MRC Medical Research Council

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MRC/Wellcome Trust workshop:

Regulation and biomedical research

13 – 14 May 2008

FULL REPORT

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Summary

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

But regulation is also complex. There are difficult balances between public benefit and participants, patient and consumer risk, and many stakeholders making competing demands on regulators. There is potential for confusion, conflict and hindrance of the very processes that the regulations aim to assist.

Developing regulations for medical research has tended to be piecemeal. There is often an inappropriate approach to the risks involved, resulting in frustration among researchers and others, and inefficiency in the system. Scientists experience delays that hold up their research, and ultimately the development of therapies and other benefits for human health.

These issues were the topic of this workshop, held in May 2008. The workshop participants – which included representatives from academia (including biomedical researchers and lawyers), industry, Government, UK and overseas regulators – discussed their views of regulation, the problems associated with it and how they might be resolved.

At heart of the problem lies a lack of communication between the various players, and the perception that rules are over-complicated and unreasonable, damage trust and confidence in the value of the regulations. It is this trust that needs to be restored.

Although it would be unrealistic, at least in the short term, to change existing regulation in a fundamental way, regulators should aim to keep the regulatory burden to a minimum. What is needed is a clarification and – if appropriate – simplification of regulations, as well as a drive to improve communication and engagement with all concerned to justify the reasons for the rules' existence.

Regulations are complex for several reasons. There is the complexity of the issues themselves, complexity of the language, and complexity in the way the regulations are designed and the process of implementing them.

Complexity of the issues cannot be avoided, but some regulation is not well-designed or well-implemented, as is recognised by the Government. The Better Regulation Executive (BRE) suggests that good regulation should be accountable, consistent, transparent, targeted and proportionate, and notes that some regulations do not meet all of these criteria.

In many cases, there is a lack of understanding of risks associated with medical research. For example, the current regulatory regime does not currently take account of the substantial difference between research that involves an intervention on an individual, which has obvious risks for that person, and that which requires access to information from his or her tissue samples or records. This absence of precision causes problems in the implementation of regulation. For example, under the Data Protection and the Health and Social Care Acts, there are serious hurdles for researchers in accessing patient records without their consent.

Poor design and implementation cause confusion. Researchers report feeling annoyed by what they see as 'constant trivia' brought up by regulators. They also recount disappointment at what they view as over-regulation, which may lead to some giving up research altogether.

We can learn positively about the design of regulation from other sectors. The Food Standards Agency, for instance, is a success because it has a clearly-defined remit, its processes are transparent and inclusive, and it approaches regulation in an integrated way.

Keeping researchers informed and helping them understand regulations will go some way in establishing trust and reducing anxiety. This we already do to some extent; the UK Clinical Research

Collaboration (UKCRC), for example, makes existing regulations easier to navigate. The National Research Ethics Service (NRES) Integrated Research Application System (IRAS) is a single on-line facility that allows an applicant to enter information about a project once instead of duplicating information on separate applications forms.

Communication is vital because it is a way of addressing the interests of researchers, to prevent the inhibiting of research that may improve human health. It also helps researchers understand that they should not set their ideals too high and that medical research is often a small part a larger issue; for example, in the Mental Capacity Act or the Human Fertilisation and Embryology Bill (now Act).

Transparency is also of value to industry, which continues to work in the UK because of the strength of the life sciences but also wants and expects regulation to be consistent, proportionate and predictable.

Regulation tends to be more effective when it complements public opinion and support. It is therefore important to consult the public, whom regulation often exists to protect, and who have the weakest voice but may not readily complain. One approach may be to work with the media to encourage them to include more issues on regulation. There is currently a lack of evidence about how regulation affects trust and confidence among the public.

Communication between regulators and those who are regulated is essential, preferably in the early stages of the process of establishing legislation. For example, in the development of European regulation, UK Government and those regulated should become involved in the process as early as possible. Europe-wide bodies should aim to organise themselves rapidly at a relevant level to provide a unified position to influence the regulation.

At the root of regulation there must be trust. Trust stems from transparency, communication and the perception that the rules are realistic and related to the magnitude of risk.

With more trust, there is more compliance. Potentially, reviewing compliance can be very expensive for the regulator. If there is a higher level of trust between stakeholders, intensive reviews would not be necessary. Regulators could instead attempt random spot checks, tailoring their inspections to particular circumstances and in accordance to risk.

The approach to regulation in other countries may be different. For example, Finland has an effective regulatory process of medical research. It is simple and straightforward, and has one Act to cover all medical research. In the Nordic countries, there tends to be greater trust in authority and participation in research – so regulation can be less strict, but this may work in those countries because of their size.

Legislation should provide the incentive for the right kind of activities and not inhibit unnecessarily what it is designed to regulate. Once this is achieved, implementation should be effective, economical and efficient, inspiring even more confidence in the process. The optimal outcome is harmony between stakeholders and the protection in various forms that the regulators initially set out to accomplish, ensuring that health benefits become available to the public as quickly as possible.

Background

The workshop arose out of discussions in 2006/07. In 2005, the MRC had published a position statement on 'Research Regulation and Ethics'[1]. The MRC's then Ethics Policy Advisory Committee (EPAC), chaired by Professor Genevra Richardson, discussed the whole issue of regulation of medical research further, and in particular whether there was more to be learned for regulation theory and from the regulation of other sectors. The MRC and the Wellcome Trust jointly commissioned, in 2007, a literature review "Regulation and Biomedical Research; a critical review", which was undertaken by

[1] www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002462

Professor Mary Dixon Woods (University of Leicester) and colleagues[2]. The full review is likely to be published in some form. The summary is at annex 1.

The aim of the review was to inform a possible workshop in the area. The workshop, jointly sponsored by the MRC and the Wellcome Trust, was held at the Wellcome Collection, London on 13th and 14th May 2008.

Workshop Aim

The aim of the workshop was "to consider ways in which the regulation of research involving human participants might be simplified, while retaining the confidence of the public". [A secondary aim was to assist funders and research organisations to develop their thinking on legislation/regulation in order to inform their discussion with policy-makers and responses to consultations.

Programme

The Programme included talks from academia, industry, medical and health regulators, and regulators from non-medical sectors. There was also an international perspective with talks from colleagues from Finland and Canada. The full programme is at annex 2. The workshop was co-chaired by Professor Genevra Richardson (Professor of Law, King's College London and Chair of the MRC Ethics, Regulation and Public Involvement Committee) and Professor Peter Smith (Professor of Tropical Epidemiology, LSHTM and Wellcome Trust Governor). The list of participants is at annex 3.

Presentations and discussions

Introduction – Professor Genevra Richardson

Professor Richardson summarised the background to the workshop. Against the background of complexity, twelve questions needed to be addressed:

1. What are the prevailing objectives of regulation in biomedical research?
2. Are they/can they be consistent - across sectors or within a single sector?
3. Should we encourage a more risk-based approach?
4. If so, who should define the risks?
5. And how do we achieve the desired encouragement?
6. What can we learn from overseas?
7. What can we learn from other sectors?
8. Should impact assessments always be carried out and how effective are they?
9. How do we best engage the public?
10. Is there a piece of regulation you would like to get rid of, what would it be and why?
11. Are there areas where more regulation or more clarity would help?
12. What key points would regulators like to make to the regulated, and vice versa?

Literature Review: Regulation and Biomedical Research – a critical review (2007) – Mary Dixon-Woods

Professor Dixon-Woods summarised the findings from the Review. She defined regulation as:

> "The sustained and focused attempt to alter the behaviour of others according to defined standards or purposes with the intention of producing a broadly defined outcome or outcomes, which may involve mechanisms of standard-setting, information-gathering and behaviour modification"[3].

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[2] Karen Young (King's College, London), Richard Ashcroft (Queen Mary, London); Roger Brownsword (King's College, London), Alan Bryman (University of Leicester)

[3] Black J. Decentering regulation: the role of regulation and self regulation in a 'post regulatory' world. Current Legal Problems 2001; 54:103-46

How did one measure regulatory effectiveness? One way would be to assess success in meeting policy goals, but then the policy goals needed to be clearly stated and it was not always obvious how one assessed success against them. Whose values and goals should prevail? What threshold should be applied? Effectiveness also meant economy and efficiency, both of the regulators and for the regulated.

To be effective, regulation also needed legitimacy; i.e. actions and values needed to be desirable, acceptable, proper and appropriate. But there was a potential paradox: making something legitimate in the eyes of one group could render it illegitimate in the eyes of another. And this was further complicated by shifting balances of views.

In addition to biomedical research, the regulatory areas reviewed were: The environment, Dangerous dogs, Food Safety, The internet, Illegal drugs and Railway safety.

What were the reasons for regulating biomedical research? The obvious one was to protect the public against the risks of untested medicines and other technologies, and this had been the reason for the establishment of the US Food and Drug Administration in the early 20th century. But research had the potential not only to cause physical harms but also to inflict moral wrongs: assaults on 'person-hood', such as privacy and dignity; well-known examples of which include the experiments on concentration camp prisoners in the second world war and the 'Tuskegee' study of people with syphilis. Another reason for regulation was to restrain commercial motives and scientific enthusiasms.

In the UK, regulation of medical research had traditionally been self regulation, but the 1967 book by Maurice Pappworth "Human Guinea Pigs – experimentation on man" highlighted the deficiencies of such a system. After that, in 1971, the fragmented and unsatisfactory nature of the arrangements for Research Ethics Committees were identified, but it was not until 1991 that the Department of Health issued official guidance on RECs. More recent problems had included the 'scandal' concerning the retention of organs at the Alder Hey Children's Hospital (1999). Biomedical research required people to rely on a system of expertise they did not fully understand and to act on faith. Such 'scandals' therefore had especially disruptive effects, and the entire research category became degraded. Increasingly, self-regulation had been called into question.

A further complication of biomedical research was that, unlike say medicine, it was not a single profession. Not only did it involve medical practitioners, but increasingly scientists (PhDs) and the variety of professions allied to medicine. Thus while researchers might claim to be undertaking a professional activity, there was no unitary professional structure. There was no single set of explicit standards of professionalism, code of conduct, or set of sanctions imposed from within. Although for a long time there had never been full self-regulation, the various 'scandals', together with other factors - such as the codes of practice for doctors being insufficient defence, arrangements between NHS organisations and universities being inadequate and the fact that 'medical research' was not a single category – have reduced the scope for researchers to regulate themselves. Current regulation has thus involved a move from an agent-based approach, relying on trust, ethics and professional culture, towards an external regulatory approach relying on formalised contractual systems. This was most clearly manifested in the NHS Research Governance Framework (RGF), first published in 2001. This systematised and codified the processes of governance of virtually all research conducted in a health care setting, and adherence was a legal obligation. It would be naïve to think that this trend could somehow be reversed.

The RGF could be understood (in part) as part of the public ritual of managing disaster, enacting a narrative of breach, fall, and then restoration. It removed privilege from an apparently elite group, a small minority of whom had abused it, and could be perceived by some as a deserved punishment. The RGF redefined research as a risky activity - legal and financial, reputational and institutional. The last required that organisations had systems in place for controlling risk, so that criticisms could be deflected. Challenges to legitimacy and demands for accountability usually provoked 'protocolisation', i.e. mechanisms for apportioning blame.

In addition to the RGF, there were a large number of other regulations concerning medical research in the UK; these included:

- Medicines for Human Use Regulations (2004)
- Human Tissue Act (2004) and Human Tissue (Scotland) Act (2006)
- Data Protection Act (1998)
- Mental Capacity Act (2005)
- Health and Social Care Act (2001) / and (2008)
- Human Fertilisation and Embryology Act (1990)
- Human Rights Act (1998)

And in addition to this primary legislation (and associated regulations), there were: international frameworks (such as the 'International Conference on Harmonisation'); codes of practice; common law; employment law; and various criminal offences.

Regulation of medical research was thus complex and becoming increasingly contested. There were claims of:

- Disproportionate weight of requirements in relation to risks
- Inefficiencies and costs
- Illegitimate intrusions into the scientific process
- Inhibiting impact on training of future generations
- Negative effects on low-risk and "public interest" research
- Negative (or overly positive) effects on "UK plc".

A 'risk-based' approach to regulation was often cited as one of the guiding principles, but there was disagreement about risks. For example, there were scientific and ethical uncertainties about the character and significance of the risks, regulated activity was not easily understood by external audiences, and how trade-offs between conflicting goals should be made was unclear and disputed. While everyone present agreed that research should be ethical and safe, there was often little agreement about what should count as 'ethical' and 'safe'. The means by which ethical adequacy should be assessed was not unambiguous, and often there were alternative accounts of what might be 'ethical'. Such inconsistency was a challenge to the legitimacy of the process. There was a strongly-held view that relatively low risk 'public interest' research (i.e. that largely funded by the public purse and charities) should be treated differently from commercially-funded research which was often higher risk, but many of the current regulations did not allow or encourage such distinctions to be made.

A 'goal-based approach' to regulation also had problems. For example, it was hard to draw lines around what activities to needed to be covered, and it was hard to reach a consensus on the regulatory regime's specific objectives. Even when objectives could be stated, there could be different interpretations. Furthermore, as indicated above, there was often little agreement about the nature of risks being regulated. Finally, apart form the avoidance of scandals, it was difficult to assess whether goals had been met.

Rule-based systems brought particular problems. For example, there might be temptation to use such systems to symbolise control and offer institutional defence. Also, they might also symbolise distrust and encourage displays of compliance rather than appropriate use of discretion. They could neglect what was 'good' within the norms of a community, and thus suppress professionalism. Formal rules led to the requirement for auditable trails, For example, patient information and consent forms that were so detailed they failed to achieve their true purpose.

Once governance had been converted into procedural form, rigidities and inefficiencies were inescapable, and it became almost impossible to demonstrate effectiveness of the system. Perceived burden and benefits became disconnected. The current system was now cumbersome, slow, unresponsive, poorly coordinated, and bureaucratic, and there was often a lack of clarity about the rules to be followed, predictability, and enforcement. While researchers might complain about regulation, it had benefits, in particular to secure the social licence. For example:

- The REC system helped to confer legitimacy
- Regulation separated (at least programmatically) decisions about ethics from the science
- It assured the public-at-large that researchers could not do what they liked
- It displaced contestation from researchers onto regulators
- And it almost certainly prevented some bad things happening (though this was difficult to prove).

In summary:

- The regulation of biomedical research was perhaps uniquely complex
- It imposed high costs and suffered problems of legitimacy and demonstration of effectiveness
- There were real problems of sustaining legitimate sources of authority, so regulation often had to be achieved by administrative fiat
- Rule-based systems were prone to default to focus on avoiding procedural violations, but agent-based systems were also prone to failure
- There was a dearth of evidence about how regulation affected trust and confidence among "the public"
- No quick fixes were available
- Changing one element of the system might provoke problems elsewhere

- High quality social science research about the effects of changing rules and systems on the "sharp end" was needed.

