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Academic clinical trials – exaggerated reports of their death

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Modern medical practice calls for an evidence-based approach. The best medicine is, therefore, built on a foundation of the best evidence. The best evidence, in turn, comes from the best research. When it comes to the use of drug therapy this is provided by the most scientifically robust and ethically sound clinical trials.

The history of clinical trials has clearly shown us that while they are essential for the progress of medical practice; their conduct may also be harmful to participants.[1] A lack of ethical conduct and failure to uphold basic human rights have prompted the introduction of several codes of practice to guide and constrain the activities of investigators. Our patients require protection and never more so than in the context of clinical research.

Quality standards and legislation

To ensure the overall quality of clinical trials of medicinal products the pharmaceutical industry spearheaded, in January 1997, the use of a set of quality standards known as Good Clinical Practice (GCP).[2] In 2001, the European Union (EU) used this approach as the basis for a new draft Directive on Clinical Trials, which would extend the coverage of GCP to include all clinical trials of investigational medicinal products in humans, irrespective of their funding and support.[3] For the first time there would be a legal framework for the conduct of clinical trials across Europe and in the UK in accordance with the principles of GCP.

On 1 May 2004, the European Clinical Trials Directive (ECTD) (2001/20/EC) was transposed into UK legislation in the form of the Medicines for Human Use (Clinical Trials) Regulations.[4] Its aims were clear: to simplify and harmonise the regulatory approach to clinical trials conducted across the EU, and to ensure the health and safety of participants, ethical soundness and the reliability of data generated from a trial.[5] Ultimately, it was hoped that this legislation would improve the quality of clinical research and create an even playing field for investigators throughout Europe.

European response to the Directive

However, despite its good intentions, many feel that the ECTD has had a negative impact on academic research.[6] The Directive, which was subsequently interpreted and implemented by each of the EU member states, carries extensive regulatory procedures, and many investigators feel that it imposes an excessive bureaucratic burden upon them.[6]

The approach used by the drafters of this legislation has been criticised as a one-size-fits-all strategy.[7] The Directive identifies minimum standards for all clinical research without taking into account the risk or financial backing of a trial. Consequently, academic researchers involved in the study of well-established drugs, used commonly in daily clinical practice, must adhere to the same stringent regulations as large pharmaceutical companies investigating the potential of a novel therapy. Many researchers feel that, in some cases, the risk to the trial participants does not always justify the financial and regulatory burdens imposed upon them by the Directive.

Furthermore, many have suggested that the prime objective of the Directive, which was to create a harmonised approach to the regulation of clinical trials across the EU, has been unsuccessful because of the variation in its interpretation in different member states.[8,9]

UK response to the Directive

Although the legislation has a pan-European dimension, 75% of clinical trials are conducted in a

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single member state.[10] What then has been the impact on clinical trials based in the UK?

The Medicines for Human Use legislation in the UK is relatively vague. For example, the definitions of an interventional versus a non-interventional clinical trial are open to different interpretations and the definition of an investigational medicinal product is unclear.[5]

The management of the implementation of the legislation since 2004 in the UK has also been imperfect. When the Directive was translated into UK law in the spring of that year, there were limited resources available to support investigators. Many were unaware of the important changes that had taken place and the opportunities for GCP training were limited.[11] It was not until a year later, with the publication of the EU Directive on GCP,[12] that investigators received confirmation of the form of GCP they were to follow. Further amendments to the legislation in 2008[13] and 2009[14] have been necessary to provide further clarification, but many investigators still report that they are ill-equipped to put the legislation into practice.[15]

The academic community in the UK has been fierce in its criticism of the ECTD and the Medicines for Human Use legislation.[6] This is based on a strong conviction that the legislation has been singularly responsible for the perceived reduction in clinical trial activity, but is this true?

