Regulation—the real threat to clinical research

Recent changes to research governance were intended to ensure that clinical trials are safe and effective. But **Paul Stewart and colleagues** argue that the regulatory burden is now obstructing high quality science

Personal experience and feedback from many clinical researchers indicates that a major hurdle to undertaking clinical research is the ever increasing bureaucracy attached to the process. It is now the biggest single threat to the UK clinical research base and warrants immediate action. Earlier threats—lack of researchers and capacity—have been addressed through major investment by interested parties including the Medical Research Council, Wellcome Trust, other charities, and the Department of Health. However, anyone taking up one of the new academic specialist registrar posts created to encourage clinical academic training is likely to spend the entire 12 month fellowship trying to obtain regulatory approval for any clinical research project. Drug companies are experiencing similar difficulties. The UK has slipped from one of the most attractive to one of the least attractive places to undertake clinical trials as a result of ignoring warnings at the start of the decade that companies cannot afford long delays in approval and initiation.[1 2] We illustrate the effect of recent regulation with two anecdotes from our experience.

Case 1

In November 2004, AS sought ethical approval (under the old system) for a single centre, double blind, placebo controlled crossover comparison of glucose tolerance in two established classes of antihypertensive drugs, beta blockers, and thiazide diuretics. The ethics committee submission was approved with no changes at the end of November 2004, and approval from the trust's research and development department was obtained in parallel. A paper request for clinical trials authorisation was submitted in early January 2005 and approved in February 2005. The first patient visit was in the same month.

In July 2007, we decided to add another phase to the study using the licensed potassium sparing diuretic amiloride. This decision followed reports that high dose amiloride was more effective than bendroflumethiazide (one of the trial drugs) in hypertension and that raising potassium concentrations may protect against diabetes mellitus.[3 4] AS submitted a

revised protocol for a further double blind placebo controlled study comparing amiloride with thiazide diuretics and beta blockers as a study amendment and received a favourable opinion from the ethics committee. However, when we sought external grant funding for the study amendment, reviewers asked for pilot data with amiloride. We submitted a further, simpler amendment for a pilot study using open label amiloride alone at half the dose we use every week in the clinic, and this is when problems started.

The local research ethics subcommittee, which comprised a pharmacist and layman with limited clinical experience, had concerns about possible drug interactions between amiloride and other drugs being taken by the study participants and hyperkalaemia and requested resubmission. Although we pointed out that the pilot was identical to one limb of the amendment that it had already approved, in September 2007 the full committee rejected the application for the pilot to be considered as a study amendment. We therefore had to make new submissions to the local ethics committee, Medicines and Healthcare Products Regulatory Agency (MHRA), pharmacy, insurance company, research and development department, and the local (Wellcome Trust) clinical research facility.

The ethics application process had been centralised since our original application in 2004. The first challenge was to find a conveniently located ethics committee with an available slot, the second was having three days to submit the newly designed online form after reading 53 pages of guidance notes.

The MHRA did not accept either online or paper submissions; all pages had to be scanned and copied on to a CD. Accidental omission of the signature page required the whole application to be resubmitted. A month later, a letter from the MHRA stated that the section on reporting of unexpected adverse events during treatment with this 40 year old drug was incorrect and that the protocol needed to be resubmitted within 14 days or the whole application would be void. This letter was sent on 21 December and by the time AS received it after the Christmas vacation the deadline had passed. Final approval was given in January 2008, six months after the initial request.

Case 2

As part of MRC and Wellcome Trust funded work investigating the role of endogenous steroid production and metabolism in the pathogenesis of obesity and insulin resistance[5] JWT wished to examine the effect of carbenoxolone. The drug has been widely used in clinical practice and in clinical research as an inhibitor of the shuttle between cortisol and cortisone.

He submitted simultaneous applications to the research ethics committee (through the central allocations system), local research facility scientific advisory committee, NHS trust research and development department, and MHRA in January 2007. The local ethics committee notified him in March that the study had been rejected because of the use of peripheral cannulas. He appealed immediately (through the central allocations system) as he thought that the committee's concerns were unjustified. Subsequent committee meetings were cancelled, and the proposal was eventually reviewed by another ethics committee on 30 May 2007. Only minor changes were suggested, and formal ethical approval was granted on 19 June 2007. In the mean time the research and development department and research facility had accepted the proposal subject to ethics and MHRA approval.

At this point, JWT contacted the MHRA, which could find no record of the application. A further application was submitted but rejected a month later on the grounds of inadequate procedures for reporting adverse events. A substantial amendment form was completed and submitted to both MHRA and the approving ethics committee. Final MHRA approval was eventually received in October. In November, 11 months after the first application was submitted, the trust research and development department approved the study.

