Objectives of quality assurance in randomised clinical trials

- Protecting the safety, rights and well being of study participants
- Ensuring the reliability and robustness of study results

Need cost-effective strategies

Put greater reliance on design strengths inherent in randomized-controlled trials

- Randomization: unbiased comparison of patient groups that differ randomly

- Control group: unbiased ascertainment of outcomes in study treatment groups

Yields unbiased assessment of treatment (which will only be reliable if large enough)

MRC review: Potential for EU Clinical Trials Directive (2001) to be a major obstacle to important trials

- Increased bureaucracy due to requirement for single sponsor (possibly the funding source)
- Burdensome drug authorisation and supply (GMP & labelling) processes
- Threat to trials of emergency treatments for patients unable to give consent
- Rigid approach to pharmacovigilance and site monitoring (through over-interpretation)
- Substantial increases in costs could result in fewer important trials being conducted

European Commission statement: Adverse impact of EU Clinical Trials Directive (October 2009)

- Increased administrative costs without added value
- Increased scientific staff demands due to inefficiencies
- Separate assessment procedures in different member states (*"to the detriment of safety of the clinical trial participants")*
- Inconsistent application leads to longer delays for starting (*"patients do not have access to new, innovative treatments"*)

"performing clinical trials … has become considerably more difficult and costly"

Academy of Medical Sciences: A new pathway for the regulation and governance of health research

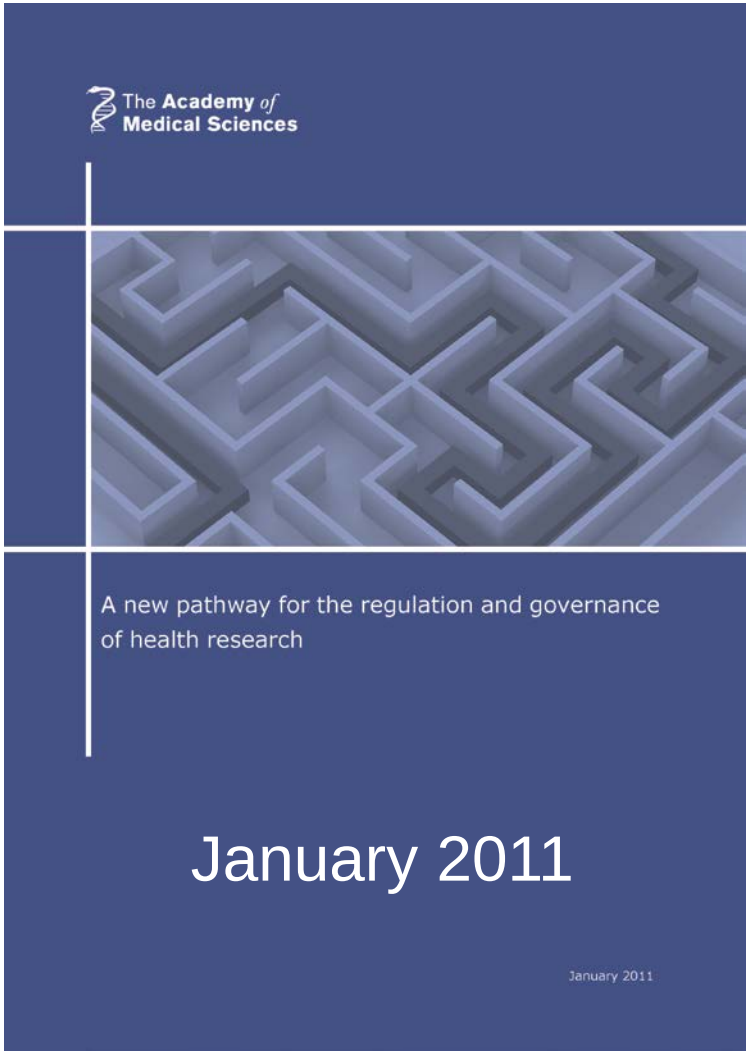
- Building on UK strengths and recent investment in research
- Government commission

