

Over-regulation of clinical research: a threat to public health

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ABSTRACT – Clinical research is subject to increasing regulation by research ethics committees and research and development offices which are responding to social and political pressures, as well as to new legislation, both European and national, some of which is still being worked out. The resulting bureaucracy, expense and confusion are putting insuperable hurdles in the way of clinical research and clinical care is compromised. What research is still possible will only be done in large organisations and may even be seriously biased. The solutions are to inform and seek the help of the public and to forge alliances with patient groups. Patients have far more to lose than clinical researchers who, if clinically qualified, can more easily pursue a fulfilling career as clinicians rather than researchers.

KEY WORDS: clinical research, Data Protection Act, Human Tissue Bill, regulation

To regulate is 'to control, govern or direct by rule'.¹ Unfortunately, there is now so much regulation that clinical research is being delayed, slowed and even stopped altogether. As a result, public health is compromised. Moreover, there is immense confusion about the regulations, and the situation has been described as a 'complex farrago quite beyond the comprehension of most mortals, including the professionals most affected by it'.² The Academy of Medical Sciences lamented the 'increasingly complex and bureaucratic legal and ethical frameworks in the UK and EU',³ and Cancer Research UK pointed out that since 1995 there have been 44 new sets of regulations governing clinical research.⁴ So what are these potentially harmful regulations?

Research ethics regulations

Although ethics committees provide crucial protection against research subjects being harmed, researchers nowadays have to spend far too much time obtaining ethics committee approval before starting the actual research, and often during it as well, even for trivial amendments to their protocol.

The whole process of ethics committee approval

has become excessively bureaucratic. The weight of the paper used after multicentre ethics committee approval, when 15 local research ethics committees each had to separately approve our study of intracranial vascular malformations, was 27 kg.⁵ The new arrangements (www.corec.org.uk) from 1 March 2004 should be an improvement, although a form of up to 68 pages has to be completed⁶ and most of the form is taken up by study methodology (which the ethics committee cannot necessarily judge), funding details, signatures of numerous officials, research governance and other administrative details. The emphasis is on process and political correctness, not on ethics.^{7,8}

Ethics committees often appear to focus on editorial rather than ethical concerns. Yet, paradoxically, their templates for providing patients with information can result in inappropriate, lengthy and unclear information leaflets.⁷ And there are many examples of the same protocol being approved by one ethics committee but not another,^{9,10} or being turned down for completely different reasons. There are even variations in the requirement for an ethics submission to be made at all, perhaps because the line between audit (no ethics approval generally required) and research (ethics approval required) is so blurred.¹¹ (Using different rules for audit and research is anyway an unsustainable double-standard.)

Ethics committees should become more professional, efficient, consistent, quicker and less concerned with trivia.⁹ Delays can cost lives. The lengthy consent procedures required of the US centres participating in the ISIS-2 trial of thrombolysis after acute myocardial infarction probably cost about 10,000 unnecessary deaths because patients could not be recruited as quickly as they were in the UK.¹² If ethics committees delay research unnecessarily, they will do more harm than good to patients – which is hardly an ethical consequence.¹³

Regulating who pays for what

The regulations governing who pays for what in research in the NHS simply do not work. They are too complicated and change so often that researchers and under-resourced hospital R&D departments do not understand them. The idea is beguilingly simple: one

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pot of money to organise the research (the original grant from the MRC, for example), another for the infrastructure on the ground (service support costs for extra clinic appointments etc, which are met by the Department of Health), and one for the treatment costs.¹⁴

However, the support costs can be extraordinarily difficult and time consuming to work out, and probably impossible to get right. Even a large teaching hospital, with agreed portfolio funding for research infrastructure, may in a sense be burdened with a research project which has been reviewed and core funded elsewhere but for which it may not be able to meet the support costs. Smaller hospitals which are less active in research have to complete a complicated 19-page form for every project, send it to their regional office of the Department of Health, which then sends it on to the Department of Health itself for final release of the money. There is delay at each stage, and the overall delay can be enormous. For researchers, this is immensely frustrating. In our multicentre trial of deep venous thrombosis prevention in stroke by compression stockings, the process of applying *ad hoc* funding for severe support costs took York nine months to agree service support costs, and Durham 11 months.

To add to the difficulties, the excess cost of any research treatment has to be applied for separately and met by a subvention from the Department of Health – yet another bureaucratic hurdle.

All this regulation breeds a burgeoning bureaucracy to support it, and if this is not properly funded and staff not adequately trained, the bureaucracy breeds inefficiency, delay, frustration and possibly failure.