Discussion

It was noted that regulation in research areas other than biomedical, such as social research, was less systematised. Were there lessons that these other areas could learn? The answer was yes – caution and wide consultation was needed before going down a rules-based approach. It would be difficult to back-track.

The comment was made that an additional purpose of some regulation was to create a level playing-field for commercial enterprises, such that there was one set of rules and they all played to them. Although this was perceived by some to have been the origin of the EU Clinical Trials Directive, in fact it was a view of the Council of Ministers and the European Parliament that the citizens across Europe needed better protection. Nevertheless, where regulation had to take into account commercial interests, publicly-funded medical research could easily become caught up with inappropriate rules and processes.

In some non-biomedical areas, the courts were frequently involved in providing final answers; why did this not happen in biomedical research? The answer was probably that a researcher (or his/her employer) would be unlikely to have the funds, the time or the will to bring a legal challenge, and certainly if the outcome were unfavourable it would damage the researcher's reputation.

How does it feel to be regulated?

(i) An academic's perspective - Charles Warlow

Professor Warlow had had a long experience of regulation, especially as a principle investigator on many clinical trials, mainly concerning stroke. How did he feel?:

- Irritated - because of the constant trivia brought up by minor bureaucrats, and the huge opportunity costs of keeping them happy
- Exhausted - because of the extreme effort to get through all the regulation from ethics to R&D to insurance issues, to sponsorship problems, to contracts with all and sundry
- Insulted - to be told how to do clinical research by people who had done little if any themselves
- Angry - because (over)-regulation could force researchers either to do bad research with misleading results, or to give up research altogether (for doctors, private practice could be very tempting)

How could he possibly justify these feelings of outrage?

Firstly, he described an observational population-based study of incidence and prognosis of intracranial vascular malformations. This had received Multicentre Research Ethics Committee (MREC) approval in July 1998, and had then had to be approved by the Local Research Ethics Committees (LRECs) of 15 Health Boards. Each LREC had required: one copy of the protocol, and a variable number of copies of the MREC application form (23 pages), a local investigator form & CV (8 pages), the MREC correspondence (6 pages) and the consent form and information sheet (7 pages). One LREC had required a total of nearly 800 A4 pages. In total, this added up to 5789 A4 pages, weighing 26.9 kg[4]. All these were for three trivial modifications, one not even within the local committee's jurisdiction.

Perhaps as a result of this (and other protestations), things were getting better. For example:

- The National Research Ethics Service (NRES) had a coordinating and supervising role
- There was now a unified (but still overlong) form with on line submission
- NRES offered more training for ethics committee members, and there was more interaction with applicants at an early stage
- There was more control of process with targets and timelines.

But there was still poor control of the quality of decision-making, no transparency of decision making (e.g. the minutes of REC meetings were not available), and in one case at least (REC A for Scotland), there was no appeal mechanism.

[4] Al-Shahi R and Warlow CP. Journal of the Royal College of Physicians of London 1999; 33: 549-552.

Another problem, which had become worse over the past ten years, was the differences in governance of Universities and the NHS. In the NHS,

- Governance was decentralised with no equivalent of COREC/NRES until very recently, at least in Scotland
- The requirements for researchers were inconsistent:
    - there was an R&D on-line form, but it was used by only ~50% of R&D Departments
    - there were few guides for Caldicott guardians and data protection officers
- Honorary NHS contracts had been required at all Trusts involved in a trial. (In 2003 the Department of Health recognised one contract at all sites, but this had only just been introduced in Scotland)
- There were additional delays through Criminal Records Bureau and occupational health checks
- The process was very slow, perhaps because the NHS R&D offices were under-resourced and/or the staff were under-trained
- The R&D offices were risk-averse, and there appeared to be strong tendency to build barriers. (Universities and Trusts were usually joint sponsors, but the latter were far more risk averse; Universities and Trusts were quite separate institutions and their interactions highly complicated)
- There were problems within Trusts as to what constituted research costs and how these would be met
- There were no incentives for Trusts to accommodate research
- Trusts increasingly wanted local control, not central coordination.

Professor Warlow then described the problem and consequences of delays in obtaining approvals. For four multicentre stroke trials, the median time taken to approve research governance applications at 57 hospitals (50 Trusts) was 44 days, with a maximum of over 340 days[5]. Three-quarters of applications incurred a delay of more than 4 weeks. If a 4 week delay was deemed acceptable, then the actual R&D delays (above this) meant that an additional 12% of the patients enrolled within the first few years of the four clinical trials could have been recruited. [Or if the delays had been funded by increasing the duration of recruitment to where it should have been without the delays, this would have cost the funders about an extra £38,000].

There was a particular problem about non-intrusive observational studies (including research, audit, service planning, public health monitoring, drug safety etc). Identifiable (non-anonymised) data were often required

- for record linkage
- to identify individuals during follow-up
- to avoid double counting
- to avoid consent bias
- for controls
- for indirect follow up via GPs, hospital discharges, deaths.

Ideally, of course, consent should be obtained from patients for use of their data, but this might be impractical or impossible (dead, demented, anxious, unaware of diagnosis, large sample etc). The Data Protection Act was a problem, but its interpretation even more so (for example by the GMC, and in Section 60 of the Health & Social Care Act, England). He cited the Deputy Information Commissioner as having said:

> "The [Data Protection Act 1998] itself does not necessarily require consent for the use of health information in medical research. The key is to ensure that people know what is happening with their information. The [Information Commissioner] takes the same view as that expressed by Mr Havers – namely, that researchers could be bolder. The statute sets out broad principles for handling personal information. It is not about absolutes".

Thus while the law said that personal data could be processed without consent (with exemptions for some forms of medical research), other guidance took a different view. For example:

- NHS Code of Practice: Confidentiality (2003): "…do not use/disclose identifiable data, unless originally understood by confider, or with permission"
- GMC Confidentiality… (April 2004): doctors should, "…seek patients' express consent to disclosure of information, where identifiable data is needed for any purpose other than the provision of care or for clinical audit…" (currently under revision)

Professor Warlow was not aware of any serious disclosures by researchers.

[5] Al-Shahi Salman R *et al*. Journal of the Royal Society of Medicine 2007; 100: 101-104.

Also double standards were applied. The Lothian Health Board, for example, had an 'opt-out' process for seeking consent for access to personal heath information for clinical audit, but an 'opt-in' process for access to the same information for research.

What was missing was a sense of proportionality of harms and benefits, and judgement of what those harms and benefits might be by allowing the research (or audit) to go ahead. This was clearly difficult in a rule-based system.

The Scottish Intracranial Malformation Study (SIVMS) presented a unique opportunity to study the effects of consent bias. [The only way to measure consent bias was by obtaining data from non-consenters – Catch 22 – but this study had had ethical approval]. The study was a prospective, population-based cohort study of all Intracranial Vascular Malformations presenting in adults in Scotland from 1999, with complete prospective follow-up. Consent could not be obtained from everyone (dead, consultant/GP refusal). Analysis of the consenters and non-consenters showed that they were systematically different in unpredictable ways: this could not be estimated in advance[6]. Insistence on consent from everyone would:

- be increasingly difficult and costly, waste investigator time on REC forms and delay research, and waste time with designing and administering consent forms
- harm some individual patients (over-consent)
- bias non-intrusive observational research
    - which would then get the wrong result
    - which would damage individual and public health
    - and less observational research would be done

Thus insistence on consent from everyone wasted money and damaged patients. One impact of this paper was that the Norwegian authorities had recently agreed to allow the proposed national stroke register to go ahead without consent (like the national stroke register in Sweden).

Finally, Professor Warlow highlighted the bureaucratic problems associated with the MRHA inspection. A huge amount of time was spent in preparation over many months, both centrally in the University and NHS, and for each trial – for example during the six weeks between being informed of the inspection and the inspection itself, one trial would use at least 50% of its MRC-funded staff time preparing for the inspection rather than recruiting more patients. An industry of regulators training even more regulators how to do it had built up, resulting in an amplification of diktats down the chain. Suspected unexpected serious adverse reactions had to be reported, but no feedback was provided. It cost several thousand pounds to train someone to use the EMEA on-line reporting system for adverse reactions. The consequences of this were immense. The cost to the funders (and sponsors) to achieve 100% perfection with GCP (Good Clinical Practice) for non commercial trials was huge. Edinburgh University had contracted a private company to train and advise the researchers on how to get through a particular inspection later in the year, and the MHRA would charge Edinburgh University c. £20,000 for the inspection. Such work distracted clinical trials units from undertaking non-drug trials, and could potentially lead to a slackening off of standards between inspections. In addition, there was continuing and lengthy interaction with MHRA after the inspection to get everything perfect. More indirectly, it led to Units avoiding doing clinical trials of investigational medicinal products in favour of unregulated interventions. He saw the solution to this being random spot checks so that researchers were 'inspection ready' all the time, but it must be lighter touch.

Discussion

One participant commented that the problems people were encountering with informed consent started with the Data Protection Act (1988). This was internally incoherent and its interpretation bore hard on medical researchers. For example, there seemed no justification for the Act to apply to secondary use of reversibly anonymised data. Yet the only way now to provide certainty would be to enact primary legislation. Professor Brownsword added that under English common law, judges had been reluctant to recognise a 'free-standing right of privacy'. Instead the issue had been massaged by re-working the right of confidentiality, as an anchor for privacy. Claims were therefore being cast in terms of confidentiality, whereas privacy would have been better. Ideally what was needed was a review of the scope and substance of three related rights: the privacy right under the Human Rights Act, the common law right of confidence/confidentiality, and the various rights protected under the DPA.

[6] Al-Shahi R. and Warlow C. BMJ 2000; 320: 713

On the issue of harms and benefits, it was noted that different people, patients or the public, may have very different perceptions of risks and benefits, and this needed to be taken into account. Professor Warlow agreed, but what was needed was more empirical evidence, and then judgment rather than a rule book.

(ii) An industry perspective - Lincoln Tsang

Dr Tsang said that the issues for industry were little different to those for academia. Industry needed regulation for economic reasons and to set the goal posts (such as the degree of clinical efficacy of anti-cancer agents required by MHRA before it would issue a licence). However, regulation must be transparent and predictable. The industry needed certainty in order to invest what could be considerable amounts of money. It now cost about $1.7 billion to take a pharmaceutical product from infancy to market, and many products never completed the journey. He highlighted three particular issues:

- the impact of regulation on R&D
- the globalisation of R&D – ie industry looked at the cost-benefit of regulation in all countries in which they were based
- how to streamline the process – equally important for academia and industry

Industry continued to work in the UK because of the strength of the life sciences. The life sciences industries contributed net exports to the value of £4.2 billion to the UK economy in 2006. Both the Pharmaceutical Industry Competitiveness Task Force and the Cooksey Report had recognised the impact of regulation on the ability of the UK to deliver high quality research. From an industry perspective, the key issues were patient safety and access of patients to treatments.

Much of the regulatory activity was now happening at supra-national levels, for example the ICH GCP guidelines included Europe, the US and Japan; and these regulations/guidelines were then transposed into national regulations. This constrained national governments and regulators in what could be achieved. It was vital therefore to influence the process at the early supra-national levels. Regulators were increasingly involved also in producing guidelines, and the courts often looked to these in coming to decisions. They therefore needed to be auditable and verifiable.

Dr Tsang cited Lord Justice Richards' recent (1 May) judgement on the National Institute for Health and Clinical Excellence when he ordered it to be more transparent about how it reached its decisions. This should be a general principle applying to regulation more broadly. In terms of streamlining, the various regulators needed to be more joined up – for example, the HTA, MHRA and EMEA needed to talk to each other more.

Discussion

Asked whether there was any difference between what industry expected and what academic researchers wanted, Dr Tsang said they were broadly similar. Industry wanted consistency, for example in the extent to which researchers are protected. The regulators changed their advice, on occasion even if this had been given in writing. Such uncertainly made it difficult to raise funding, for example from venture capitalists.

The comment was made that scientific evidence came early in the licensing process, so it was perhaps not surprising that regulators sometimes changed their views later. A further point was that industry had appeared to be reluctant to provide information to regulators about studies that had not demonstrated efficacy, and this was affecting public perceptions of research. Dr Tsang confirmed that more information-sharing was now required, but this change could not be imposed retrospectively.

The contrast between the 'angry' viewpoint of Professor Warlow and the more sanguine view of Dr Tsang was remarked upon. Professor Warlow said he was angry because so much money was being spent unnecessarily and the rules forced him to do the wrong research. It was depressing because there seemed no way to change the system. Companies tended to be less anarchic than universities and were structured better to deal with regulators; they found it easier to employ more people, cover the extra costs and then if necessary pass them on to the customer - often the NHS.

Turning to the Data Protection Act, it was noted that some industry contracts now stated that patient data might be used world-wide for any purpose, and the Act was one of the few ways in which a person's privacy could be protected. While there remained a need for a data protection act, there was a need also for better legislation to protect personal privacy.

Another important issue was who guarded the guardians (the regulators)? – there were better and worse ways, say, of implementing the EU Trials Directive. But the only come-back subsequently was through judicial review, and researchers seemed unwilling to pursue this route. One reason was that much of the regulation was in guidelines which were soft law and therefore more difficult to challenge. Furthermore, those who might make such a challenge would have to work with the regulators in the future. In one university, a researcher said he had suggested going to judicial review, but had been advised not.

In summary, there was a clear view that there was substantial difference between research that involved an intervention on an individual (which usually had obvious risks for the person) and that which required access to his/her tissues or records (which generally had much lower risks), and the current regulatory regime did not adequately recognise this difference. In terms of patient information, the DPA was often invoked when other laws (eg the common law of confidentiality) were more appropriate. Nevertheless, a new DPA and clearer laws on privacy could certainly make research easier to undertake, while retaining the confidence of patients and the public.

Approaches to improving and streamlining regulation

(i) UK Clinical Research Collaboration (UKCRC): A summary of current efforts to streamline the regulatory burden - Liam O'Toole

Dr O'Toole explained that the UKCRC had been established in 2004 in response to several reports. It had established a 'Regulatory and governance environment' workstream with the strategic aim to "Streamline the regulatory and governance environment whilst respecting the rights, dignity and safety of participants". A major issue that had been identified was the institutional complexity of biomedical research:

- Lack of consistency and duplication with administration and IT processes
- Variation in interpretation of regulations
- Organisations working in isolation

The focus of the workstream had therefore been on reducing the resulting administrative burden. The process had involved buy-in from all (nearly 40) stakeholders and a coordinated UK-wide approach. The workstream involved making the existing regulations easier to navigate, rather than aiming to change the regulations themselves. The workstream had six elements:

a) UKCRC Research and Governance Advice Service

The issue here was that the research and governance environment was complex and changing. Advice tended to be inconsistent, and there were multiple providers.
To address this, the UKCRC:

- supported local advice providers;
- provided a route for handling complex queries;
- offered web based resources (toolkits, Q&A).

