



Impact of EU Directive 2001/20/EC on investigator-led clinical trials in the UK

Professor Morris J Brown, MA, MSc, MD, FRCP, FAHA, FMedSci

Patient welfare has benefited enormously from clinical trials. The UK, as one of the world leaders in research, has been suffering due to well-intentioned legislation yet oppressive implementation. The results have been delays, denials, and expenses for otherwise meritorious research initiatives.

The EU Clinical Trials Directive 2001/20/EC, which was accepted by the European Parliament 1 April 2004 and came into force across the EU a month later, concerns the implementation of Good Clinical Practice (GCP) in the conduct of all clinical trials in humans, including those with medicines (investigational medical products, IMPs) [1]. According to the Directive, “Good clinical practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.” In October 2005 the EC promulgated detailed guidance for applications for clinical trials [2]. Additional guidance on recommendations for inspection of GCP at trial sites, monitoring, and pharmacovigilance have also been published by the EC in recent years [2]. While the goals of these regulations have been the protection of the rights, safety, and well-being of patients who participate in clinical trials, compliance with these rules by investigators has entailed a huge burden, including a confusing welter of delays, significant increased expenses, and obstacles to the initiation and conduct of clinical trials.

This article explores the negative consequences of the Directive published in 2004, particularly with regard to the way it has been implemented in the UK.

Effects of the rules on clinical research in the UK

While the intention of Directive 2001/

20/EC by its legislators was to protect the rights and safety of patients participating in trials, its implementation in the UK has had the opposite effect. By forcing investigators to comply with a confusing and lengthy set of rules for setting up a trial, and being subject to the decisions of administrators who may not have a full or valid understanding of the virtues of the proposed research, the result has been damaging to patients, investigators, academic trainees’ careers, and the economy as a whole.

In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) implements the EU Directive and provides guidance as to what is an IMP and what constitutes a clinical trial. All clinical trials require a sponsor, a EudraCT number uniquely identifying the trial, and a protocol that includes the information listed in the guideline for GCP. The MHRA must authorise the trial and it must also be approved by the Research Ethics Committee and the National Health Services’ R & D department. The Chief Investigator of the trial is required to provide annual progress reports to all these bodies during the course of the trial. During all these steps numerous rules must be complied with, adjudicated by officials who may have little experience or understanding of the ins-and-outs of clinical research, thus offering the potential for delays or even outright refusal of an otherwise meritorious clinical investigation.

Consequently, clinical research is now governed by parties who may never have

conducted a clinical trial themselves, have no direct contact with patients, and may not have a full understanding or appreciation of the conduct of research. Clinical research has beneficial effects on patients worldwide, reducing morbidity and mortality while contributing to the advancement of science. In the UK, clinical trials contributed significantly to the economy through its effect on the pharmaceutical industry which has benefited greatly from its effects. All this is now under threat, at the very time when largesse and enthusiasm for clinical translational research has been at an all-time high, and the UK depends more than ever on a thriving pharmaceutical industry [3, 4].

Such a threat is particularly concerning given that clinical trials also directly benefit the patients themselves who participate in a trial. The existence of the protocol, a plan that states in advance who is to receive what treatment and how, affords clinical research advantages to patients that are not present to them were they to simply walk into a doctor’s office and seek treatment. Numerous exclusion criteria, diagnostic checks, and scrupulous attention to detail help determine the suitability of a patient for a trial and consequently the medication and concomitant care they are to receive. For these and other reasons research carries with it a high benefit–risk ratio that unfortunately the MHRA, Ethics Committees, and R & D may fail to appreciate with their allegiance to procedure, the filling out of

What may be necessary is an expert legal opinion of what exactly are the minimum requirements of the 2004 regulations.

forms, and administrative compliance matters extrinsic to the merits of the research. At the heart of research governance is the assessment of benefit–risk, and it is hard for those lacking expert knowledge to determine whether a proposed piece of research will be beneficial or safe. Whenever offered participation in a research study, patients are effectively offered a choice between research and everyday medicine. What the ‘transparent and honest’ information sheets are not allowed to tell participants is that research is the safer option (no unexpected deaths in the UK in the last 30 years), and often likely to improve the quality of health care worldwide. This stems partly from all the extra care and monitoring intrinsic to a study. Examples of drugs that have failed after faring worse than control in long-term studies do not undermine the argument that over-regulation is bound to increase overall risk–benefit. In part this is because patients on the ‘worse’ treatment, even placebo, may fare better than patients outside trials. Regulators need reminding that the securest way to reduce risk in trials is to close them down altogether: no trials, no risk – but no benefit.