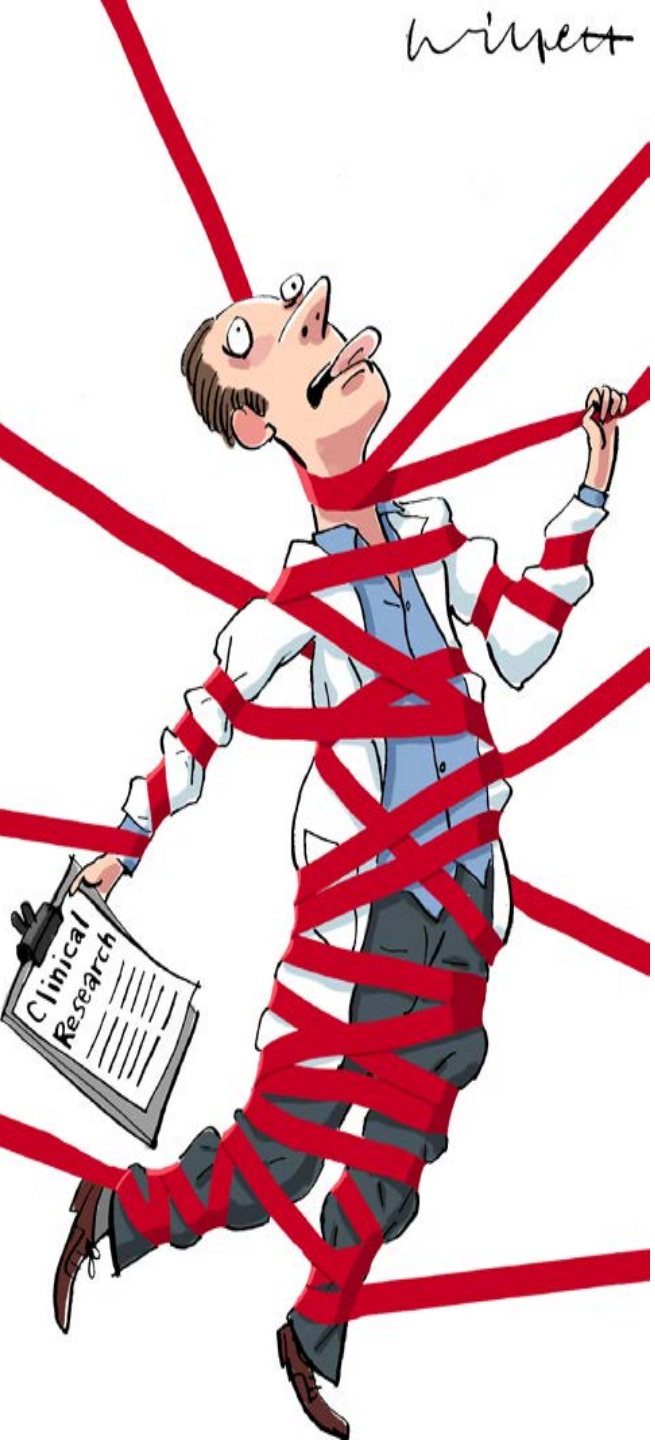
Scope:

- “Health research”.
- Make recommendations to increase speed of decision-making, reduce complexity and eliminate unnecessary bureaucracy and cost.

Process:

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





AMS report on regulation: Key bottlenecks identified

- Delays and duplication in obtaining research permission from **NHS R&D Trusts**.
- **Complexity and inconsistency 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 support the value and benefits of health research.