It was supported by a network of regulators, governance bodies and policy makers (e.g. MHRA, HTA, NRES, UK Health Departments), and was delivered by MRC Regulatory Support Centre and the UKCRN Coordinating Centre, funded by NIHR.
The service had been launched in April 2007.

b) Research Passport

The issue here was that the process for applying for honorary research contracts for carrying out research in NHS was inconsistent and repetitive.
The solution to this was a new system, a 'research passport'. This had been developed under the auspices of UKCRC by NHS R&D Forum, UK Health Departments, and HEI research management and HR. This meant that:

- Pre-engagement checks were carried out once only;
- The passport was accepted and shared by all;
- Administrative times were reduced.

The passport had been launched October 2007.

This had already proved successful. For example, in a previous randomised controlled trial that had involved 21 researchers in 7 Trusts, 147 contracts had had to be issued, which had taken an average of 21 weeks. In another, more complex, trial, started after the passport scheme had been introduced, 8 researchers and 12 Trusts had been involved. This had required 8 passports, all of which had been issued within 14 days.

c) Streamlining Permissions and Approvals

The issue here was the institutional administrative complexity involved in granting permissions. Multiple application forms were needed, duplicating information.
The solution was an Integrated Research Application System (IRAS) – a single online system for applications, in which the information common to all forms needed to be entered only once. Seven organisations were involved.
Phase 1 of the system had been launched in January 2008[7]; this would become mandatory. (EudraCT functionality had been launched earlier in May).

d) A Suite of Model Agreements/contracts

The issue here was that negotiating de novo agreements between sponsors and sites could lead to long delays and variation, and there was unnecessary time and cost in negotiating contracts.
The solution was to develop model agreements which consisted of standard templates for common contractual situations, and hence a faster contracting process.
The model clinical trials agreement (mCTA) had been launched October 2006. The mCTA for contract research organisations had been launched October 2007. Two others were to follow shortly.

e) NHS R&D Permissions

The issue here was that the process for obtaining permissions was inconsistent and bureaucratic, and there was great variation in requirements of different Trusts.
The solution was to streamline the R&D systems in Trusts. This was being achieved through the Health Departments implementing standard systems to reduce duplication, and ensuring an interface between these and IRAS. However, out of necessity, the streamlined systems were different in each nation, and part of UKCRC's role was to ensure harmonisation of systems across UK.
At present, the systems were at different stages of development in each country, but roll-out would begin later in the year.

f) Coordinated research and governance (R&G) Training

The issue here was that many organisations provided R&G training, but more needed to be done to share and coordinate resources, such that regulators and the regulated were trained in the same way. A 'UKCRC R&G Training Coordination Group' had been set up tasked with sharing information on existing/planned initiatives, facilitating coordination of training, and identifying requirements for additional training. This work was ongoing.

About 80% of regulation now originated in Europe, and there was a very fragmented approach to responding to consultations and intelligence-gathering. It was essential for the UK to become involved as early as possible in the process of regulation. The UKCRC was playing a role in the sharing of information, for example though the European Biosciences Intelligence Coalition.

To conclude, Dr O'Toole said that this was a summary of work in progress. But there was already the start of a culture change throughout the UK R&G environment. The regulators deserved credit for their positive participation. The full benefits would only be felt when all the pieces of the jigsaw were in place. A different environment should be visible in 2009.

Discussion

The work of UKCRC was commended, but it did not address the main issue as to whether all the current regulations were needed in their current form, nor how to minimise the tendency for there to be constant changes. Concerning the MHRA, there was no reason why the same organisation could not fulfill both an advisory and an audit function, but one difficulty that had been identified was that the MHRA dealt mainly with the commercial sector, and academics had often failed to understand what had been asked of them.

[7] https://myresearchproject.org.uk

It was noted that one recommendation of the 'Better Regulation Task Force' had been that whenever one regulation was added, another should be removed. Was this concept being followed? There was no clear answer to this as no one organisation owned the whole system. Dr Davis commented that the Clinical Trials Regulations had been amended on 1 May to remove some of the regulations for example concerning the Gene Therapy Advisory Committee. Indeed since 1 May 2004, the Regulations had been amended three times.

(ii) A Government view of regulation - John Dodds

The Better Regulation Executive (BRE) had been in the Cabinet Office until June 2007, but was now part of the Department for Business, Enterprise and Regulatory Reform (BERR). The Government's view was that regulation was needed, not least to retain public confidence, but some current regulation was not well-designed or well-implemented.

The BRE adhered to the five principles of good regulation - regulation should be: accountable, consistent, transparent, targeted and proportionate. Some existing regulations did not meet all of these.

The BRE worked in partnership with Departments and regulators to:

- improve the design of new regulations and how they were communicated;
- simplify and modernise existing regulations;
- change attitudes and approaches to regulation to become more risk-based.

The BRE thus sat at the top of the regulatory pyramid. It used examples of success as showcases for others and to encourage culture change. It had its own research arm, and had a number of teams with expertise to advise in specific sectors. The BRE operated in three main ways:

- Reforming the process for making and reviewing regulations. This should be evidence-based, and not as knee-jerk responses to events. A key principle was to create the right incentives and structures.
- Intervening in specific policy areas- support and challenge departments and regulators;
- Listening to and being the voice for business, third sector bodies and public sector front-line workers on regulation and bureaucracy. The BRE looked for examples from the bottom-up to provide the fuel to inform change.

In terms of progress in the biomedical field, the following were highlighted:

- The Animal Scientific Procedures Act (ASPA) Better Regulation Steering Group – this Group had been established to simplify the regulations concerning adherence to the Act. Unusually it was chaired by BERR itself, rather than the host Department
- The 'better regulation of over the counter medicines initiative' (BROMI) – this was a new regulatory process for approving over-the-counter medicines
- Supporting the better regulation aspects of the Human Fertilisation and Embryology Bill

More generic progress was being made in the following ways:

- BRE was currently reviewing existing regulation to ensure it was fit for purpose and not over-burdensome
- There was a programme (2005 – 2010) within Government Departments to achieve a 25% reduction in administrative burdens. The Department of Health, for example, had published a simplification plan which would be updated every December
- The Treasury had commissioned the 'Davidson Review', on the implementation of EU legislation, which had reported in November 2006[8]. The Review considered different forms of over-implementation – gold-plating, regulatory creep and double-banking. It had found that inappropriate over-implementation of European legislation might not be as widespread as was sometimes claimed; however, there were some cases of over-implementation in the stock of existing legislation that should be addressed. These included consumer sales, financial services, transport, animal scientific procedures and waste legislation.
- The Treasury had also commissioned the 'Hampton Review', "Reducing administrative burdens: effective inspection and enforcement", which had reported in March 2005[9]. The Review had found that there was much good practice in UK regulation, but also that the system, as a whole, was complicated and good practice was not uniform. Overlaps in regulators' activities

[8] www.hm-treasury.gov.uk/media/E/F/davidson_review281106.pdf
[9] www.hm-treasury.gov.uk/media/7/F/bud05hamptonv1.pdf

meant there were too many forms, too many duplicate information requests and multiple inspections imposed on businesses. The Review proposed entrenching the principle of risk assessment throughout the regulatory system, so that the burden of enforcement fell most on highest-risk businesses and least on those with the best records of compliance.

- Consequent changes had included:
    - There were lots of regulators with overlapping remits – 32 regulators had now been merged into seven
    - There was no consistent approach to how regulators related to those they regulated – BRE's approach was to offer advice
    - Government had codified what 'good' looked like and had conducted "implementation reviews" of five key regulators.
    - The Regulators' Compliance Code, which requires regulators to perform their duties in a business-friendly way, by planning regulation and inspections in a way that causes least disruption to the economy, had been given statutory force on 6 April. It gave more teeth to judicial reviews
    - A review of consultation policy
    - A plan to reform impact assessments

Concerning the EU, around 80% of UK legislation was now based on EU Directives. More progress was needed at the Commission. Processes were in place, but there were too few concrete improvements in the real world. EU impact assessments were of mixed quality and/or lacking, and there was ineffective consultation. Proposals for simplification were often delayed, insignificant, and packaged with wider proposals with larger burdens. There was buy-in to reform at the top of the EU, but ongoing resistance at a working level. The UK was fully engaged in trying to accelerate change.

The conclusions from the Davidson Review were now being embedded in the UK, for example by:

- Not retaining more burdensome national standards
- Reviewing existing UK legislation before transposition – amending or repealing existing legislation, if necessary
- Not pre-empting upcoming European legislation
- Timing post-implementation reviews to tie in with Commission reviews
- Ensuring that effective knowledge was transferred between negotiators and implementers

(Gold-plating was picked up in UK impact assessment process).

Looking to the future, there would be more Hampton Implementation Reviews (including HFEA, HTA and MHRA). The Government was consulting on introducing regulatory budgets for Departments and was introducing a new approach to developing regulation to ensure that the practicalities of implementation in small businesses were taken into account, including exemptions where appropriate.

Finally, Mr Dodds said that the BRE welcomed ideas for improving or simplifying regulation. These could be submitted directly via the BRE website: www.betterregulation.gov.uk. Replies would be given.

Discussion

The premise that regulation should be risk-based sounded sensible, but raised the questions: risks to whom, and whose perception? Mr Dodds said that those proposing regulation should make clear at the outset what risks the regulation was intended to address in a way that invited comments. Ultimately regulation should focus on where risks were greatest. He agreed that perceptions could be very different; for example, the HSE and local authorities had different perspectives on risks in the workplace. There were often differences too between actual risks and public perceptions of them, and politicians had often in the past focussed too much on the latter. An example was the regulations brought in for outward bound centres following the drowning of four canoeists at Lyme Bay in 1993. About half the centres in the UK were driven out of business, which was not the intent of the policy.

In considering regulation, one of course had to know what the nature of the risk was, and then tailor the regulation to that (or those) risk. However, sometimes there were strongly opposed views. The political system had to make trade-offs. In general, the business sector was better able than the public sector to manage regulation as businesses had a more institutionalised approach to operations generally. A risk-based approach did not in itself obviate the need for trade-offs.

Mr Dodds was asked how one knew whether an activity was over- or under-regulated? He replied that there was no explicit process; it was more an art than a science. Views were obtained from a range of stakeholders, and the decision usually was a judgement. Sometimes it was clear that improvements could be made; in other cases less so.

Mr Dodds was also asked how one measured administrative burden. He said that the BRE had adopted an approach – a 'standard cost model' developed in the Netherlands. This had been piloted in the UK in 2005. The method divided the administrative process into components and put costs against each. It could identify which bits of regulation were of greatest cost to the economy. This was being used to audit the 25% reductions in EU administration burden he had referred to earlier. The methodology mainly focussed on where the costs lay among the regulated (business and voluntary sectors), rather than among the regulators, but the same process could, in principle, be applied to the latter. It was suggested that the identification of costs of new regulations should cover not just the new steady state, but also the costs of transition.

Mr Dodds was asked how much control the BRE exerted over the way impact assessments were done, with particular reference to the trials regulations, where the impact on the NHS, academics and funders had not been adequately assessed in advance of implementation. He replied that there was now better guidance on how impact assessments should be undertaken, including earlier opportunities for those concerned to submit their views. It was noted that Lord Hunt, then a health minister, had invited the MRC and AMS to write a report on the possible impact of the trials regulations, but at the time it had been a difficult question to answer.

Comments were than made about the quality of consultations. There were examples (the trials directive being one) where critical comments were submitted, but then apparently had not been taken into account. Consultations needed to be genuine and should include open questions.

It was noted that BRE guidance (the Impact Assessment template) stated that Departments must actively look for opportunities to simplify or remove existing requirements when they wanted to introduce new regulation. Mr Dodds was asked whether he was aware of any cases where this had happened. He was not, but he added that if the regulatory budgets were introduced in 2009, this would introduce ceilings to costs of regulation, and should further encourage simplification.

Different approaches to regulation

(i) UK Regulators' perspectives: Human Tissue Authority – Adrian McNeil

Mr McNeil said he was speaking in part formally as CEO of the HTA, but also to some extent in a personal capacity.

The HTA had been set up in 2004 as a requirement of the Human Tissue Act 2004. Its regulatory aim was:

> "To create a regulatory system for the removal, use and disposal of human tissue and organs that is clear, consistent and proportionate and in which professionals, patients, families and members of the public have confidence".

The areas covered included: public display, post mortems, anatomy, storage for research, storage for anatomical examination and approval of organs for donation (though the last was not by licensing). The legislative framework included not only the HT Act, but also secondary legislation and the EU Tissues and Cells Directive, which was now UK law - it had come into force for storage on 1 April 2006, and would come fully into force on 5 July 2008. The HT Act had set a framework, with the Authority being given powers to issue guidance and make decisions. In contrast, the EU Directive was very detailed and left little room for flexibility. In his view the former model was preferable.

As well as its regulatory role, the HTA also advised Government, stakeholders and the public. The HTA advised ministers from a practical point of view, for example on unintended consequences, as well as on issues such as secondary legislation.

The HTA worked closely with those regulated to develop standards. These were then used in compliance reports under four headings: Consent, Governance and quality systems, Premises, facilities and equipment, and Disposal. The HTA also published advice and guidance for its stakeholders and offered training programmes for Designated Individuals; to date 14 events had been held, with almost 1000 people trained. It offered an E-learning programme for Designated Individuals, accessible via the HTA website.

The HTA's inspection process was structured to minimise burden on those inspected; it was in two phases: 1) a desk-based evaluation of information, and 2): site visits. In the research sector, so far 147 Phase 1 and 10 Phase 2 inspections had been completed. Fourteen Phase 2 inspections were scheduled for 2008/09. The findings so far were that there was great respect for tissue for research and premises were suitable; however, quality management could be improved, for example in coding and records systems, traceability, schedules of audit and Standard Operating Procedures (SOP).

Early feedback from the research sector, and from the public, had been generally positive.

Plans for 2008/09 included:

- A summary of inspection activity for the research sector
- Regulatory methods development – licence renewals
- A new research code of practice (consultation in July 2008)
- Evaluation of impact of HTA and HT Act on research
- New sector-specific information including research web pages
- A Key messages guide for professionals communicating with the public (in order to help maintain the confidence of the public)

(ii) UK Regulators' perspectives: Human Fertilisation and Embryology Authority – Alan Doran

Mr Doran explained that the HFEA was set up in August 2001 as a requirement of the Human Fertilisation and Embryology Act 1990. (This in turn had followed the birth of the first test-tube baby, Louise Brown, in July 1978 and the Warnock Report of 1984). The main principles identified in the Warnock Report were:

- Human embryo had special status
- Respect for human life
- Rights of people to seek treatment
- Fully informed consent
- Welfare of the child
- Responsible pursuit of medical and scientific knowledge

The regulatory aim of the HFEA was: to maintain a sound regulatory system that met the needs of the professionals, the legislators and the patients; that made decisions that commanded respect; and which sustained public confidence.