Reasons to be unhappy

Dissatisfaction with the remit and performance of ethics committees is not new. The current system dates back to the Department of Health's research governance framework and European Union directives in 2001. It was introduced not because of concern across the UK research community about the previous system but in response to EU disquiet about governance elsewhere in Europe.[6 7] Ironically, the stated objectives of the legislators in Brussels were "to simplify the administrative provisions governing clinical trials," and "to establish a transparent procedure to harmonise trial conduct." However, there is little harmony among regulatory bodies. The application paperwork now requires up to 40 hours to complete, and there is uncertainty about what requires ethical approval (audit versus research, medical student research projects, etc), inconsistency and delays in review process, and inappropriate requirement by many committees for scientific peer review.[8 9] The Warner report in 2006 made sensible recommendations such as consolidation of committees across strategic health authorities and introduction of scientific triage officers, but little has changed.[10]

Local governance and indemnity further delay study implementation.[9] Nothing better illustrates the legalistic red tape strangling clinical research than the hair splitting between mistakes in the writing and the execution of protocols, with academic consultants protected by NHS indemnity only for the execution because protocols are not written in NHS time. Some universities have insurance policies, but other investigators need to fund personal insurance for their peer reviewed protocols before applying for ethical approval. Clinical research by university contracted and NHS funded staff is subject to local scrutiny, often including a highly complex "risk analysis" exercise. How can closely monitored research require such painstaking scrutiny when researchers holding honorary NHS contracts with just an annual joint appraisal process are deemed "safe" to undertake much riskier clinical practice?

Recommendations to cut research bureaucracy

- A single and simple web based submission form for all research studies
- Automatic indemnity by National Institute for Health Research for all research protocols involving NHS patients
- A national and consistent ethical review process
- Medicines and Healthcare Products Regulatory Agency to focus on its remit to ensure medicines work and are safe

The regulatory burden must be . . . seen to support clinical research rather than close it down

The recently formed National Institute of Health Research (NIHR) is aware of these issues and has established a "bureaucracy busting" mission that has much to deliver.[11] Ensuring that indemnity rests with the NHS for all clinical research, and that this is brokered centrally through NIHR in collaboration with its regional networks, would be one major advance.

But the problems do not end there. As a result of the European legislation in 2001, all clinical trials conducted in the UK also require separate approval by the MHRA. The process is far from efficient. The application is difficult to complete, cannot be submitted online, and is sometimes lost by the MHRA. As our case studies highlight, the process adds long delay for no perceived benefit, particularly when approval is sought for an already licensed drug. No improvement in patient safety has been demonstrated as a consequence of the extra tier of bureaucracy for such studies. On the contrary, the MHRA notably failed to prevent the TeGenero disaster at Northwick Park—or even acknowledge its failure.[12] MHRA was primarily instigated to oversee new investigative medical products yet its extended remit is now counterproductive.

Streamlining

We fully endorse the need to ensure that clinical research is conducted to the highest standards. However, the current bureaucracy placed on investigators is poorly coordinated, lacks consistency at all levels, and at times is completely illogical. Those who make and enforce the rules often seem detached from the reality of clinical research and act as though they are protecting patients from rapacious researchers. Contrary to the enforced untruth of patient information sheets that "Your decision whether to take part will not influence your care," participants in research studies self evidently receive much more than routine attention, are often more likely to reach treatment targets, and can have unsuspected, major disease diagnosed by screening tests.[13]

What can be done? We suggest a four point plan (box). Firstly, a protocol is a protocol and should not need to be presented differently to every research funding and governance organisation. A single web based form is required: why does the supposedly "integrated research application system" require a separate paper application to the MHRA? Secondly, indemnity for patients participating in research should be brokered by NIHR irrespective of who employs the investigator. Thirdly, the ethical review process needs to change from a postcode lottery to a slick and (in most cases) predictable formality. Automatic grading of applications (from the information provided) will make patient safety self evident. Committees should be limited to determining whether the research and its description are ethical, honest, and comprehensible. The national research ethics committee website should publish individual committees' productivity and time to approval, with rankings according to the number of approvals that lead to published studies and improvements in medical practice.

Finally, the MHRA needs to concentrate on core activity and adopt the lightest of touches when asked about studies of old drugs. First dose studies of novel compounds in healthy volunteers are different from the majority of experimental and clinical trials. In a single protocol web based system, EU law could be met by notifying the MHRA of a protocol number and leaving local research and development departments to decide when they need more detailed advice. There should be one seamless department for each trust and university, led by a researcher with experience of designing and publishing clinical trials.

Increasing bureaucracy . . . is now the biggest single threat to the UK clinical research base

All major funders, including the NIHR, MRC, Wellcome Trust and other charities, now place the highest priority on the translation of science into medicines.[14] If their lofty ideals and generous funding are to be translated into productive research, the regulatory burden must be simplified and be seen to support clinical research rather than close it down. In a risk-benefit arena that is now heavily stacked towards perceived risk, the instigators of over-regulation must bear responsibility for the real and emerging risks of a failure to deliver the potential lifesaving benefits of clinical research promptly.[15]

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