AMS report on regulation: Main recommendations

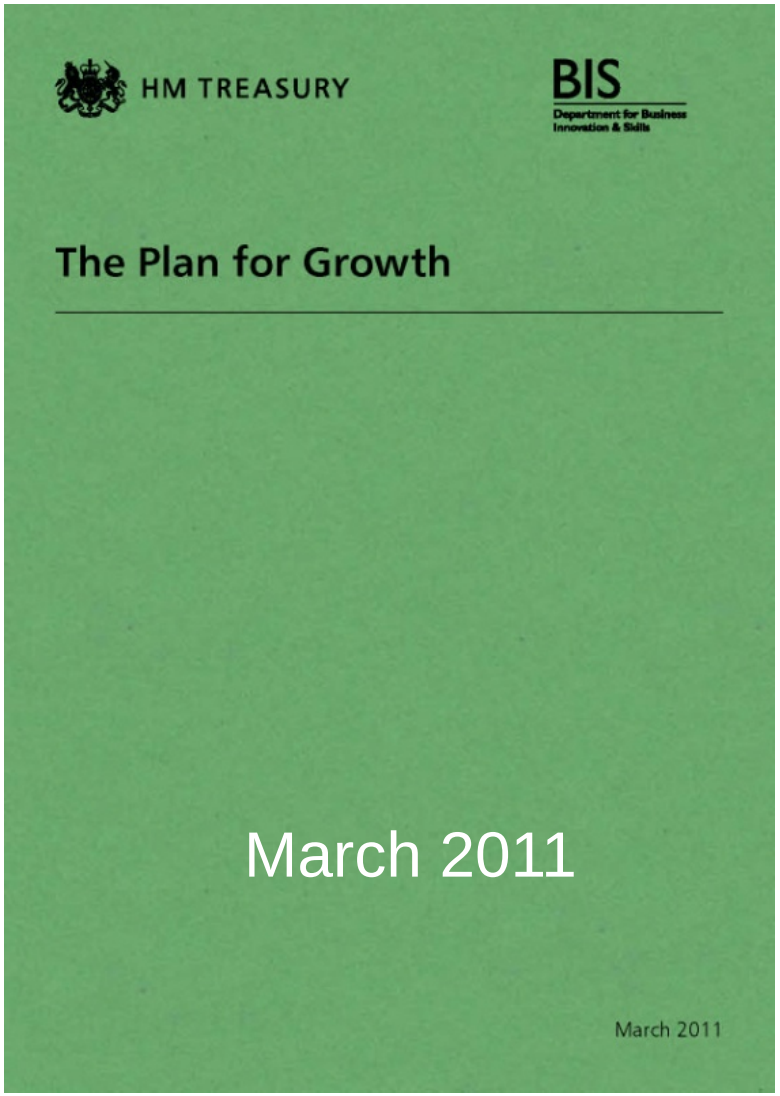
- The creation of a new **National Research Governance Service**.
- As one core component within a new **Health Research Regulatory Agency** that would also undertake ethics and specialist approvals.
- **Streamlining access to patient data** while maintaining appropriate safeguards.
- **Revision of the 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.

$\Rightarrow$ Broad support from across the political parties and the commercial and non-commercial research community.

UK Government's response to AMS report

George Osborne: *"In life sciences … we will radically reduce the time it takes to get approval for clinical trials."*

- Focus on "healthcare and life sciences" as a key sector for long-term growth.
- Commitment to take forward many of the recommendations from the AMS report.



UK Government: “The Plan for Growth” 2011

- *“Set up a new health research regulatory agency (HRRA) this year to combine and streamline approvals for health research”*
  - To be established as Special Health Authority by October/November 2011.
  - In the first instance, this is likely to consist solely of the National Research Ethics Service (NRES).
- *“Link NHS research funding to hospital performance on R&D approval and patient recruitment”*
  - 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.
  - Trusts will publish metrics on their performance.

Clinical research: time for sensible global guidelines (Lang, Cheah & White; Lancet May 2011)

"Clinical research is being strangled by bureaucracy because guidelines that were developed for product-registration trials are being applied rigidly to all types of clinical research. Complex, often confusing, and readily misinterpreted regulations, and their consequent spiralling costs, are a dangerous disincentive to medical progress."

Draft US FDA Guidance on a risk-based approach to monitoring (August 2011)

"There is a growing consensus that risk-based approaches to monitoring, such as focussing on the most critical data elements, are more likely to ensure subject protection and overall study quality, and will permit sponsors to monitor the conduct of clinical investigations more effectively than routine visits to all clinical sites and 100% data verification."

The current situation (2012)

Progress

- US FDA: Draft Guidance on a risk-based approach to monitoring (2011)
- EMA: Reflection paper on risk based quality management in clinical trials (2011)
- MRC/DH/MHRA Joint Project report on risk-adapted approaches to the management of clinical trials of investigational medicinal products (2011)

Challenge

- Ensure that these helpful initiatives are widely propagated, understood and adopted.