Regulation was needed, not just because of the HFE Act, but also because of scientific and technological change and the changing views, behaviours and expectations of society. The HFEA

- Licensed and monitored fertility clinics, embryo research centres and storage facilities
- Issued codes of practice
- Maintained a register of information on: patient and partner registration at a clinic, donors, donor gamete (insemination) treatments, in vitro fertilisation (IVF), embryo creation, embryo use and pregnancy outcomes
- Provided information for patients, donors and clinics
- Reviewed developments and provided advice

The HFEA currently licensed 141 clinics and research centres and carried out over 160 inspections each year. Most of the activity was in the private sector; it was an industry worth over £500m a year, and was growing - in 2005, 35250 women were given IVF, resulting in 9664 births and 11907 babies.

The HFEA's licensing responsibilities were:

- To issue treatment, storage and research licences to centres
- To define and promote good clinical practice and high ethical standards
- To ensure clinics complied with the requirements of the 1990 HFE Act and the European Tissues and Cells Directive
- To renew licences on an annual basis

In terms of research, there were three criteria for licence decisions: Legality - Was it within the scope of the HFE Act? Necessity - Was there an alternative method? Desirability - Would it further scientific knowledge? Key constraints were that an embryo had to be destroyed within 14 days of fertilisation, and no research embryo could be implanted into a woman's uterus. There were currently 28 HFEA research licensed projects. Each application was considered case by case. Research was usually at the

cutting edge, and thus proper consultation was essential; this could take up to a year. Approved research projects were monitored and inspected regularly.

Public opinion on research was finely balanced; for example, survey results (MORI 2005) had shown:

- 73% - thought research could improve the quality of life for future generations with inherited diseases
- 43% - thought that benefits of embryo research outweigh the risks
- 20% - believed that the risks outweighed the benefits
- 41% - thought embryo research was ethical
- 34% - thought embryo research was unethical
- 46% - trusted in the UK regulator

Also, an ICM survey in 2007 had shown that when asked initially, 56% of people thought that human embryo research should be allowed (and 22% believed it should not), and 35% supported cytoplasmic hybrid embryo research. However, when asked whether they supported research to find out more about diseases, 79% supported human embryo research and 61% supported the use of cytoplasmic hybrid embryos.

Thus, in order to improve and maintain public confidence, regulation needed to be firm and independent, and context was extremely important.

In terms of the immediate future, much revolved around the HFE Bill currently going through Parliament. If passed, this would widen the definition of an embryo and enable the release of identifiable information to facilitate research. It would also give the HFEA increased flexibility in how it managed its business. Planned improvements in inspections included a better risk assessment, allowing longer breaks between inspections and integration with other regulators.

(iii) UK Regulators' perspectives: Medicines and Healthcare products Regulatory Agency – Brian Davis

Dr Davis spoke specifically about the 'Regulation and conduct of clinical trials'; on the sources of regulation and on ways to influence regulation.

The trials regulations had arisen through an international body, the 'International Conference on Harmonisation' (ICU), which involved the US, Europe and Japan, and had been driven by the need for a common approach to marketing medicinal products. The ICH guidelines (ICH E6) had then been adopted by the EU in 2001 in the form of EU Directive 2001/20/EC. The UK regulations – 'The Medicines for Human Use (Clinical Trials) Regulations 2004' had come into force on 1 May 2004. The Directive and the Regulations only covered 'investigational medicinal products', which meant 'pharmaceutical forms of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a clinical trial'.

The process had thus been extremely lengthy and complex. Agreement of the Directive had involved the EC Commission, the Council of Ministers and the European Parliament with detailed work going on through a large number of committees and working groups. The UK had been involved at all stages, but of course was just one of the member states aiming to shape the Directive in a way that met its overall aims, while making it adoptable in individual countries.

The aims and provisions of the Directive were:

To protect the rights, safety and well-being of those participating in clinical trials by standardisation of:

- Procedures for consideration by ethics committees and authorisation by competent authorities;
- Good clinical practice (GCP) for commencing and conducting all clinical trials;
- Good manufacturing practice (GMP) for investigational medicinal products; and
- Inspections against internationally accepted principles and standards of GCP and GMP, supported by powers of enforcement.

Because of the scope and complexity of the Directive, the Commission had produced a lot of supporting guidance, and this too had required extensive and time-consuming discussions, both within the Commission and between the national regulatory agencies.

Adoption of the Directive into UK law had also been a long and complex process, involving the Department of Health, the Devolved Administrations, the MHRA, both Houses of Parliament, and a lot of advisory bodies. There had been an extensive stakeholder consultation involving over 2000 organisations. This had included an impact assessment, to which the ABPI, smaller industries, charities and academic organizations had responded.

Having been involved in the Trials Regulations for much of their development and implementation, Dr Davis' main conclusions were:

- Government and those likely to be affected by the legislation/regulations needed to dedicate people to understand and interact at the earliest stages with all sources of regulation;
- Such bodies needed to organise themselves at a relevant level rapidly to provide unified position to influence the regulation. (To influence the EU, this usually needed to be Europe-wide bodies, not national ones, and thus it was difficult for academics to make their views known).

Dr Davis acknowledged that the ICH guidelines, the EU Directive, and the UK Regulations had been aimed primarily at commercial enterprises wishing to market new drugs, rather than at academic researchers, whose research mostly involved evaluating products that were already licensed. The MHRA was aware of the concerns of the latter group, in particular:

- Too much paper was generated; too much had to be reported to too many;
- Trial costs in the non-commercial sector had increased 2- to 4-fold;
- The Directive had not improved the quality of trials;
- The definition of non-commercial needed changing;
- Data from non-commercial studies should be allowed as part of marketing authorisations;
- The approval of multicentre, multinational studies was more complicated owing to the requirement to have a single European sponsor.

A European Commission/EMEA meeting had been held in October 2007 to review the Directive. The preliminary conclusions were that the principle aims of the Directive had been achieved – there had been harmonisation, and greater compliance with GCP. However, there was a need for greater harmonisation by further, tighter guidance, and the public wanted more information: a European trial registry was a likely development. A report was being prepared for the Commission, and it was thought that most changes could be made quickly within the current structure, but some might require changes to Directive itself.

Discussion

A concern was raised that because of the time needed to engage with the development of regulations, within academia it was difficult to identify people with the time to dedicate to this work. However, it was pointed out that Universities had large research budgets – up to £40m a year – and it was in their interests to ensure that staff expertise and time were available. The fact that universities were independent organisations and were not traditionally structured to manage such issues was also a problem.

It was pointed out that because the Directive and the Regulations were aimed mainly at the commercial sector, many in the non-commercial sector had been caught unawares until it was very late in the process. Lessons had been learned, and it would be necessary in future to watch for 'mission-creep' as legislation/regulations developed. However, Dr Davis pointed out that the European Parliament had always maintained that, from the patients' perspective, there was little difference between a commercial and a non-commercial trial, and thus the Directive should apply equally to both. Nevertheless the MHRA had built in a simpler process for trials involving products that had already been licensed.

(iv) An academic lawyer's perspective – Roger Brownsword

Professor Brownsword proposed five 'desiderata' for getting the regulatory environment right; these were based on legitimacy and effectiveness:

- Drawing the red lines in the right places (i.e. defining what was off-limits)
- Having the right kind of precautionary approach (this was related to risk)
- Incentivising the right activities (and disincentivising the undesirable)
- Keeping the regulation 'connected' to what was being regulated
- Effective, economical, and efficient implementation

Drawing the red lines in the right places: This was not straightforward for several reasons. Firstly, there was ethical pluralism; there were too many views on what was the 'right thing'. Secondly, there were at least three different starting positions for coming to a view: goals, rights and duties, which could lead down different routes. These could be articulated as a bioethical triangle: of utility (often the scientist's approach), human rights, and the dignitarian view – how communities identified themselves. Thirdly, certain important factors such as consent and harm to others were non-neutral – ie they were not black and white, and different people would have different views in different circumstances. The recent debate over cytoplasmic human embryos was a good example, where in general there had been opposition from dignitarians, support from utilitarians, and lack of concern from proponents of human rights. Thus there were many competing views about where the red lines should be drawn, some moral, some simply self-interested; and even those who took a moral standpoint could have fundamentally opposed views about what was required if regulators were to do the right thing.

Having the right kind of precautionary approach: The Precautionary principle was frequently used where evidence of hazard or risk fell short of scientific standard. (There were at least 18 different articulations of the principle!). But there were obvious criticisms of the principle, for example, the variables were invariably unclear, and there was usually a one-sided view of risk. Nevertheless, some kind of ex ante precautionary approach needed to be adopted in most instances; the problem was how best to do it. Regulators could not count on the public trusting the judgments of expert risk assessors, and the way that the public framed issues of risk (including low risk/high risk) was not always the same as that of risk assessors and risk managers – examples included the risks associated with nuclear power stations and with GM crops.

Incentivising the right activities: One key incentiviser was the ownership of intellectual property, but modern biotechnology had caused huge upheavals in the patent regime. This was a complex area with no obvious solutions. Was it that there were too many patents (patent thickets), or too few? Were patents too broad? When, if ever, should patentability be denied on moral grounds? In terms of solutions about incentives, there needed first to be agreement about what should be permitted, and about what should be encouraged but, as indicated above, this was usually just not possible.

Keeping the regulation 'connected' to what was being regulated: Professor Brownsword quoted John Perry Barlow:

> "Law adapts by continuous increments and at a pace second only to geology in its stateliness. Technology advances in…lunging jerks, like the punctuation of biological evolution grotesquely accelerated. Real world conditions will continue to change at a blinding pace, and the law will get further behind, more profoundly confused. This mismatch is permanent".

Although this was said in relation to information technology, it was applicable to most modern technologies. Such a view applied particularly in the case of the Human Fertilisation and Embryology Act 1990, for example whether non-fertilised eggs into which additional genetic material had been inserted were covered by the Act. In formulating new legislation, it was important to include provisions for ensuring that the law was responsive to change, while retaining clarity of what was lawful and what was not. The courts could not (and should not) be relied on to maintain the regulatory scheme where legislation was seriously disconnected. Courts were not accountable; politicians were.

Effective, economical, and efficient implementation: Clearly all these were ideals but the devil was in the detail. In most cases, we did not know what worked, and even if an approach worked in one sphere, it might well not work in another. How might regulation be made 'smarter'[10]? Ways might include expanding the regulatory repertoire to maximise the tools available. Greater clarity of purpose by regulators would clearly help, as would consensus amongst regulatees (or knowing who was most likely to resist). Often researchers were too compliant and did not voice their views early or clearly enough. Regulation tended to be more effective when it ran with the grain of opinion. The long-term prospects of any regulatory position that lacked broad public support were poor.

In summary Professor Brownsword said that

[10] S (specific, significant, stretching); M (measurable, meaningful, motivational); A (agreed upon, attainable, achievable, acceptable, action-oriented); R (realistic, relevant, reasonable, rewarding, results-oriented); T (time-based, timely, tangible, trackable).

- Regulating the field of biomedical research was far from easy. There were difficult balances between public benefit and participant, patient and consumer risk.
- The regulatory context was increasingly 'cosmopolitan'. Compliance was shaped by standards that originated from international, regional and national regulators. This could make the regulatory environment dense and complex.
- It was also a field of rapid technological innovation and change.
- But, the bottom line was that, in pluralistic communities, there were too many stakeholders making too many competing and conflicting demands on regulators.
- In such circumstances, the final fact of regulatory life was that it was not going to be easy!

Discussion

Professor Brownsword was asked if he thought it a truism that the more complex the process leading to the regulation, the more complex the regulation? He replied that he thought this was not necessarily the case.

A distinction was made between regulators that were also enforcers (such as the HTA and HFEA) and those that were not. In the former case, there was a unitary system and it was clear where researchers had to go. But in other areas, a lot of intermediary bodies were involved and this was a recipe for confusion.

(v) A Government Department perspective – Mark Bale

Dr Bale said that the Scientific Development and Bioethics Division of the Department of Health (DH) covered a wide range of activities related to [biomedical] research. These included: NHS Genetics, Gene therapy, Human Genetics Commission, Stem Cells and Cloning, Consent to treatment & examination, End of life, the Human Tissue Act / Organ Donation Task Force, the Human Fertilisation and Embryology Authority (and the current Bill), parts of the Mental Capacity Act, and a lead role in international bioethics activities.

The Department's main reasons for legislation were to ensure safeguards for patients and their families and to maintain public confidence. The second was vital and required anticipation of precautionary safeguards. The Government may have no choice but to act if there was a public scandal, and this might involve the introduction of new legislation or regulations. The Department's requirement to foster medical research and progress had to be balanced against these wider pressures. The Government was committed to having a modern, comprehensive and flexible system of standards and regulation, and to limit new regulatory burdens in order to provide stability for market entrants. As had been discussed earlier, there were wider and international interests, including at present:

- OECD: Collaborative IP handling; Biobanks; Pharmacogenomics
- UN: Cloning; Bioethics declaration (UNESCO); Disability Convention
- Council of Europe: Biomedicine convention; Protocols on research, biological materials, genetics
- EU: Stem Cell Research (EU FP 7); EC activities in genetic testing; Cells & Tissue Directive; Tissue Engineering Regulation

In the rest of his talk Dr Bale focussed on the Mental Capacity Act 2005 as an example of how DH handled the introduction of new legislation. The Act covered a wide range of issues and research was only a small part. Initially the Government had not been minded to include research, but it was researchers themselves who had asked for inclusion as the previous legislation and common law had been unclear.

In 1995, the Law Commission in their report proposed safeguards on research because of "the desirability of eliminating painful and distressing disabilities, [if] progress can be achieved without harming research subjects". But responses to the 1997 Green Paper, "Who Decides" showed controversy and little consensus. Thus research was not included in the draft Bill. In November 2003, the Joint Scrutiny Committee recommended clarifying common law provisions:

> "If properly-regulated research involving people who may lack capacity is not possible then treatments for incapacitating disorders will not be developed".
> "We are concerned that if research were to take place in the absence of statute or any regulation the opportunity for abuse would be greater".

"It follows that the inclusion of statutory provisions governing such research would enable the ethical requirements that must underpin research involving people with incapacity to be clearly enshrined in statute".

The Government accepted recommendation that Bill "should include provision for strictly-controlled research to fill the gap that exists in the current law and the uncertainty and inequity this creates", and revised clauses based on ethical norms were inserted. These had to be consistent with other statute, human rights and international instruments. There was then a healthy debate in Parliament and valuable input to the debate from bodies such as COREC (now NRES), research funders and charities. Research (and end of life issues) was one of the most controversial aspects of the Bill, and was subject to a lot of debate. A balance needed to be struck between the desire to enable essential research whilst respecting and protecting vulnerable individuals.

There were five sections of the Act that provided lawful authority for research to be carried out involving people without capacity: s.30 – Research; s.31 – Requirements for approval; s.32 – Consulting carers etc.; s.33 – Additional safeguards; s.34 – Loss of capacity during research project. The Act codified common law principles of capacity and best interests, and left to Research Ethics Committees to decide whether in particular cases the proposed research met the relevant s.31 requirements. RECs were also required to satisfy themselves about the process for consulting carers and the other safeguards to protect the individual. Dr Bale pointed out some of the apparent complexities for researchers because the Act did not apply in Scotland (which had its own legislation), and it did not apply to clinical trials of medicinal products (as these were covered by the EU Directive – see above). A particularly complex issue during the debate was what happened to participants who lost capacity during the research – there were separate regulations covering research that started before the Act had come into force.