Countless hours have been wasted filling out forms and entering data into databases to conform to the regulatory submission procedures. In fact, the time spent in EU countries to get authorisation exceeds that spent in non-EU countries. Since the 2004 the costs associated with preparing for a clinical trial increased substantially. Not surprisingly, clinical trial recruitment since 2004 has dropped precipitously.

Difficulties in meeting compliance

The decline in clinical research may in

part be due to reluctance of investigators to engage in clinical research given the current regulatory environment, but also the difficulties and delays they encounter upon submitting applications for new trials. Obstacles now present include the inefficiencies and perils of parallel and serial applications for approval, as well as the risks of overbearing inspections by the MHRA. Even MHRA leaders privately admit that inspectors can be overzealous, and acknowledge that the recommendations of the International Conference on Harmonisation Good Clinical Practice are simply recommendations, and are not mandatory. Yet this does little to allay the rampant oversight of inspectors as they monitor and assess under-resourced R & D departments. Because they hold the power to close down a investigator’s research, the use of these threats allow them to introduce demands that take time to comply with and may end up closing down the research anyway. The current situation has been attested to by numerous researchers, myself included, from ongoing experience where current regulation will have delayed projects by at least one year – for no conceivable gain, but at immense financial and human loss.

While the EU Directive may be to blame, that only captures part of the story. Updates to the Directive are not the problem either. These updates include changes in 2009 to the clinical trials application form. The 2004 regulations asks the Secretary of State to appoint committees who will consider 13 points [1]. With the exception of patient information and indemnity all other points are much better considered during expert peer review. Indemnity should be as standard as for any routine NHS care, and taken for granted for any

NHS research. One of the 13 points, paragraph (g), concerns “the adequacy and completeness of the written information to be given, and the procedure to be followed, for the purpose of obtaining informed consent to the subjects’ participation in the trial”. Does this really require six (or more) detailed pages of information, a step that is often the main excuse for delaying decisions? As for the MHRA, the regulations require documents to be submitted (to the national competent authority) that largely duplicate those submitted to the Research Ethics Committee, with the addition of information about IMPs. This duplication has been partially alleviated by introduction of the Integrated Research Application Service. However, even experienced researchers are continually tripped up, and delayed, by differences in procedure between agencies, the inability of any to receive online submissions, and failure to communicate with each other. Worst of all are the local R & D departments in the UK. Ethics Committee and MHRA more or less stick to their timelines (less, because their clocks may only start months after submission when the committee has a space, and all the irrelevant small print on the forms has been complied with). R & D has no timelines or agreed procedures, taking months to complete a tick-box exercise that has no bearing on the quality of research being undertaken. Scotland has an extra tier of national R & D, which delays local R & D from starting their approval process until they have finished – an inefficient process which is supposed to communicate seamlessly with the UK R & D process but in reality can be delayed for months while individual documents are mislaid, found, re-sent, etc.

Thus, it is not the rationale of the EU Directive that is causing trouble, but rather the anxiety borne from dealing with officials who have to implement/inspect compliance. Because the EU Directive and subsequent regulation leave room for interpretation an inex-

perienced official may be more interested in protecting themselves than doing what is in the interest of the investigator's trial and ultimately the patient.

The MHRA also requires information about certification of a manufacturing pharmacy, e.g. doing the re-encapsulation. Since the MHRA will have granted the certification in the first place, and there are few such pharmacies in the NHS, a single drop-down field should replace the delays and paper required to satisfy current demands. It is pleasing to report that behind the unsigned letters which MHRA sends out, it is with persistence possible to find some individuals who are anxious to help, and every application brings the hope that the next one will be easier. The real tragedy however is not the months, indeed years, that people like me wait before a low-risk piece of research can be started but the complete turn-off to aspiring clinical academics, who never make it to first base. Why propose a research project that might not start until the third year of a three-year grant, when a laboratory project can start the day after a grant is awarded?