Personal data protection and records-based research

The Data Protection Act 1998¹⁵ is so difficult to understand that guidance provided by professional and other organisations varies widely. In order to collect and analyse non-anonymised data from routinely collected health records (as was done for decades before the Act, seldom with patient consent but without any complaint), researchers in England (but not Scotland where there is no specific legislation) are now regulated by Section 60 of the Health and Social Care Act 2001, a transitory measure.¹⁶ The researchers must – after obtaining ethics committee approval – apply to the Patient Information Advisory Group. Furthermore, if approval is given, it has to be reviewed annually and the researchers have to ‘provide evidence of how they are moving towards informed consent or anonymisation/pseudoanonymisation’. Yet for audit and running the health service, consent is unnecessary – an amazing double standard, particularly as patients are more concerned about their records being seen by non-medical than medical staff.^{17,18} In *Confidentiality: protecting and providing information*, the General Medical Council (GMC) seems to permit research using non-anonymised patient data where it is impracticable to seek consent (sections 16 and 18), but in section 31 it puts the onus on research ethics committees to decide (subject to the possibility of a legal claim for breach of confidentiality!),¹⁹ and it

adopts the same position in section 32 of *Research: the role and responsibilities of doctors*.²⁰

One apparent solution is to ask patients during their routine clinical care if their data can be used for research. This sounds reasonable until the consequences are thought through. Are the records of previous patients – who may no longer be contactable, or even dead – to be denied to researchers? In much epidemiological research thousands of patients are involved, so prospective consent would be impossible or extraordinarily costly. How can continuing consent be obtained, particularly if the patient data are for a new research project at some future time? Exactly how can we arrange to ask each and every patient in the course of their normal clinical care if their data can be used, with no risk whatsoever to them, for observational research, specified at the time or at some time in the future – and record their consent? And finally, how can any refusers be reliably identified for ever more, and what if they – or indeed the consenters – change their mind? And what if they refuse some things but not others?

Anonymisation of patient data sounds a reasonable solution until the complexity of implementation and therefore huge costs are calculated. And what exactly is meant by ‘anonymous’, which can vary from slightly to completely anonymous? Anyway, for much research, anonymisation is impossible, because, for example, a patient may need to be contacted for follow-up.

The GP-held personal healthcare record system dating from the start of the NHS in 1948 contains prospectively collected data on millions of people over more than 50 years, with follow-up until death. But all of this could be lost to research if the regulatory hurdles make these data so hard to access that the researcher has no energy left to do the study, let alone the tenacity to obtain the funding.

If access to patient records for *bona fide* research is refused, researchers should challenge the decision and ask how the Data Protection Act is being invoked, and then check it. The third schedule states that any use of identifiable data relating to the ‘physical or mental health or condition’ of a living individual requires his or her informed consent. However, it then qualifies that statement and gives an alternative to consent: ‘or ... [that the] processing is necessary for medical purposes’, which includes research undertaken by a researcher owing a duty of confidentiality. The Act is undoubtedly confusing to researchers untrained in legal argument,²¹ but they can take some comfort from Lord Falconer, the Constitutional Affairs Secretary, who was reported in the *Guardian* on 18 October 2004 as saying:

The problem about the Data Protection Act is that it is almost incomprehensible. It is very difficult to understand. The precise limits of it are problematic. There are constant difficulties about what information you are allowed to share between departments for instance. I just think it should be looked at again at some stage to make it more simple.

Adult incapacity regulations

In Scotland, before the Adults with Incapacity Act 2000²² was trumped by the European Clinical Trials Directive,²³ for a trial in the emergency management of cardiac arrest, status epilepticus,

traumatic brain injury or stroke, it was necessary to seek consent from a guardian, welfare attorney or nearest relative if the patient was unable to give their own consent – often the situation in severe cases. (Notwithstanding the vexed issue of how closely a proxy reflects the wishes of the patient, this was another huge double standard because routine care which depends on previous research could go ahead without proxy consent.²⁴) The longer treatment is delayed, generally the worse the outcome, and yet trial treatment was delayed while a proxy was found, or if there was no available proxy the treatment was not tested at all. One can only imagine how many millions of brain cells were killed unnecessarily by the legislators and regulators. It has even been suggested that researchers should inform research ethics committees ‘each time consent for a patient is obtained from a personal representative’.²⁵

However, since 1 May 2004, the European Clinical Trials Directive allows a professional legal representative to provide proxy consent. This could be the doctor responsible for the patient’s care (but unconnected with the trial – which is distinctly unlikely) or a person nominated by the hospital (which smacks of tokenism and must raise questions of conflicting interest).^{25,26} It remains to be seen how this works out in practice but a better solution must surely be formal ‘waiver of consent’, as used in the USA.²⁷