Experience had already shown the complexity of applying the Mental Capacity Act to existing policy areas. In terms of research, this included participants aged under 18 and comparisons with the consent requirements for the creation of stem cells. Research might also need to be part of a wider campaign to encourage people to think about what would happen if they lost capacity in the future.

In conclusion, Dr Bale summarised the steps in the ethical approach to including mentally incapacitated people in research:

i) The ethical requirements for research involving people with incapacity were clearly enshrined in statute;
ii) RECs were in the best position to make these careful judgements in the light of the specific circumstances;
iii) Professionals, families and those who lack capacity needed advice and assistance to feel confident taking part in safe and ethical research.

Discussion

There were many different types of regulatory design, and it was not that the Mental Capacity Act did not have an enforcement agency to ensure that its provisions were met. Dr Bale agreed; there were no criminal penalties written into the Act; the role of the Act was to make clear what was lawful and what was not lawful. It was up to the RECs and employers to ensure that the Act was followed, using the powers at their disposal. In extreme cases, the penalties associated with offences such as neglect or assault may apply.

It was noted also that the MCA was underpinned by a Code of Practice and required guidance on some aspects. However, it did not itself require statutory guidelines on all aspects of research. Dr Bale explained that it would have been difficult to draft guidelines as this would have meant translating the general to the particular types of research into the different causes of incapacity. The primary objective had been to take a once-in-a-lifetime opportunity to develop a broad legal framework on what was a very complex issue. Others noted, though, that researchers needed guidelines, and it had therefore been up to others, such as the MRC, to draft guidelines for their communities.

Turning to the general issue of drafting legislation, several participants were of the view that there was a loss of public trust in legislation, and that a significant contributory factor was the complexity of the legislation; not so much the complexity of the issues (this was unavoidable), but in the fact that the legislation was drafted in a way that non-lawyers could not readily understand. The loss of trust affected not just the general public, but professionals and institutions. Dr Bale agreed to some extent, and added that much effort was put into codes of practice. However, others thought that this was a cop-out; it was far better to make the Bills/Acts intelligible in the first place – both for regulatees and

for the courts. Similarly, the way legislation was drafted meant that much detail, which would be better contained in the main body of the Act, was inserted into separate schedules appended at the back. Dr Bale responded that Bills were structured in this way by Parliamentary Counsel.

(vi) Health information/personal data – David Evans

Mr Evans briefly went over the history of the Data Protection Act 1998. Its origins lay in the 1972 UK Report of the Committee on Privacy (the Younger Report), which was in response to concern about widespread availability of private information through new fangled computers, a worry then, and no less of a worry now with increasing sophistication of technological developments. In 1980, the OECD published a report in which it expressed concern that moves towards privacy legislation might create trade barriers, for example through different countries developing very different legislation. The 1998 Act had been drafted using a principles-based approach; it was not prescriptive. He added that the Information Commissioner's Office (ICO) staff could not be experts in the different areas upon which the provisions of the Act had a bearing.

The eight principles of data protection were essentially common sense:

Personal data:

1. Shall be processed fairly and lawfully
2. Shall be obtained only for one or more specified and lawful purposes, and shall not be further processed in any manner incompatible with that purpose(s)
3. Shall be adequate, relevant and not excessive in relation to the purpose or purposes for which they are processed".
4. Shall be accurate and, where necessary, kept up to date.
5. Processed for any purpose or purposes shall not be kept for longer than is necessary for that purpose or those purposes.
6. Personal data shall be processed in accordance with the rights of data subjects under this Act.
7. Appropriate technical and organisational measures shall be taken against unauthorised or unlawful processing of personal data and against accidental loss or destruction of, or damage to, personal data.
8. Personal data shall not be transferred to a country or territory outside the European Economic Area, unless that country or territory ensures an adequate level of protection of the rights and freedoms of data subjects in relation to the processing of personal data.

But the law was seen as difficult to understand.

Mr Evans said that the ICO tried to live in the real world. Staff were selective in when they intervened, focusing on where the risks of serious harm were greatest and where they could make a difference - it could be expensive to take regulatory action. Also they took the view that prevention was better than cure, not least because they then had to deal with fewer complaints. [In 2007 the ICO had had 25,000 written enquiries and complaints, and over 150,000 phone calls]. He stressed the importance of retaining public confidence. At present he thought that most people were happy about the way their personal records were handled, but they worried about their data being misused without their knowledge. There had been very few complaints about medical research, but of course one reason for that might be that people did not know that their personal data were being used in this way (whether legitimately or not) because of confidentiality.

He then explained further the way the ICO operated. It focused on fairness and promoted privacy-friendly approaches rather than 'saying no'. It aimed to strike a balance between legitimate 'social' interests and individual rights/freedoms. His own understanding was that patients were generally happy for their personal data to be used for legitimate research. There was nothing in the Act to say that researchers had to have consent to use personal information. This fell under the much older common law of confidence, and thus very much depended on patient expectations. The ICO did not see it as one of its roles to dispute the reasonable judgements of health professionals.

Looking to the future, Mr Evans said the ICO was looking to find more time to have an early influence (before projects started), and was aiming for long term reductions in data protection risk rather than short term fixes. The ICO had produced a handbook for organisations wishing to undertake a 'privacy impact assessment' (eg regarding systems for charging for road use), using a risk-based approach; this was consistent with the requirements of the BRE (see above).

Finally, he said the ICO operated an enquiry line (01625 545745) and encouraged researchers to use it. He was also happy to receive comments directly (David.evans2@ico.gsi.gov.uk). It was clear that few, if any, participants were aware of the enquiry line; this was welcomed.

Discussion

Mr Evans was asked about the National Staff Dismissal Register (NSDR) being set up by the retail sector. The database would allow employers to search for potential workers by name, address, date of birth, national insurance number and previous employer. Was this lawful under the DPA? Mr Evans replied that it was, but the status and circumstance of any accusations should be clear and there would have to be a process to allow people to challenge their entries.

The use of personal data for research without consent was a major issue; people or groups who were in a position to prevent research taking place – for example Research Ethics Committees and research offices in NHS Trusts – often declined research proposals on the grounds that such use was prohibited by the Act. Mr Evans agreed that the Act was not clearly drafted so it was easy to hide behind. If people took that view, they had either misunderstood the Act, or wished to use the Act as an excuse when the real reason might be something else. He thought a reason might be that those making the judgements were attempting to take the lay person's view of the concept of 'fair processing', which was somewhat woolly, and erring on the side of saying no rather than yes, as this was lower risk to them and their organisation. Mr Evans stressed again that data protection was different from confidentiality - confidentiality concerned issues of when it was appropriate or inappropriate to disclose information, while data protection was about when it was legitimate, or otherwise, to process data and what safeguards were needed for personal data. [Nevertheless, the two were integrated in the sense that the first data protection principle incorporated the common law duty of confidentiality (data must be processed fairly and lawfully - the "lawfully" embraced the common law duty of confidentiality).

The comment was made that the main purpose of the DPA was to protect civil liberties; there were two aspects to this, firstly to stop bad things happening, and secondly to protect uninformed individuals. Ethics committees focussed on the latter, and the Act on the former. The Act was principles-based, and although the ICO's approach to using enforcement powers was risk-based, this made it difficult for researchers to predict how the Act applied to particular projects, and how the ICO might react. Mr Evans agreed, and added that because there was such a wide range of types of research, any formal 'universal' guidance that the ICO might publish would have to apply in so many different contexts, and would therefore have to be so 'bland' as to be almost useless.

One view was that this was a clear example of regulatory failure – a law that was difficult to understand and a regulator that could not provide guidance. Mr Evans replied that the ICO did offer advice on particular cases, but this was not often used by researchers, ethics committees or Trust managers. But the counter view was that this was a clear sign that new legislation was needed. Mr Evans added that in 2008 the ICO was planning a research project to advise on how the EU Data Protection Directive (95/46/EC) might be revised. Much had changed since the Directive had been brought into UK law. Mr Evans agreed that it was not feasible for all researchers to consult the ICO about their projects. When they did, they often wanted yes/no answers, but the issues were rarely that straightforward. It was equally unfeasible to write guidance that covered all possible questions. As the ICO did not get many inquiries (perhaps because there were increasing levels of expertise among the community), it was difficult for them to spot problems and trends.

(vii) National Research Ethics Service (NRES) – Janet Wisely

Dr Wisely said that there were three main reasons for research ethics committees (RECs): i) to protect research participants, ii) to protect researchers, and iii) to facilitate ethical research. The history of research ethics in the UK was long. The Declaration of Helsinki was published in 1964, but it was not until 1991 that RECs were formally established within the NHS in England. The difficulty of undertaking large multi-centre studies was recognised and Multi-centre RECs were set up in 1997. There was still too little coordination between Ethics committees, so in 2000, the NHS set up the Central Office for Research Ethics Committees (COREC), and the first national standards ('Governance arrangements for NHS Research Ethics Committees' - GAfREC) were published in August 2001. The EU Clinical Trials Directive led to the UK developing standard operating procedures for RECs in 2004. COREC became the National Research Ethics Service, within the National Patient Safety Agency (NPSA), in 2007. Research Ethics Committees now had statutory responsibilities, as laid

down in the Clinical Trials Regulations (2003), the Human Tissue Act (2004), and the Mental Capacity Act (2005).

The NRES was responsible for facilitating ethical research in the UK through provision of an efficient and robust service for ethical review. It provided funding, training, operational framework, guidance, quality assurance to ensure that RECs were 'fit for purpose' - to make independent ethical decisions on research applications. Currently, NRES had 27 staff in its head office; there were 118 RECs in England, and about 2300 volunteer members of RECs. The total number of research applications to RECs was about 7000 per annum, and there were 65,000 registered users of the ethics form. The number of applications being submitted was decreasing. The service had improved in recent years: the average time between receipt of application and decision was now about 35 days.

Dr Wisely said that a focus in the past year had been on reducing bureaucracy through improvement to the procedures, structures and technologies that supported ethical review. One important development had been the launch in January 2008 of the Integrated Research Application System (IRAS). This was a significant milestone involving collaboration with a wide range of UK regulatory bodies, all working together to bring some relief to researchers' navigation of approval processes. IRAS was a single on-line facility which enabled the applicant to enter the information about the project once instead of duplicating information on separate application forms. It used filters to ensure that the data collected and collated were appropriate to the type of study, and consequently the permissions and approvals required. Information was exported for research funding and approval So far the system had received very good feedback and the formal consultation would close at the end of June.

Dr Wisely added that other NRES work piloted this year had included the fast track process and early provision of advice, both of which had the potential to make a difference for researchers and research ethics committees. In addition, NRES had implemented a comprehensive quality assurance programme designed to improve consistency of REC decision-making. Also NRES was working to increase the transparency of decision-making in order to improve the confidence researchers and the general public had in the research ethics system.

Discussion:

Dr Wisely was asked why the numbers of applications were decreasing. She thought there might be several reasons; less research requiring LREC approval being undertaken by students, a better understanding among researchers of what was within scope, and bigger chunkier studies, but she could not rule out the fact that some researchers had simply given up doing certain types of study because of the bureaucracy involved.

She was also asked whether the drive towards greater consistency between RECs might have the intended consequence of leading RECs to focus on process, rather than on fostering research and on protecting participants. Dr Wisely commented that the move towards consistency was in the form of a framework, not details of process. The main role of RECs was indeed to protect participants (not institutions); Committees did focus on issues such as consent and patient information. With respect to the DPA, she added that committees did not make legal decisions, but did aim to ensure that the research complied with the Act – all RECs were familiar with issues of consent and confidentiality. REC decisions were ethical ones, not legal, though they made these decisions within a legal framework in some respects.

Dr Wisely said that embedding NRES within the NPSA had not in itself changed the culture of the NRES. The NPSA was a federal structure, and NRES operated relatively independently, so although there had been changes in NRES, these had not been a direct consequence of the change in its overall governance.

She was asked whether NRES worked closely with University ethics committees. She replied not; the committees themselves were outside the NHS responsibility, but NRES would be happy to work with them as it was already working with Phase 1 Healthy Volunteer trials committees and with the Social Care Institute for Excellence (SCIE) to establish the social care committee.

(viii) Food safety – Andrew Wadge

Dr Wadge said that the Food Standards Agency (FSA) had been in existence since 2000. It had been formed for a number of reasons. In particular in the 1990s the public had lost trust in the Government

(mainly the Department of Heath and the then Ministry of Agriculture Fisheries and Food) as a source of advice about food, and particularly food safety. Although the FSA was formally a Government Department, it was not headed by a Minister, and it reported to a Board; it was thus at arm's-length to Government.

Consumer awareness of the FSA remained at a constant high of 82%. Trust in the FSA was also high at 60%, up from 44% when this question had first been asked in 2001. 65% of consumers now described themselves as confident in the Agency's ability to protect health with regards to food safety, compared with 50% in 2000. Why was this?

The main reason he gave was that the FSA had adopted from its outset an open and transparent approach to handling risks, and had engaged with consumers; for example by:

- Seeking advice and challenge from scientists with no vested interests. An independent Advisory Committee had been set up.
- Acknowledging uncertainty. Often the FSA was dealing at the margins of certainty. It was important to be clear about what was known, what was not known, and what (if anything) was being done about unknowns.
- Recognising the risk appetite of consumers. (For example, generally people were happy to eat beef on the bone).
- Helping consumers to make their own judgements, for example through labelling.
- Actively engaging with stakeholders at all key stages.

The processes for handling risks were complex. Essentially there was a circular process of: scientific information gathering, risk assessment, considering options for risk management, and developing policy and advice, which then helped to identify where more scientific information was needed. Stakeholders were involved at all main stages.

The process was thus risk-based, but of course there was no such thing as zero risk. The issue was to establish what consumers expected and what the FSA was able to deliver. People and organisations had different appetites for different types of risk. The FSA's risk assessments were based on evidence from the scientific literature and work commissioned by the FSA. They were carried out by in-house scientists with the support and challenge of independent scientific advisory committees. [Some of the research the FSA commissioned involved human subjects and hence needed ethical approval, and the FSA would welcome discussions with other funders to learn how best to seek ethical approval].

Risk management was less easy (than risk assessment) to describe and codify through accountable processes. Far wider evidence bases, not only the science, needed to be considered. Ultimately risk management was about judgement, but it had to be accountable through open, transparent processes. Within the FSA, risk assessment and management were functionally separate; RA through the independent Scientific Advisory Committees, and RM through the FSA's Board, which made the final decisions. Nevertheless, the integrated model of risk analysis had public engagement at its heart - openness and transparency were key to accountability and winning trust.

