etc	**Misconduct**	GMC						
	Other legal duties							
NHS body	***Gives permission, accepts liability***							
Social Care								
Sponsor	***Takes on responsibility***							

Five NIHR aligned programmes

- **NIHR Research Support Services**
  NHS processes, tools, behaviours

- **Coordinated System for gaining NHS Permissions Improvement Programme**
  CSP processes, behaviours

- **North West Exemplar roll out**
  Network/ industry/ NHS processes, people, leadership

- **R&D Management Information Sysyten**
  IS support for information, collaboration and workflow

- **Performance management**
  with and for NHS trusts

Research Support Services

Aims

- improve **consistency** of R&D management and governance processes across organisations.
- **clarity** on roles and responsibilities of stakeholders in these processes.
- **streamlining** of processes - particularly when setting up research studies.
- raises awareness of **competencies** and training for NHS R&D management staff.
- **proportionate** risk management
- publication of **performance**

Research Support Services

Requires

- Customer focus from Research Management & Governance service

- Responsible and engaged researchers (particularly before CSP submission)

NIHR Research Support Services Outcome Indicators

- The proportion of studies where Trusts respond quickly to study information provided by sponsors (using the framework study planning tools)
- The proportion of studies which achieve NHS Permission in an agreed timescale
- The proportion of studies from NHS Permission to finish successfully (i.e. achieve agreed study 'targets' such as recruitment)
- The average (median) difference between planned and actual times to gain 'NHS Permission'
- The average (median) difference between planned and actual times from NHS Permission to 'start of study'

- From Autumn 2011 – new contracts include conditions that organisations are playing their part in the national research governance system and delivering competent performance against benchmarks.
- From 2013 – NIHR funding subject to evidence of outcomes demonstrating professional management of the initiation and delivery of health research.

Summary of Comprehensive System of Permission revisions

- Previously 37 (18 global/22 local) checks
  now 22 criteria (12 study-wide/16 local)
- Global checks based on the R&D Form with study-wide documents done only once
- Local checks based on the SSI Form with local documents done for each site
- Each site does not repeat global checks so subsequent sites can be set up quicker
- Revision of clock start/stop criteria
- Checks standardised, consistent and allow for judgment
- LEAN approach to Comprehensive Local Research Network / Trust processes

NHS permission to first patient first visit

- Comprehensive Clinical Research Network commercial studies only

- Time taken from NHS permission granted at first network site to the first patient, first (consent) visit at a network site (based on 42 studies):
  - **Average number of days – 38 days**
  - **% studies achieved within 30 days – 40%**

- *Point to note: if the Site Initiation Visit is performed before NHS permission then 85% of studies achieve FPFV within 30 days of first NHS permission.*

The European Clinical Trials Directive

- *Reduce the perceived gold-plating and increase the proportionality of the EU CTD and its application." (Plan for Growth)*

- EU concept paper (May 2011): agreement across UK submissions on the need to clarify Directive scope and adopt a proportionate approach.
- Revised Directive → UK law: 2016-2018. Offers an opportunity to further reduce regulatory burden on academic trials.
- Changing current practice in the UK: adopting a proportionate approach and clarifying the scope.

MHRA new Notification Scheme for Clinical Trials – Apr 2011

- Output of MRC/DH/MHRA joint project on risk adapted approaches
- Available for trials involving medicinal products authorised in any EU Member State if:
  - they relate to the licensed range of indications, dosage and form
  - or, they involve off-label use (such as in paediatrics and oncology, etc) if this off-label use is established practice and supported by sufficient published evidence and/or guidelines.
- May include randomisation to different marketed products or repackaging and/or relabelling of the marketed product(s).
- Not eligible: placebo controlled trials
  modification of marketed product e.g. over-encapsulation.
- Following valid notification submission, sponsors receive an acknowledgement letter to say that the trial may go ahead after 14 days, if the MHRA has not raised any objections.
- A risk assessment based on the potential investigational medicinal product (IMP) risks should be made by the sponsor.
- Future guidance on risk-proportionate approaches to the management and monitoring of clinical trials.

Pilot Assessment Risk Adapted Approach

SUMMARY FINDINGS

- Nearly all participants thought the risk-adapted and risk-proportionate guidelines and templates were valuable and timely.
- Feedback on the process of using the new approach was mixed with several participants finding the process straightforward whilst others finding it lengthy, complex and unclear.
- Specific criticisms of the process included the subjective nature of assessing Type B trials, the length of time caused by the need to involve many people in the application process, and the need for clarity on what happens if the MHRA disagrees with the investigator's / sponsor's risk assessment.
- Recommendations for modifying the approach typically focused on the need for greater clarity and improved structure.
- Participants had a mixed response when considering the impact of the approach on current practice. Several participants reported little change in the way trials are managed and monitored whilst others reported a beneficial or detrimental impact.

NIHR Evaluation Trials and Studies Co-ordinating Centre Questionnaire

- Research Project Teams – 6
- Clinical Trials Units – 5
- NHS Trust R&D Offices – 4

Key challenge – culture around health research in the NHS

- NHS Management – often poor understanding of research and it's value, perception that it is high risk
- NHS staff - cultural disconnect with research, particularly primary care
- Researchers – poor understanding of benefits of appropriate regulation and governance and role in building public confidence. Need to communicate value of research and relevance to the NHS
- NHS R&D Teams – frequent focus on protecting the Trust, complying with legislation and the Research Governance Framework rather than delivering research
- Will the Health Research Regulatory Agency have sufficient authority to drive through efficient working?