Post-mortems, tissues and the end of histopathology research

The emerging regulations on consent for post-mortem examination, separately for diagnosis, research and teaching, and separately for various parts of the body, exactly what can be retained for what reason and for how long, precisely how tissues should eventually be disposed of, and all bearing in mind what the deceased may or may not have wanted and how much the post-mortem information is confidential and to whom, will make the consent process far too long to be practical. Furthermore, too much detail may well distress the bereaved unnecessarily. As a result of this complexity, the number and extent of post-mortems have declined,²⁸ pathologists have been vilified, diagnosis is compromised, audit and clinical governance suffer, and research withers. Teaching withers too; in New Zealand, students have even been banned from attending autopsies.²⁹ In the wake of concern about the dead, many archived tissue banks from the living have been disposed of, so destroying future research opportunities. We are in grave danger of losing what has been called solidarity – current knowledge comes from research using patient data and samples collected in the past.³⁰

Three million tissue specimens, as well as 100 million blood samples, are collected from the living in the NHS every year.³¹ It would be quite impossible, or at least prohibitively expensive, to get consent for research for each one, even prospectively, let alone for the old specimens. Are they all to be destroyed, even though empirical evidence suggests that the vast majority of patients would consent to their use for research?³² This wilful destruction of valuable material, to satisfy the autonomy of a tiny minority of refusers, was reflected in the original draft of

Key Points

Regulation of clinical research is now extraordinarily bureaucratic, expensive and confusing – and is getting worse

This will delay and sometimes even stop research, except where supported by industry which has the resources to comply with the regulations, but this will inevitably lead to an over-concentration on new drugs

Over-regulation may very well lead to serious bias in clinical research and therefore the wrong conclusions being drawn

Losing the clinical research base in the UK will damage present and future patients, and compromise the public health

Informing and working with the public and patient groups may lead to a wider recognition of the problem, and pressure for change

the Human Tissue Bill in England which referred to any material containing human cells. There were even threats of jail for any transgressors (although audit escaped, yet again).³³ And the GMC’s *Research: the role and responsibilities of doctors* makes no concessions at all: consent must always be obtained.²⁰ Fortunately, in June 2004, the Bill was amended and consent from living patients will no longer be required, provided the residual tissue is in some sense anonymised, but there will be more amendments to come.

European regulations

Strenuous efforts are now being made to prevent the legislators and managers from over-interpreting the new European Clinical Trials Directive, which is supposed to standardise and simplify the rules governing clinical trials, and protect patients.^{23,34} The Directive will cause bureaucracy, delays, over-intrusive monitoring, unnecessary pharmacovigilance, data monitoring and ethics committee involvement during the trial, over-long and incomprehensible patient information sheets, and confusion around who exactly the ‘sponsor’ should be (a term previously unheard of in non-commercial trials). According to Cancer Research UK, this will increase the cost of trials four-fold without enhancing patient protection.⁴ Randomised trials are already withering,³⁵ and future patients will undoubtedly be harmed if trials are replaced by far less reliable non-randomised comparisons based on routine clinical practice which can pass as audit, and so avoid ethics scrutiny and regulation by the European Directive.

The consequences for patients and public health

Research: too time-consuming, difficult and expensive

Compliance with current regulations is so complex, time-consuming and therefore prohibitively expensive, that research will become unaffordable except by industry, and so inevitably

will be shaped by their legitimate need for profit. Evaluation of non-patented drugs, surgical techniques, interventional radiology, and the myriad of nursing and hands-on treatments, such as physiotherapy, will vanish. The little money the NHS devotes to research may well be wasted on over-intrusive, unjustifiable and sometimes harmful regulation.

Clinical care: compromised

Over-regulation will make clinical research so difficult that it will cease. This matters because better clinical care clearly depends on research, both directly and indirectly. A few examples illustrate this:

- Variant CJD was quickly discovered in the 1990s because the atmosphere was conducive to post-mortems and examination of the brain, and patient data could be easily collected without a weighty consent procedure. It would not have been discovered so quickly these days, and possibly not at all if post-mortems disappear altogether.
- Patients often receive better care, better information, better follow-up and perhaps better outcomes when they are part of a clinical trial, than if they are treated in the NHS where proper follow-up of patients may be compromised by pressure to satisfy performance targets and see new patients.²⁴
- During the Scottish Intracranial Vascular Malformation Study, it soon became clear that there was no proper information for patients, so a booklet was written for them.³⁶
- In the PINE study of Parkinsonian disorders in Aberdeen, instead of waiting weeks for evaluation, patients are seen within days because they are contributing to a research project: they benefit and knowledge improves.

Harm to patients

Over-emphasis on consent for research can cause unnecessary distress. For example, a colleague about to have a Caesarean section was asked if stem cells for research could be collected from the cord blood after delivery. Even though the woman was a doctor, in the stress of the situation she did not immediately appreciate that cord blood, along with the cord and placenta, is normally disposed of, and she became quite agitated about her baby's blood being taken. When she finally understood, she wondered why it had been necessary to make such a trivial request. In fact, an ethics committee had demanded it, not the researcher.