How did the FSA try to ensure that its responses were proportionate? Firstly, the FSA's advice was based on a robust analysis of the best available evidence, setting out the uncertainties. Legislation was not always the answer. An example where legislation had not been appropriate concerned the safety of artificial colours in foods/drinks. There had been a lot of important science on this question, but little evidence of cause and effect. The UK had therefore decided not to legislate. There had been subsequent discussions in the EC, and now the food manufacturers were phasing out artificial colours voluntarily. Secondly, the industry and the FSA had to respect the reality of people's concerns even when there was no supporting evidence. An example of this was the presence of bisphenyl A in babies' bottles; Walmart had withdrawn the bottles on commercial grounds. Dr Wadge believed that the trust that the FSA had engendered in its food safety role had provided the mandate for its work on healthy eating.

Discussion:

Dr Wadge was asked how the FSA influenced the public's understanding of its decisions, and how it influenced journalists. He said that the FSA attached great importance to communicating the science and staff were always willing to engage, in particular on the radio and television. One had to adopt new techniques, for example he was now writing a blog. It was important to explain the risks and the dietary advice that was given, and help people understand the detail. He encouraged others to be more open about what they did and more proactive about media engagement.

Dr Wadge was asked about the pros and cons of being a non-Ministerial Department. The main disadvantage was that there was no Minister arguing the FSA's case in Government or in Parliament. This added to the work of the FSA Chair. The main advantage (for the FSA, as well as for Ministers sometimes) was that Ministers did not have to be engaged. On balance he thought the advantages outweighed the disadvantages.

He added that the level of trust of consumers (65%, above) was good for a Government Department.

Dr Wadge was asked how the FSA chose the independent scientists. He said they were appointed through the government process built on the Nolan principles. Not only was the appointment process open but also, unlike some of the predecessor committees, their deliberations were now open too, so people could see what they did and said. It was of course difficult to find experts who were 100% independent, but openness meant that they had to be objective. Not many members of the public attended the Scientific Advisory Committee meetings, but the agendas were published. The 'reserved' activities included discussion of unpublished research, and genuine commercially confidential topics (such as novel foods). Safety data should never be secret. Some SAC members had been fearful of meeting in public, but they were still able to have brainstorm type discussions.

It was pointed out that another advantage of transparency was that it made plain that there were many different aspects to medical research; many people saw it as one amorphous activity and often tarred the whole with the same brush as for the least good elements.

In conclusion, the general view was that the FSA had been born out of a disaster (BSE), and had been very successful, primarily because of its openness.

(ix) Regulating Britain's railways – Bob Chauhan

Mr Chauhan explained that he had been invited to present a perspective on regulation from well outside the health/medical sector, and where most of the regulation was invested in one body, rather than the large number for medical research.

The Office of Rail Regulation (ORR) was the combined safety and economic regulator for the rail industry; as well as being the competition authority for the rail sector. The ORR had been set up by statute and was classed as a non-Ministerial Government Department (like the FSA). Its functions and duties were set out in statute (Railways Act 1993, 2005). It was thus independent of both government and the industry, and was accountable directly to Parliament. It was led by a Board of executive and non-executive members with 'the statutory freedom to balance the achievement of the objectives in the way they think is best calculated to promote the public interest'. The ORR had no direct control for example over fares or seating. It was funded by a safety levy and licence fee.

The structure of the industry comprised three main elements:

i) Funders - Department for Transport, Passenger Transport Executives, Scottish Executive, Welsh Government
ii) Infrastructure owner - Network Rail
iii) Train operators - Passengers/freight

The Funders were predominantly in the public sector, but Network Rail and the Operators were in the private sector. The ORR was in the centre of these regulating the relationships and contracts between them.

What were the challenges? Passenger-kilometres per year had fluctuated between 30 and 40 billion between 1947 and 2002, but the Department for Transport had estimated (July 2007) that by 2014 there would be a 30% growth over 2004 figures. The Department also had an aspiration that by about 2029 there would be about twice as many passengers as in 2007. Industry costs (at 2005/06 prices) had been falling since 2003/04, and were projected to continue to fall until at least 2013/14. 'Industry precursor risk values', a proxy measure for safety, had been falling since 1999. One of the most dramatic improvements had been reductions in 'signals passed at danger' which had had an engineering solution. However, significant further falls would depend more on behavioural changes. For example, level crossing misuse had shown the second biggest fall, but was now the greatest risk of an accident.

The initial privatisation of the railways had brought in a very complex structure, including a perception of tension between Safety Regulation (the responsibility of the then HM Rail Inspectorate (HMRI)), and Economic Regulation (the responsibility of the then Office of the Rail Regulator). There was recognition that the structure was flawed, and the White Paper "The Future of Rail" (2004) changed both the industry and regulatory structure, merging the two previous regulators to create the ORR, a single, integrated, safety and economic regulator for the industry. Bringing regulation of all aspects of the rail industry - safety, reliability and efficiency - together under a single public regulator was aimed at streamlining the regulatory system, reducing bureaucracy, and ensuring that these issues were looked at as a whole, and not in isolation from one another.

The ORR's main tasks included:

- Enforcing and proposing health & safety legislation for railways;
- Determining Network Rail's allowed revenue to deliver government's specified outputs;
- Monitoring and enforcing delivery of those outputs;
- Establishing an access and licensing regime and approving individual applications;
- Exercising competition law functions concurrently with OFT, where these related to the railways;
- Providing 'advice, information and assistance' to Ministers.

The ORR, as regulator, was a proxy for competition; more specifically: in economic terms, it held a monopoly to account, and in doing so ensured the requirements of customers and funders were met; and in safety terms, it provided independent assurance that risks were being effectively managed. The rail industry was a partnership - publicly specified, privately delivered – and as such it needed an independent 'arbiter' to:

- Assure funders of value for money without them having to undertake detailed monitoring
- Assure private investors of reasonable long-term returns subject to risks and efficiency
- Ensure the industry delivers in the public interest
- Ensure (and demonstrate) due process (eg closures of stations)

The specified aim of the ORR was "To apply independent, fair and effective regulation to enable the railway to be safe, well maintained and efficient and to ensure that it provides value for money for users and for its funders". It had more than twenty objectives set by statute that it balanced in a way that it considered best promoted the public interest.

The ORR's starting point was the five principles of good regulation. The key elements of its approach were:

- Risk based: identifying and targeting the biggest risks to the industry (such as level crossings)
- Engagement - with the industry and governments; why is the ORR intervening?
- Monitoring & publication of performance and cost information (so that all parties worked from the same data set).
- Open and transparent processes - to reduce uncertainty and risk.

Mr Chauhan ended by saying that there were clear benefits of a single regulator. It streamlined the regulatory system and brought a "whole industry" view to decisions. There was evidence that the industry had a favourable view of the regulator. Research in 2006 revealed that on the whole the ORR was effective, the level of consultation and engagement was valued, and independence was seen as critical. In terms of tensions, the expectation on formation of the ORR had been of a tension between economics and safety, but in fact this had not materialised and the view that good safety was good business was widely accepted. Integration brought a "safety ethos" into the regulatory stance, and the ORR's processes ensured the safety voice continued to be heard. Ministerial influence was not an issue from the Department for Transport; indeed independence was to their benefit, for example it allowed DfT to test its strategies. There was greater risk from other parts of Government, for example the ORR was resisting the drive from BRE towards regulatory budgets.

Discussion:

Mr Chauhan was asked how effective enforcement was. He said that enforcement was used as a last resort; earlier steps were usually effective. These included reputational risks, and the knowledge that shareholders would suffer if operations were not efficient; budgets were usually fixed, so additional costs had to be met from what would otherwise be profits. He was also asked whether the regulator had the necessary controls to reduce the risks from level crossings, for example who decided whether a level crossing should be replaced by a bridge? – presumably an expensive undertaking. He replied that this was the responsibility of Network Rail, which took into account the costs, benefits and risks of each option including that of prosecution in the event of accidents and guidance from the Rail

Inspectorate. Others might also be involved in the decision, for example Local Authorities if removing the level crossing relieved traffic congestion.

International perspectives

(i) A view from Canada - Susan Zimmerman

Ms Zimmerman outlined the medical research regulatory environment in Canada, which was undergoing some changes. The ethics of research involving humans was governed in large part by a policy statement developed jointly by Canada's three research agencies (the Canadian Institutes of Health Research, the Social Sciences and Humanities Research Council and the Natural Sciences and Engineering Research Council). The Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans ("the TCPS") covered all research involving humans, whatever discipline or methodology was employed. Its scope extended to all research conducted under the auspices of any institution that was eligible to receive funding from any one of the three research agencies. This covered the academic sector directly, but only covered privately-funded research if it was carried out by researchers affiliated with a university or college. The evolution and the interpretation of the TCPS was the responsibility of the Interagency Secretariat and Panel on Research Ethics.

In her view, the notion that all research involving humans should be governed by one set of ethical principles is an excellent one. In practice, however, there had been a strong sense, particularly in the social sciences and humanities research communities, that the TCPS represented a biomedical approach to research ethics, one that over-emphasised the dangers of research and the need for close scrutiny of research projects. For their part, clinical researchers were frustrated by what they perceived as the procedural hoops they must jump through to receive the approval of research ethics boards (REBs), the bodies responsible for reviewing the ethics of a research project prior to its commencement.

After 10 years' experience with the TCPS, the Panel and Secretariat were preparing a second edition, designed to address these concerns, as well as others. The main concerns with the current governance of research ethics in Canada were:

- lack of comprehensiveness (in particular, privately-funded research conducted in physicians' offices);
- lack of consistency in the interpretation of the TCPS by REBs;
- over-emphasis on procedure in research ethics review;
- multiplicity of reviews for multi-site research;
- inadequate implementation of proportionate review, that is, review of research that is proportionate to the risk presented by the research.

There were a number of perspectives in the research and the research ethics communities on the proper weight to be accorded to these problems. Some viewed the governance of research ethics in Canada as in a state of crisis. Others viewed it as needing improvement, but generally functioning adequately in ensuring that research participants were not exposed to undue risks of harm.

There was a governance reform initiative underway in Canada. A collection of research sponsors from government, academia and the private sector had formed a loose association known as the Sponsors Table, to explore ways to improve the governance of research ethics in Canada and in particular, to make it cover research in all sectors comprehensively. This was a challenge because research was not an area of federal authority under the Constitution; while there was a limited area of regulation with respect to the regulation of clinical trials, a legislative model for research ethics review was not a realistic option.

The Sponsors Table had appointed an Experts Committee to report on different models of governance that could address the weaknesses of the current system. One particular focus of its work was to propose a model of governance that would include the accreditation of human research protection programs. The Experts Committee, which submitted its final report in late spring 2008 (www.hrppc-pphrc.ca/english/movingahead.html), had recommended the creation of a relatively large (50+ staff) not-for-profit corporation to be known as the 'Canadian Council for the Protection of Human Research Participants'. The intention was to have this Council integrate the functions of policy development, education and accreditation.

Ironically, while the thrust of the Experts Committee's message was the need for immediate action, the estimated time to put the proposed Council into operation is at least three years. More importantly, there was a concern that the focus on accreditation, which was a priority only for the clinical research community, would once again alienate researchers in the social sciences and humanities. Finally, the cost of such a Council – estimated at roughly $10 million annually – was a far greater investment than was currently being made in the sector of research ethics, and it was not clear who would sustain the funding, as the federal government would not likely be willing to shoulder the entire burden.

The Secretariat and Panel had proposed a model of expanded scope using a combination of existing mechanisms. The Sponsors Table was now contemplating next steps. [A brief update since May - the Sponsors Table released a communiqué on July 18 stating its four priorities as it moved ahead: policy development, education accreditation and proportionate review (www.hrppc-pphrc.ca/english/communiquejuly182008.html)].

The understandable desire for clarity and consistency in the review of the ethics of human research often led to an interest in establishing rules both for the conduct of ethics review and for the conduct of research. In the view of the Panel and Secretariat, sound ethical judgment could not be codified, legislated or prescribed. The next edition of the TCPS would therefore place a greater emphasis on defining and expanding upon the underlying ethical principles that should guide the design of research involving humans and the review of the ethics of such research. The focus of the work of the Panel (and arguably, any future body with responsibility for the conduct of human research in Canada) should be on the education and training of both researchers and members of REBs.

On more than one occasion, the Secretariat had heard from representatives of the research ethics community in the United States a plea not to follow the route the US had taken, with its emphasis on regulation. Increasingly, they were noting that the financial and human burden associated with their plethora of regulations had not demonstrably led to increased protection of research participants. This sentiment had also been expressed by some of the earlier speakers (above) – ie a preference for a framework rather than a set of detailed rules as a regulatory mechanism.

It was the view of the Panel and the Secretariat that an emphasis on guiding principles and on proportionate review held the best hope for ensuring that ethical research involving humans proceeded in a timely fashion, and in a manner that provided adequate protection to those who participated in it.

Discussion:

In relation to the proposed accreditation scheme to be operated by the Canadian Council for the Protection of Human Research Participants, Ms Zimmerman was asked who would make the judgements and how. Standards would need to be developed first and inspectors would be appointed; the latter may have to be voluntary. She added that there was scope for standardisation of ethics committee procedures and forms, though there was already some progress in this; Quebec was in the lead. However, there was some resistance from institutions, which valued their autonomy and which had concerns about ceding any authority for ethics review, given that they would continue to be legally liable for any harm resulting from the conduct of the research.

(ii) A view from Finland and some other Nordic countries – Salla Lötjönen

Dr Lötjönen said that in Finland medical research was regulated though the Medical Research Act No. 488/1999. This had been drafted pre-emptying ratification of the Council of Europe Biomedicine Convention, and had been amended in 2004 when implementing the EU Clinical Trials Directive. It was supported by 'decrees'. The Act defined medical research quite narrowly: "Research involving intervention in the integrity of a person, human embryo or human foetus for the purpose of increasing knowledge of the causes, symptoms, diagnosis, treatment and prevention of diseases or the nature of disease in general". Thus it did not cover research involving solely interviews/questionnaires or other non-medical research such as nursing, psychological experiments and sports studies. The Act was only fourteen pages, so contained little detail; powers were left to others in the regulatory system, mainly research ethics committees.

The three supporting decrees were:

- Clarifications on the Research Ethics Committee (REC) system, contents of the consent documentation, documentation needed for the licence for embryo research

- Clarifications on the National Research Ethics Committee system (NREC) and the delegation procedure
- Payments that may be made to members of RECs (max €1200) and compensation for research subjects (€50-510).

The Finnish National NREC system comprised four National Advisory Boards (Healthcare ethics; Research ethics (ORI); Biotechnology; Animal experimentation), and three decision-making Boards (National Medical Research Committee; Board for Gene Technology; Central Board for Animal Experimentation).

The National Medical Research Ethics Committee ('TUKIJA') handled international multi-centre clinical trials on pharmaceuticals (delegates 75% of its research protocols to Regional RECs). It also had a role in co-ordination, training and provision of advice (see: www.etene.org/e/tukija/index.shtml), and functioned as an appeal body. Its current composition was a Chair and 11 others (8 expert/4 lay). The Regional system comprised 21 Regional Hospital Districts with 25 Committees. Members were nominated by Hospital Districts and each included a chair and a minimum of six others, of whom a minimum of two had to be lay.