Joint statement from non-commercial and commercial organisations on revision of the EU Clinical Trials Directive (September 2011)

"We welcome the proposal to revise the EU Clinical Trials Directive … Revisions should focus on reducing bureaucracy, which also acts as a disincentive to setting up clinical trials… include streamlining authorisation processes; adoption of a proportionate approach to the regulation of clinical trials; and the provision of clearer guidance."

PROBLEMS: general consensus

SOLUTIONS: lack of consensus

Can we move forward or shall we just continue going round in circles?

MHRA draft Guide to GCP (643 pages + index)

Potential to substantially harm trial quality.

For example:

- Persistent assumptions of value of Source Data Verification
  - "The purpose of monitoring clinical trials is to verify that…the reported trial data are accurate, complete and verifiable against the source documents"
- Responsibilities and delegation
  - Investigator and sponsor have defined responsibilities
  - "Responsible for" ≠ "will do"
  - Quality may be enhanced by delegation to staff/institutions with appropriate experience and training, provided there is appropriate support & supervision (mentoring), e.g. consent; assessment of eligibility and of relatedness

MHRA draft Guide to GCP (2012)

Question: *"Who was involved in developing it?"*

Answer: *"A number of different groups … have been involved in developing the GCP Guide and include CTU (MHRA), HRA through NRES, the GCP, GLP, GPvP and GMP/GDP Inspectorate. Also statistical unit within the MHRA licensing Division have reviewed the statistics chapter and Association for Clinical Data Managers have reviewed … the Data Management chapter."*

MHRA draft Guide to GCP (2012)

Question: *"Given that it is over 650 pages long, why is the review process so short?"*
[Sent on 8 May for comment by 25 May]

Answer: *"We appreciate the extent of this document but we are asking for a high level review to be performed by our external reviewers. During the consultation process, we identified a number of areas that stakeholders needed guidance on which ultimately resulted in a need to cover a large range of topics, to include a number of practical examples and inspection findings…and hence the length."*

Bad news: *"The intention ... provide practical advice to key stakeholders such as both commercial and non-commercial sponsors of clinical trials….Given the international nature of clinical research it is envisioned that a UK GCP guide can be produced in such a way as to be useful in both a national and international context."*