Potential solution

The problems facing clinical research in the UK should be met with an open review of current regulation, undertaken by a body representing all those funding, practising, and benefiting from clinical research. The Office for Strategic Co-ordination of Health Research (OSCHR) in the UK seems an obvious choice [5]. The aim of the review should be to consider the model of The Netherlands and devise a way, compatible with the 2004 regulations, in which investigators of clinical trials can start recruitment within at most three months of the grant decision.

To fix the shortcomings of the 2004 regulations, the OSCHR would do well to eliminate all non-mandatory provisions present in the regulations. They should create a situation that empowers the NHS and universities to develop and implement their own methods for indemnifying and sponsoring licensed clinical

investigators. In 2004, Lord Warner as Minister of Health told the Academy of Medical Sciences that the new legislation "does not change the underlying liabilities in clinical trials. NHS indemnity for clinical negligence continues as it did before 1 May [2004]. A big safety net for clinical researchers" [6].

What may be necessary is an expert legal opinion of what exactly are the minimum requirements of the 2004 regulations and any other relevant legislation, and how best judicial review could be mounted if any of the bodies continue to obstruct research. With patient health as the ultimate judge of the effectiveness of any regulation, we cannot afford to lose any more time in the conduct of clinical trials and must reform the system now.

Clinical research: The Netherlands model

In The Netherlands, as in other countries, clinical research needs the approval of a competent authority—here the Central Committee on Research Involving Human Subjects (CCMO). However, the evaluation of all material takes place by a number of ethical review boards in (academic) hospitals, who are in a legal sense fully independent, but work under the umbrella of the CCMO. This implies that for most studies (advanced therapies and research with children excluded) both technical, e.g. product information, and ethical review takes place at a hospital site by committee members whose prime jobs are research and patient care. For a multicentre trial only one IRB evaluates and reports. The submission system is fully electronic.

It is a one-stop shop, run by scientists and not by civil servants, and the CCMO trial database is complete and public. In addition, patients are covered by a national no-fault insurance scheme.

For more information, see: <http://www.ccmo-online.nl/main.asp?pid=1&taal=1>

This article was based in part on the article of Brown MJ. The impact of clinical trials legislation on clinical pharmacology: problems and solutions. Br J Clin Pharmacol. 2009;67(5): 487-93.

Author

Professor Morris J Brown, MA, MSc, MD, FRCP, FAHA, FMedSci
Clinical Pharmacology Unit
University of Cambridge
Addenbrookes Hospital for Clinical Investigation (ACCI)
Cambridge, CB2 2QQ, UK
Tel: +44 12 2333 6743
Fax: +44 12 2376 2576
morris.brown@cai.cam.ac.uk

References

1. The Medicines for Human Use (Clinical Trials) Regulations 2004. [cited 2009 September 21]. Available from: <http://www.opsi.gov.uk/si/si2004/20041031.htm>
2. European Commission website. Available from: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm
3. Cookson C. £1bn for new health research body. Financial Times 2006; 6 Dec. [cited 2009 September 21]. Available from: http://www.ft.com/cms/s/0/467338c8-8538-11db-b12c-0000779e2340.dwp_uuid=4d1501ce-6a81-11db-83d9-0000779e2340.html
4. Jack A. Big drugs companies shift trials overseas. Financial Times 26 June 2008. [cited 2009 September 21]. Available from: <http://www.ft.com/cms/s/0/0c102bce-4318-11dd-81d0-0000779fd2ac.html>
5. The Office for Strategic Co-ordination of Health Research (OSCHR). Background on the Review of Health Research in the UK and OSCHR. 2008. [cited 2009 September 21]. Available from: http://www.nihr.ac.uk/about/Pages/about_oschr.aspx
6. Speech by Lord Warner, Parliamentary Under-Secretary of State in the Lords, 29 June 2004: Academy of Medical Sciences - New Fellows Admission Ceremony. [cited 2009 September 21]. Available from: http://www.dh.gov.uk/en/News/Speeches/Speecheslist/DH_4085207