Dr Lötjönen saw the advantages of the Finnish system being:
- It was simple and straightforward.
- All medical research was covered by the same Act (with additional provisions for medicinal products).
- It empowered regional committees.
- It empowered the investigators in charge.

And the disadvantages being:
- Practices in Regional RECs varied. For example, although the Act excluded nursing, psychology, and questionnaires, some Regions insisted that such work was led by a medical practitioner. Also, local requirements, such as consent documentation and financial resources, varied.
- The above imposed an administrative burden and delays.
- The delegation procedure by NREC added an extra step.

In Sweden, the regulation of medical research was covered by two Acts: the Medicines Act 1992 (medicinal products), and the Ethics Review Act 2003 (all other medical research). The scope of the latter was wider that the Finnish Act. It included all research with an obvious risk of affecting the research participant physically or psychologically, but also deceased persons, non-anonymised biological material, and research on sensitive data with or without the participant's consent. As of April 2008, research on sensitive data with the participant's consent was also added to the list. The Ethics Committee System comprised a Central Committee (with a judge as chair plus four expert and two lay members), and six Regional Committees (each with a judge as judge chair plus six expert and four lay members)

In Norway (which was not part of the EU), at present only research on medicinal products was covered by legislative measures (Regulation on Clinical Trials - FOR 2003:1202), but in the near future the Government was planning a comprehensive Health Research Act (though separate regulation on medicinal products would remain). The Research Integrity Act 2006 made it compulsory to submit all medical research to ethical review, but it did not give details on standards. There were three national ethics committees with the overall responsibility to advise on research ethics issues within their research disciplines: the National Committee for Research Ethics in Medicine (NEM), the National Committee for Research Ethics in the Social Sciences and the Humanities (NESH), and the National Committee Research Ethics in Science and Technology (NENT). Each had one to five expert members and seven lay. In addition there was a national Office of Research Integrity. There were four Regional Committees in medical research: North, West, Central and South-East, each with five expert members and four lay.

In Denmark, there was one Act that covered all medical research, the Ethics Committee Act 2003. This included separate provisions for medicinal and non-medicinal research. The Act covered biomedical research only. Interviews and questionnaire studies came under the Act only if the information was connected to biological material in the study. In practice the Act covered studies in psychiatry and clinical psychology. There was a Central Research Ethics Committee with a chair and five members. Members were nominated by the Ministry of Science (Chair and one member), the Ministry of Internal Affairs and Health (two members) and the Regional Ethics Committees (two members). Unusually for the Nordic countries, the majority of members were lay. There were also Regional Ethics Committees; members were nominated by municipal authorities (9-15 members each), and again the majority were lay.

In summary, Dr Lötjönen said that in the Nordic countries, compared to the UK, people tended to have greater trust in authority and participation in research was greater. This was a reason why regulation was lighter touch. Based on her knowledge of the UK and Nordic systems, she made the following suggestions for the UK:

- A single Act to cover all medical and health-related research, with considerable simplification of present regulations (for example the EU Clinical Trials Directive was 11 pages, but the UK Regulations were 71 pages – why?)
- Provision of all guidance should be delegated to NRES
- There were multiple professional guidelines; these should be abolished or harmonised.
- The REC system should remain untouched
- Organised training should be provided throughout the system - REC members, researchers, administrators, et al.

Discussion:

There was a comment that in the UK, there was now a plethora of documents that governed research, including primary legislation, statutory instruments, and different forms of guidance. With respect to the problems of consent, much could be attributed to the wording of the Declaration of Helsinki, most recently the 2004 version, which people skirted around, largely through hypocrisy. Dr Lötjönen said that the Declaration itself was not law, and that people had to abide by their national legislation; but it was pointed out that the EC, in producing the Clinical Trials Directive, had insisted that the Declaration of Helsinki was incorporated.

In response to a question, Dr Lötjönen said that in Finland access to patient records without consent was governed by the Finnish Data Protection Act, the Act on the Status and Rights of Patients, Act on the Openness of Government Activities and the Act on National Personal Data Registries in Health Care. Consent was needed from the holder of the records, and from the Ministry of Social Affairs and Health if more than one site was involved.

It was suggested that the regulatory system in Finland was 'idyllic' in that regulation was effected less though primary legislation and more through guidance. Dr Lötjönen said that this was possible perhaps because Finland was a small country, fewer people were involved, and society was more compact. However, it was pointed out that in addition Finland had a civil code tradition, with decisions being handled administratively. This would not be easy to transpose to the UK, where the structure of the civil service also intrinsically led to disjointed approach. Nevertheless, the principle should be that the legislation and regulations should be easy to understand, particularly by those regulated.

Dr Lötjönen was asked if the high levels of trust and of recruitment in Finland were reasons for the legislation being as it was. She thought that there was a connection, and suggested that in the UK greater emphasis should be put on public engagement in the process of research.

Summing-up – Richard Ashcroft

Professor Ashcroft summed up by commenting on the complexity of the regulatory landscape. There ware many different players, the issues crossed a large number of jurisdictions, there were commercial interests, people had careers to progress and reputations to protect, the public clearly had an interest (in outcomes, if not in process), and there were moral values to consider (which could change with time). Given this complexity, it was not surprising that the regulation of medical research itself was problematic. One clear conclusion was that personalities mattered. Those with charisma and ability to understand others' perspectives were the ones most likely to effect change.

He then gave giving his own thoughts on the questions posed in the introductory session:

1. What are the prevailing objectives of regulation in biomedical research?

There was no one set of objectives, but a key question regulators should ask was: do the underlying rules and the proposed regulation satisfy key principles (for example as published by the BRE)?

2. Are they/can they be consistent - across sectors or within a single sector?

On the basis of the discussion at this workshop, the answer to this had to be no on both counts.

3. Should we encourage a more risk-based approach?

It was still a little unclear what this was; was it consistent with an approach based on principles? On the latter basis, some research might be wrong, for example if there were a gross violation of human rights, even if no harm came to individuals.

4. If so, who should define the risks?

There was no normative answer to this question. Anybody who had an interest could see themselves as identifying risks. The question should be: who had the power to define risks? The answer to this was not always clear. There were some examples of good practice. The public should be consulted, as they were often the most affected and with the weakest voice, but might not complain.

5. And how do we achieve the desired encouragement?

The likely routes were through participation in conversation and persuasion.

6. What can we learn from overseas?

Finland seemed to have an effective regulatory process, but it was a small country and its approach might not suit a larger and less cohesive country like the UK (and its devolved structures). With respect to the EU Clinical Trials Directive, the UK had taken an 'outlier' approach; other countries had adopted the Directive in a way that was less disruptive.

7. What can we learn from other sectors?

Other sectors seemed better at defining their objectives. Biomedicine could learn from this, even if the issues were more complex.

8. Should impact assessments always be carried out and how effective are they?

Formal impact assessments were difficult to do prospectively. One had to ask the right questions which may not be obvious at the outset. It might be more realistic simply to consult those who were to be regulated.

9. How do we best engage the public?

This was a job for experts such as the Wellcome Trust or the DANA Centre, rather than for researchers or civil servants. The public might not see engagement on regulation as relevant to them as other issues they are consulted about. One approach might be to work with the media to encourage them to be more serious about some of the issues they cover, which might then include more about regulation.

10. Is there a piece of regulation you would like to get rid of, what would it be and why?

Rather than specific pieces of regulation, other things needed to change, for example:

- The culture of risk adversity, particularly in NHS Trusts
- An assumption that problems were insuperable
- Complexity within some institutions

But it was encouraging that some solutions, mainly concerning simplifications within the current regulatory system, had been identified and put into effect by UKCRC and by NRES. Confidence had grown as a result.

11. Are there areas where more regulation or more clarity would help?

This was presumed to be a rhetorical question!

12. What key points would regulators like to make to the regulated, and vice versa.

It was important that the regulators and the regulated should listen to one another; they should not be too defensive – that was not a good basis for drafting effective regulation. Researchers and funders should insist on a principles approach to regulation, and the interests of researchers must be taken

seriously; otherwise, there was a risk of inhibiting research that may improve human health, albeit with the best of intentions. However, researchers needed to be modest in their aims and be realistic. Medical research was often a small part of a much bigger picture (eg the Mental Capacity Act and the Human Fertilisation and Embryology Bill). Some of the activities in simplifying existing procedures were likely to yield the quickest wins.

Conclusions and recommendations

The need for regulation

- Regulation of biomedical research was necessary – in order to protect the public against the risks of untested medicines and other technologies, to restrain commercial motives and scientific enthusiasms, to protect participants, and to protect researchers.

- There were different types of regulation, including internal management systems, inter-organisational management systems, non-regulated law and legislation involving regulatory bodies; these might have different drivers and thus require different approaches to address them.

- The regulation of biomedical research was perhaps uniquely complex, but in the UK the current regulatory environment was overly complex. While it would be unrealistic to change existing regulation fundamentally, at least in the short term, prospectively all parties should be aiming to keep the regulatory burden to an absolute minimum.

Principles underpinning legislation/regulation

- Much legislation was too complex; not so much the complexity of the issues (this was unavoidable), but in the fact that the legislation was drafted in a way that non-lawyers could not readily understand. Bills/Acts should be intelligible in the first place, both for regulated and for the courts; people should not have to rely on separate guidance. [Also, the way legislation was drafted meant that much detail, which would be better contained in the main body of the Act, was inserted into separate schedules appended at the back].

- The five principles of regulation – that regulation should be accountable, consistent, transparent, targeted and proportionate - were endorsed. In particular, regulation should be risk-based and proportionate. For example, there was substantial difference between research that involved an intervention on an individual (which usually had obvious risks for the person) and that which required access to his/her tissues or records (which generally had lower risk – see below), and the current regulatory regime did not adequately recognise this difference.

- Risks should be viewed in terms not only of physical harm; there were also risks, for example, to emotional and psychological harm to individuals, to rights, to reputation, and to delivery of inter-related systems (e.g. risks to clinical service of research activity).

- The recommendation of the 'Better Regulation Task Force' that, whenever one regulation was added, another should be removed did not appear to be being followed.

- Rule-based regulatory systems were prone by default to focus on avoiding procedural violations; a better approach was for the law to set the framework and clear boundaries where these were needed, but for the implementation to be more flexible through the regulatory bodies. This rule-based approach was exemplified in the US where the financial and human burden associated with their plethora of regulations had not demonstrably led to increased protection of research participants.

- Regulation tended to be more effective when it ran with the grain of opinion. The long-term prospects of any regulatory position that lacked broad public support were poor. Similarly research suggested that regulation which was contrary to the traditions/values of those regulated was also less successful.

Planning of legislation/regulation

- With respect to EU legislation, it was essential for the UK (Government and those regulated) to become involved in the process as early as possible. Government should involve stakeholders in the early stages of the EU legislative process. Such bodies needed to organise themselves at a relevant level rapidly to provide unified position to influence the regulation. (To influence the EU, this usually needed to be Europe-wide bodies, not national ones, and thus it was difficult for academics to make their views known).

- Effective communication between the regulators and the regulated was key. An approach that involved wide communication through guidelines was more likely to be effective than one in which the regulator pointed to the law and held separate conversations with individuals each requiring interpretation.

Implementation/compliance

- Compliance with regulation could be very expensive, both for the regulator and for the regulated. Rather than intensive review of all activities, a better approach, building on trust, would be for the regulators to undergo light touch random spot checks. In this respect, regulators should tailor their inspections to the particular circumstances.

- Researchers rarely challenged decisions. There were good reasons for this, but the occasional legal challenge might a) clarify the regulation, and b) highlight areas where research was being inhibited through a wrong or over-defensive interpretation.

Lessons from other areas of regulation

- The Food Standards Agency had clearly been a success story. There may be several reasons for this: they had a clearly defined and not too broad remit; they had started with a relatively clean slate (in how they approached regulation, rather than in existing regulation); and their processes were very transparent and inclusive. In addition, the Agency had separated the identification of risks, the management of those risks and the need to address concerns of the public. This was obviously a model from which other regulators might learn.

- For the railways, there were clear benefits of a single regulator. It streamlined the regulatory system and brought a "whole industry" view to decisions. However, notwithstanding the systems in Nordic countries, medical research in the UK was probably too complicated to sit under a single regulator. The ORR and the FSA clearly showed, though, the benefits of the regulator being independent of government and Ministers.

- The workshop included examples of different regulators and how they had achieved their objectives at very diverse levels. More in-depth study might throw light on why some had succeeded more than others. Also, high quality social science research about the effects of changing rules and systems on the "sharp end" was needed.

- In many areas, regulators stressed the quality of regulation and the confidence this engendered. Public confidence in systems could be developed through greater public engagement in the processes.

Facilitating existing regulation

- The work of the UK Clinical Research Collaboration (UKCRC) to streamline the regulatory burden was very much welcomed, though it was noted that the workstream involved making the existing regulations easier to navigate, rather than aiming to change the regulations themselves.

- The recent launch of the Integrated Research Application System (IRAS) was also welcomed. IRAS was a single on-line facility which enabled the applicant to enter the information about the project once instead of duplicating information on separate application forms. Information was exported to all relevant bodies for research funding and approval.

- However it was simply not possible to provide signposts for every conceivable pathway (and, as noted above, rules-based approaches have problems),

- Organised training should be provided throughout the system - REC members, researchers, administrators, et al – in a consistent way to help ensure a common understanding and

purpose. This would also foster greater understanding the principles behind "regulation", and help researchers navigate the most suitable path.

Specific issues

- The current Data Protection Act had led to serious problems for researchers in accessing patient records without their consent. The Act had been poorly drafted in this respect, and clarification was needed urgently, even a revision of the Act, that would facilitate such research. [There might be a need for other legislation to protect personal privacy]. In the meantime, the ICO operated an enquiry line (01625 545745) and researchers were encouraged to use it.

- There was a dearth of evidence about how regulation affected trust and confidence among "the public". There should be greater emphasis for example on public engagement in the process of research.

February 2009

Regulation and biomedical research: a critical review

Mary Dixon-Woods☐, Karen Yeung☐, Richard Ashcroft, Roger Brownsword☐, Alan Bryman .

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SUMMARY AND CONCLUSIONS

1. In the report we examine the current regulation of biomedical research. Concerns that current forms of regulation impede valuable biomedical research are often expressed. So too, however, are concerns that regulation is inadequate in protecting research participants and future patients.

2. This report concerns only biomedical research that involves people. It does not have a remit for research on animals, pathogens, radioactivity, or other areas.

3. Using a literature review and case studies within and outside the biomedical research sector, we address questions about the effectiveness and legitimacy of current regulation of biomedical research. Effectiveness concerns the success of a regulatory regime in achieving its stated policy goals. Legitimacy might be defined in terms of how far the actions and values of an institution are perceived to be desirable, acceptable, proper and appropriate both by those it seeks to regulate and those on whose behalf it purports to regulate.