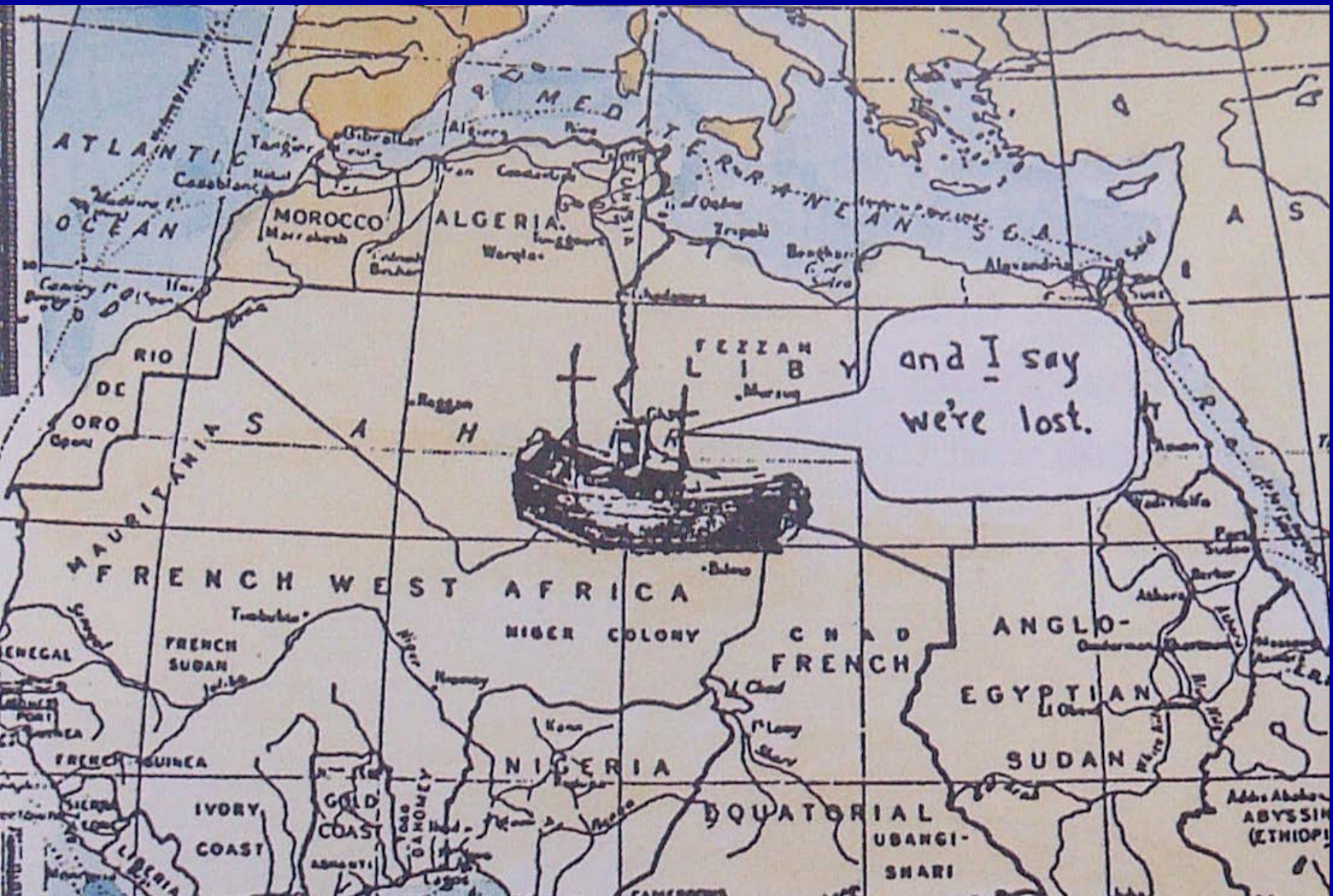
Good news: *"Please note that the GCP Guide is Crown Copyright and is <u>not</u> for general distribution without permission of the MHRA"*

Re-engineering the European Union Clinical Trials Directive (Kenter & Cohen; Lancet 2012)

"The European Commission is currently considering a revision of the EU CTD, but this will simply build further on the current directive's flawed foundations.

Available evidence and funds should be directed towards the creation of an integrated EU assessment system rather than upgrading the regulations of the existing flawed system. In other words, do not fix the roof when the foundations are shaky."

British comedian: Spike Milligan (ex-Goon)



“1984” by George Orwell
(prequel to “1996 ICH-GCP”)

“The Ministry of Peace concerns itself with war, the Ministry of Truth with lies, the Ministry of Love with torture, and the Ministry of Plenty with starvation. These contradictions are not accidental, nor do they result from ordinary hypocrisy; they are deliberate exercises in DOUBLETHINK.”

"Don't you see that the whole aim of Newspeak is to narrow the range of thought?... Orthodoxy means not thinking – not needing to think. Orthodoxy is unconsciousness.“

"Until they become conscious they will never rebel, and until after they have rebelled they cannot become conscious.“

*"*Sanity is not statistical."

Moving forward (rather than in circles): radical change to regulatory environment for clinical trials

- Replacement of ICH-GCP (not revision or further guides to the guidelines) by brief description of key principles (not prescribed, often evidence-free, requirements).
- Substantial revision of EU Directive on Clinical Trials with, again, emphasis on aspects of trials that really matter for protection of patients in trials and beyond.
- Streamlined centralised processes for ethics, regulatory and governance approval for conducting trials in a region (rather than repetitive, sometimes contradictory, review)

AMS Report on Personal Data for Public Good (January 2006)

- **Interpreting the legal framework:** Identifiable data can be used for research without consent (when necessary and proportionate)
- **Improving regulatory processes:** Need to develop clear guidance and simple review process for use of personal data in research
- **Developing good practice in use of personal data:** Need for regulatory and professional bodies, research community and the public to develop guidance for research using personal data
- **Harnessing the opportunities of the NHS IT Programs:** Urgent steps should be taken by NHS IT to address the needs of research
- **Engaging the public:** Funders should encourage research into public awareness and attitudes about research using personal data