Biased research

If the individual right to opt out is extended too far, then the patient data that are collected could come from an unquantifiably biased sample. Those who are contactable and allow their data to be used may be systematically very different from the refusers or the non-contactable (who may even be dead), thus leading to so-called authorisation or participation bias. The results could then be misleading and harmful to future patients.³⁷⁻⁴⁰

Sometimes, with the best of intentions, patients in routine practice are not told about certain apparently trivial abnormalities that appear, for fear of causing unnecessary anxiety. To find out whether these anomalies are definitely trivial, the patients have to be followed for decades, and the only way to do so is through their medical records, without their consent. For example, follow-up of incidental venous anomalies on a magnetic resonance brain scan, for investigating, say, headache, has never been done, and never will be if the current regulations are over-interpreted.

In acute stroke, perhaps a new treatment could be tried only on patients who are able to consent. But they would have had mild strokes, where the hazards of treatment may outweigh any benefits because they may recover without treatment. Hence they would differ entirely from unconscious patients close to death where the treatment hazard might be worth accepting for greater potential benefit. A trial in mildly ill consenting patients could therefore lead to the abandonment of a potentially useful treatment for severely ill patients. The autonomy of several hundred trial patients would have been dutifully respected, but possibly to the detriment of millions of stroke patients in the future.

Goodbye to the little man

Over-regulation, because it requires an army of administrators, forces people into large research groups. It would have driven out the innovator in a 'mere' district general hospital, like Patrick Steptoe in Oldham who developed *in vitro* fertilisation, and John Charnley in Wigan who invented the artificial hip joint. The notion that we should fund only a few large successful research groups who can afford the bureaucracy of today's over-regulation is like only funding Manchester United but destroying what they depend on for their future stars – a huge pyramid of players from schools, local amateur teams and the lower professional divisions.

The reasons for over-regulation

Over-regulation afflicts not only researchers but also the police, social workers and teachers – professionalism and trust are being replaced by 'stupid accountability' reflected in league tables, targets and performance indicators.⁴¹ 'We are swimming in a bureaucratic sludge awash with consultancies, incomprehensible accountancy language, over-management, juvenile debate on aims and strategies, pseudo-business practice and the dreaded mission' – this could have been written by a despairing clinical researcher but in fact it was written by the director of a small Scottish theatre.⁴² Why are we all so afflicted? Lack of trust may be the most important reason. Other possible contributors are: a culture of complaining encouraged by government and consumer organisations; a modern obsession with the rights of individuals as opposed to their responsibilities to the society that nurtures them; an obsession with accountability and the administrative control of professional life using targets of the easily measurable rather than the relevant; refusal to compare

the risks and costs of over-regulation with those of less regulation; over-centralisation of control; and fear of litigation which encourages over-interpretation of the law. Much of the problem emanates from over-emphasis, particularly by the media and politicians, on outliers – Bristol and Alder Hey, for example – to the exclusion of the commonplace. Doctors are still the profession most trusted to tell the truth, and yet we are persecuted by the least trusted professions – politicians and journalists.⁴³

Some solutions

How could regulations be made less burdensome? As a start, the public should be informed about and involved in what is going on. At the moment, patients are generally told what research will be done with their personal data, or tissues, not what they and we will all lose if it is not done. Researchers should forge alliances with groups representing patients, such as the Brain and Spine Foundation, a suggestion being taken up by the recently launched James Lind Alliance.⁴⁴ Such groups are far better able to campaign and lobby government than researchers, and will probably be paid more attention. It is also important to educate the media, politicians, ethicists, lawyers and opinion-formers so that they do not mislead the public simply because they are too far from the front line of research, or do not have the hands-on experience, to think through the consequences of over-regulation. These people make many of the rules but whether they represent an informed public is doubtful.

It will not be easy to make changes. There is now an enormous vested interest in regulating – the army of regulators, implementers of the regulations, and all those who check that we are being well regulated do not want to be out of a job (and in the meantime insist that they are doing their best to reduce the regulations). And nor do the editors of the 24 journals concerned with medical ethics, all initiated since 1970.²⁴

A final thought

Over-regulation is but one nail in the coffin of UK clinical research, just when advances in genetics and molecular research require the translational work of clinical researchers now that the basic epidemiological methodology has been resolved.⁴⁵ Why should clinicians go on doing research at all? Why subject yourself to harsh judgement by possibly biased peers pursuing the same limited pot of money each and every time you apply for a grant, or submit a paper? What is the incentive to get involved when you could be an NHS consultant or GP principal and regarded as being good at what you do, not bad, by default? Scotland is second – after Sweden – in the ranking of clinical research citations per capita and England is seventh, both ahead of the USA at ninth.⁴⁶ Somebody with their hands on the levers of power might like to notice before we go the same way as ship building and steel making, other skills for which the UK once had a worldwide reputation.

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