4. Assessment of effective achievement of regulatory goals requires specification of those goals. But this is problematic in the case of biomedical research, because there is no clear consensus over regulatory objectives. Instead, there are multiple and potentially conflicting regulatory objectives and some objectives are only vaguely formulated. It is also difficult to find measures of effectiveness which could allow objective evaluation of the strengths and weaknesses of regulation. In particular, it is very difficult to assess whether research is "over-" or "under-regulated" by use of objective measures.

5. A further difficulty in assessing the effectiveness of regulation of biomedical research is that there is (often intense) disagreement about the nature of the risks being regulated and their significance. Ethical issues are often contested; biomedical research is carried out by people who have a high level of expertise that is not easily understood by those who are not researchers; research is frequently carried out in settings where the workplace is highly professionalized; there is scientific and moral uncertainty about the nature and quantity of the risks; and claims of public interest are not easy to verify.

6. The regulation of biomedical research is extremely complex. There is no single regulatory regime for biomedical research, nor is there a single regulator, let alone a single, central source of regulatory oversight or control. Instead, there are many examples of specific regimes that influence the conduct of research but have been devised to respond to a variety of social and political imperatives, and have often been designed with wider purposes than regulation of research in view. Biomedical research is thus characterised by institutional complexity and multiplicity of regulators, many with overlapping and potentially conflicting requirements. Researchers can become answerable to a number of different regulatory agencies whose rules, principles, and procedures conflict or fail to cohere, and who demand different information – or the same information in different forms – and impose varying requirements. There is no set of reasonably clear, stable rules, which are readily understood by the regulated community and can be applied in a transparent and accountable manner. These weaknesses threaten both legitimacy and effectiveness.

7. Institutional complexity involves overlapping competences, jurisdiction, standards, powers, and sanctions. This kind of complexity can cause major problems of efficiency and of proportionality, where the weight of regulation is perceived to be on the wrong scale for the risks involved.

8. Drawing across our case studies, it is clear that people often disagree about the proper goals of regulation, and how potentially conflicting goals should be traded off. This is true in areas outside of biomedical research, but biomedical research is especially characterised by disagreement and

dispute. However, it is important to recognise that regulation often provides significant benefits for researchers by displacing this kind of conflict onto regulators and away from the researchers themselves. Regulation can also provide a moral warrant for activities that might otherwise be seen as illegitimate.

9. One notable feature of the existing regime for regulating biomedical research is the strong emphasis placed on controlling entry. Once approval has been granted, relatively little energy, particularly outside of clinical trials, is committed to overseeing compliance with the conditions upon which approval has been granted and in sanctioning non-compliance.

10. Regulatory norms arise from many sources; legal standards are just one important source. Regulatory demands are increasingly imposed internationally and may represent significant constraints on what can be done at a national level. Such externally imposed restrictions may generate particular legitimacy concerns. In addition to legal standards, the pressures that arise socially (for example to do with people's expectations) can be equally, if not more, important in shaping and constraining the behaviour of regulatees. Apparent violations of the 'social licence' upon which biomedical research activity rests may have much greater social significance than formal breaches of the regulatory code.

11. "Smart" regulation, where the core concern is that the least interventionist response to tackle the problem is identified, can only take us so far in tackling regulation of biomedical research. This is because setting the appropriate standard, and determining when and to whom it should apply, presents formidable challenges.

12. On the face of it, there is a damning indictment to be made of the sheer complexity of the regulatory environment for biomedical research. However, it needs to be recognised that there is inevitably a degree of complexity in regulating biomedical research because this is an activity that presents two faces to the public. One face is that of researchers doing their best to improve our understanding of disease and its treatment; the other is that of researchers who are prone to exploit participants and to abuse trust. This creates a tension between the two key regulatory objectives. While one regulatory objective is to facilitate and to encourage biomedical research, the other is to build limits and safeguards into the system so that the public is protected. With the regulatory regime set up in this way, there are bound to be difficult balances and trade-offs between the competing objectives (e.g., balancing privacy against public health, accountability against bureaucracy, and so on).

13. Securing the social licence for medical research will remain one of the key tasks of regulation, but better evidence is needed about people's trust and confidence in biomedical research and about the consequences of different regulatory approaches for trust and confidence.

14. Overall, biomedical research is noteworthy for its dense and complex regulatory environment, which invites criticism (not least by the Government's own standards for good regulatory practice). But it is not gratuitously complex: there are competing objectives, and there will be never be consensus on many of the questions with which regulation must engage. Regulation is charged with identifying and creating authorities to adjudicate on these issues, but full agreement will be unattainable. Although reforms to the governance system are underway, the relief provided to researchers' perceptions of regulatory burden, though welcome, is likely to be only partial.

Conclusions

15. Our review has clearly identified that regulation of medical regulation is highly complex and produces many frustrations and costs for researchers. There are (good) reasons why the area is so complex and it needs to be emphasised that to some extent the problems are intractable. This is because many regulatory interventions are trying to do multiple things and to serve multiple values; every time a change is made to favour one particular purpose there is the potential for clash with the achievement of other objectives. Even when interventions or actions are undertaken with good intentions, they may fail or produce unwanted or unanticipated effects.

16. Our analysis of the non-medical research case studies shows that there is no easy solution to problems of regulation in medical research. Medical research is a perhaps uniquely complicated area characterised by extreme institutional complexity. Quite simply, there is no quick fix that can be identified; on the contrary, the failure to find ways of resolving problems in other areas underlines the conclusion that regulation of medical research may be especially resistant to easy resolution.

17. Perhaps one area where there may be scope for some change is in how rules are applied. Many of the problems that researchers complain of seem to arise when regulatory goals are converted into procedural form. The particular institutional structure of the NHS, where each trust functions as a legal entity, adds to the difficulties here. It is possible that there is something to be learned from looking at how regulation works in other countries, particularly those that have implemented - say - the EU clinical trials directive in different ways. In exploring the potential for change in this area, it would also be helpful to have an analysis of how the current system tends to produce and tolerate different types of research misconduct (bearing in mind that there will not always be agreement on what misconduct involves). Both of these issues would require further research outside the scope of our review.

August 2007

MRC/WT Workshop: Regulation in biomedical research

Venue:	Conference Centre, Wellcome Collection, 183 Euston Road, London NW1
Date:	Tuesday 13 May – Wednesday 14 May 2008
Time:	Day 1: 10.30 – 18.30 (+dinner)
	Day 2: 09.00 – 13.15
Co-Chairs:	Professor Genevra Richardson (Professor of Law, King's College London and Chair of the MRC Ethics, Regulation and Public Involvement Committee)
	Professor Peter Smith (Professor of Tropical Epidemiology, LSHTM and Wellcome Trust Governor)
Workshop aim:	To consider ways in which the regulation of research involving human participants might be simplified, while retaining the confidence of the public.

PROGRAMME

Day One: Tuesday 13 May

Each speaker's session includes 10 minutes for immediate questions.

10.30 – 11.00	Registration/Coffee
	(Franks and Steel Rooms)
11.00 – 11.15	Welcome and Introduction
	Genevra Richardson (Chair of the MRC Ethics, Regulation and Public Involvement Committee)

SESSION 1: How does it feel to be regulated?

11.15 – 11.45	Literature review: Regulation and biomedical research- a critical review (2007)[11]
	Mary Dixon-Woods (Professor of Medical Sociology, Leicester University)
11.45 - 12.10	An academic perspective
	Charles Warlow (Professor of medical Neurology, University of Edinburgh)
12.10 – 12.35	An industry perspective
	Lincoln Tsang, (Chair of the BIA Regulatory Affairs Committee)
12.35 – 12.50	Discussion
12.50 – 13.35	Lunch

[11] Authors: Mary Dixon-Woods, Karen Yeung, Richard Ashcroft, Roger Brownsword, and Alan Bryman.

SESSION 2: Approaches to improving and streamlining regulation

13.35 – 14.00	UK Clinical Research Collaboration: A summary of current efforts to streamline the regulatory burden Liam O'Toole (Chief Executive, UKCRC)
14.00 – 14.30	A Government view of regulation John Dodds (Managing Director, Regulatory Reform BERR)
14.30 – 15.10	Discussion

SESSION 3: Different approaches to regulation

15.10 – 15.35	UK Regulators' perspectives: Human Tissue Authority Adrian McNeil, (Chief Executive, HTA)
15.35 – 16.00	UK Regulators' perspectives: Human Fertilisation and Embryology Authority Alan Doran (Interim Chief Executive, HFEA)
16.00 – 16.25	Tea/coffee
16.25 – 16.50	UK Regulators' perspectives: Medicines and Healthcare products Regulatory Agency Brian Davis (Clinical Trials Unit manager, MHRA)
16.50 – 17.15	An academic lawyer's perspective Roger Brownsword (School of Law, King's College London)
17.15 – 17.40	A view from Canada Susan Zimmerman, (Executive Director, Secretariat, Interagency Panel on Research Ethics) moved from day 2 to day 1
17.40 – 18.30	Discussion
18.30 -	Drinks and dinner in Rooftops, Wellcome Trust, 210 Euston Road

Day Two: Wednesday 14 May

Each speaker's session includes 10 minutes for immediate questions.

SESSION 3: Different approaches to regulation (continued)

09.00 - 09.25	Health information/Personal data David J Evans (Senior Data Protection Practice Manager, ICO)
09.25 – 09.50	National Research Ethics Service Janet Wisely (Director, NRES)
09.50 – 10.15	Food safety Andrew Wadge (Chief Scientist, Food Standards Agency)
10.15 – 10.40	Regulating Britain's Railways Bob Chauhan (Head of Policy Unit, Office of Rail Regulation)
10.40 – 11.05	Discussion
11.05 – 11.45	Coffee/tea

SESSION 4: International perspectives and workshop conclusions

11.45 – 12.10	A view from Finland Salla Lötjönen, (Secretary-General of the National Advisory Board on Research Ethics, Finland)
12.10 – 12.35	A Government Department perspective Mark Bale (Deputy Director of Scientific Development and Bioethics, Department of Health) – moved from day 1 to day 2
12.35 – 12.45	Workshop Conclusions: How might regulation be different? Richard Ashcroft (Professor of Bioethics, Queen Mary University of London)
12.45 – 13.10	Final discussion
13.10 -	Lunch/close

Delegate list

Role	Name	Position/Capacity
Participant	Dr Martin Anthony	Deputy Director, Bioscience Unit, BERR
Speaker	Professor Richard Ashcroft	Professor of Bioethics Queen Mary, University of London School of Law ERPIC member
Participant	Dr Jane Armitage	Reader on Clinical Epidemiology, Clinical Trial Service Unit, University of Oxford
Speaker	Dr Mark Bale	Deputy Director of Scientific Development & Bioethics, DH
Participant	Ms Amanda Brewster	Policy Officer, Wellcome Trust
Speaker	Professor Roger Brownsword	Centre for Technology, Ethics, Law & Society (TELOS)
Participant	Dr Sarah Bunn	Adviser Biological Sciences & Health, Parliamentary Office of Science and Technology
Participant	Mr David Carr	Policy Adviser, Wellcome Trust
Speaker	Mr Bob Chauhan	Office of Rail Regulation
Participant	Dr Joanna Dally	Committee Specialist, Innovation, Universities, Science & Skills Committee
Speaker	Dr Brian Davis	MHRA Clinical Trials
Speaker	Professor Mary Dixon Woods	Professor of Medical Sociology, University of Leicester
Speaker	Mr John Dodds	Managing Director, Regulatory Reform, Better Regulation Executive, BERR
Speaker	Mr Alan Doran	Interim CEO, Human Fertilisation and Embryology Authority

Speaker	Mr David J Evans	Senior Data Protection Practice Manager, Information Commissioner's Office
Participant	Professor Christopher Hood	Gladstone Professor of Government and a Fellow of All Souls College, Oxford
Participant	Ms Eve Jagusiewicz	Policy Adviser for health issues, Universities UK
Participant	Dr Susan Kerrison	Assistant Director, Joint UCLH and UCL Biomedical Research Unit
Participant	Dr Rachel Knowles	Clinical Research Fellow, MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health
Participant	Dr David Lalloo	Head, Clinical Research Group, Liverpool School of Tropical Medicine ERPIC member
Participant	Professor Graeme Laurie	Professor of Medical Jurisprudence, University of Edinburgh
Participant	Ms Nancy Lee	Policy Adviser, Wellcome Trust
Participant	Dr Graham Lewis	Director, Centre for Prospective Regulation/research fellow, SATSU
Speaker	Dr Salla Lötjönen	Secretary-General, National Advisory Board on Research Ethics, Finland
Participant	Dr Neil Manson	Senior Lecturer in Philosophy, Institute for Philosophy and Public Policy, Lancaster
Speaker	Mr Adrian McNeill	CEO, Human Tissue Authority
Participant	Professor Tom Meade	Professor of Epidemiology (Emeritus), London School of Hygiene and Tropical Medicine. ERPIC member
Participant	Mr Nick Meade	Policy Officer Genetics Interest Group
Participant	Dr Janet Messer	Deputy Director NHS R&D Forum
Participant	Mrs Helen Munn	Director, Medical Science Policy, Academy of Medical Sciences

Participant	Dr Julie Norman	Head of the Chief Scientist Team, Food Standards Agency
Participant	Baroness Onora O'Neill	Peer; President, The British Academy
Speaker	Dr Liam O'Toole	Chief Executive, UK Clinical Research Collaboration
Participant	Mrs Rosa Parker	Corporate Governance Business Manager, Medical Research Council
Participant	Dr Tony Peatfield	Head, Corporate Governance and Policy, Medical Research Council
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Co-Chair	Professor Peter Smith	Professor of Tropical Epidemiology, LSHTM Wellcome Trust Governor
Participant	Professor Robert Souhami	President, BACR
Participant	Dr Andrew Stainthorpe	Director, UK Research Integrity Office
Participant	Professor Steve Sturdy	Deputy Director, ESRC Genomics Forum, University of Edinburgh
Participant	Dr Carolyn Tarrant	Wellcome Trust VP Fellow
Participant	Mr Marc Taylor	Deputy Director of R&D Systems and Governance in the Department of Health's Research and Development Directorate

Participant	Ms Karen Thomson	Policy Manager, PIAG
Participant	Dr Lincoln Tsang	Chair, BIA Regulatory Affairs Committee
Participant	Lord Turnberg	Peer; former President of the Royal College of Physicians
Speaker	Mr Andrew Wadge	Director of Food Safety Policy and Chief Scientist, Food Standards Agency
Speaker	Professor Charles Warlow	Professor of Medical Neurology and Co-Director, Edinburgh Neuroscience ERPIC member
Participant	Professor David Wield	Director, Innogen
Participant	Dr John Williams	Clinical Portfolio Manager, Wellcome Trust
Speaker	Dr Janet Wisely	Director, National Research Ethics Service
Participant	Professor Karen Yeung	Centre for Technology, Ethics, Law and Society (TELOS)
Speaker	Ms Susan Zimmerman	Executive Director, Interagency Secretariat on Research Ethics, Ottawa, Canada