Example of continuing problems with access to health records: Request for hospitalisation data

Death and cancer data being provided for Heart Protection Study and request made to extend linkage to hospital data

HPS consent form says *"I agree that information about any serious illnesses (such as heart attacks, strokes, cancers, etc) may be supplied to the study coordinators by my own doctors and by central registries"*

IC says that this does not cover *"centrally held electronic health records"* and instead patients should have been asked for access to *"information held and maintained by the Health & Social Care Information Centre"*

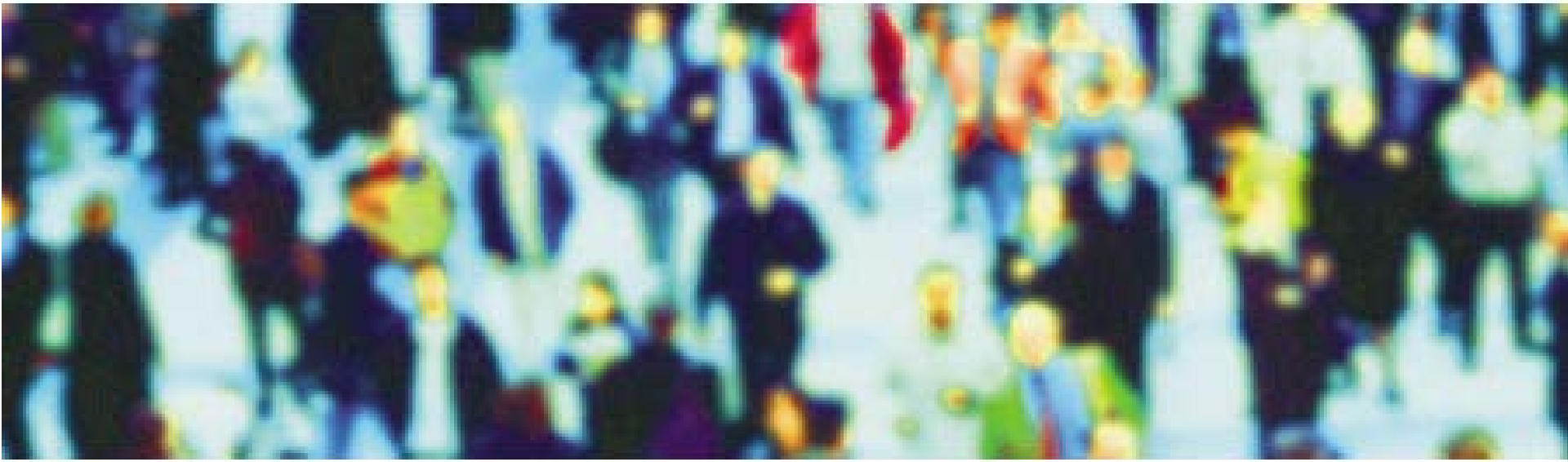
H&SC Information Centre did not exist when the consent was obtained during the recruitment of patients (1994-97)

Clinical research: time for sensible global guidelines (Lang, Cheah & White; Lancet 2011)

"WHO produced research guidelines that incorporated ICH-GCP and aimed to cover all types of research in human beings. Unfortunately these WHO guidelines are no less cumbersome that the original ICH-GCP guidelines from which they were developed, and because of their rigidity are difficult to implement. Far from enabling, we believe these guidelines have been an impediment to clinical research in developing countries."

The Academy of Medical Sciences

January 2006



Personal data for public good: using health information in medical research

AMS report on regulation: What else is needed?

- A clear and comprehensive vision of the future functions of the HRA and its role in providing coordination and oversight across a single regulatory and governance pathway.
- There is an urgent need to establish the HRA in 2011 to ensure the continued functioning of the National Research Ethics Service (NRES).
- There needs to be a single streamlined approval pathway that encompasses both the HRA and an improved NHS R&D permissions process.
- The HRA needs to be a “one-stop shop” for specialist approvals and accompanying guidance.