Trends in research activity across Europe and in the UK

When data are compared pre- and post-implementation of the ECTD, a number of interesting points emerge. The European Forum for Good Clinical Practice (EFGCP) recently conducted a Europe-wide survey of the impact on clinical research of European legislation.[9] The EFGCP compared data which predated the implementation of the ECTD with that in the three years following it. Between 2003 and 2007 the number of commercially sponsored clinical trial authorisations (CTAs) submitted and the number of such trials conducted actually increased by 11% and 30%, respectively. In contrast, the number of applications from academic trialists remained unchanged, but the number of trials actually conducted decreased by approximately 25%. However, the EFGCP noted that while some countries experienced dramatic decreases in non-commercial CTA applications, others showed an increase. Also, not all countries report a decline attributable to the implementation of the ECTD. In Denmark, although both academic and commercial clinical trials were on the decline between 1993 and 2006, there was no noticeable change after 2004.[16]

The European Organization for Research and Treatment of Cancer recently analysed the effect of the Directive on European cancer clinical trials.[8] The number of new trials fell by 63% between 2004 and 2005. Similarly, there have been claims that academic clinical trials have fallen by 75% in Finland, 70% in Ireland, 25% in Sweden[17] and 66% in Austria.[18]

Perhaps the most robust UK data come from our competent authority, the Medicines and Healthcare Products Regulatory Agency (MHRA) and the National Research Ethics Service (NRES). The MHRA data on the number of CTA applications show a fairly flat response between 2000/01 (1,144 applications) and 2008/09 (1,173) with a dip in 2004/05 (818), which recovers the following year.[19,20] Similarly, the NRES data for England show no marked trend in ethics applications for clinical trials of an investigational medicinal product (CTIMPs) between 2005/06 (1,059 applications) and 2007/08 (1,033).[21] When the overall numbers of ethics applications are compared before and after 2004 there is an apparent 30% fall. However, this must be interpreted in the light of changes to the ethics service, which resulted in fewer duplicate applications to multiple ethics committees.[21]

Overall, the quality of all these data are difficult to assess for a number of reasons:

1. The current definition of a CTIMP was not used prior to 2004 and even in the early years post 2004 it was variably interpreted. This means that making comparisons of figures across different years is fraught with difficulty.
2. In many published reports, e.g. those of the MHRA and NRES, clinical trial data are not broken down into commercial and academic studies. It is, therefore, impossible to discern if there has been a difference in the trends for each type of study.
3. In 2003, in preparation for the introduction of the new legislation, many investigators pushed forward with their applications in an attempt to avoid the increased complexity they perceived would result from the implementation of the Directive. This means that 2003 figures may be unusually high and, if used as a baseline to calculate changes, may result in inflated differences.
4. Most studies that have reviewed this issue have not taken into account other confounders that may have had a significant impact on the set-up and conduct of new clinical trials.
5. Equally, most studies have also failed to take into account pre-existing trends in the numbers of clinical trials prior to 2003.

Confounding factors

While the implementation of the ECTD may account for a portion of the alleged change observed in the pattern of clinical trial conduct in the UK, it is certainly not the only potential culprit. At, or about the same time, five major changes took place in the clinical research landscape. These may have had a potentially detrimental effect on research activity, but were quite distinct from the ECTD.

First, the introduction of the National Health Service (NHS) Research Governance Framework in 2001 presented a set of guidelines for the conduct of clinical research, including clinical trials, in the NHS.[22] Adherence to the principles of GCP were promoted, but not legally enforced, by this document.

Second, the Research Ethics Service in the UK underwent extensive re-organisation in 1997 and in 2004.[23] This restructuring, while ultimately of benefit to investigators, did, undoubtedly, create periods of relative confusion.

Third, in 2003, the new Consultant Contract was introduced in the UK, which affected the available time for clinical research.[24]

Fourth, a variety of changes in the patterns of medical training in the UK have, for many junior medical staff, resulted in changed priorities given to clinical research and fewer opportunities to conduct research as part of their career paths.

Finally, although the majority of concern rests with changes in the pattern of academic research, the numbers of commercially sponsored clinical trials are also changing as a result of shifts away from the UK and Western Europe to Eastern Europe and the Far East.[25]

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Pharmaceutical companies are responding to increased costs, and perhaps increased levels of regulation in the UK, by turning to alternative host nations. A fall in commercially sponsored clinical trials may have a knock-on effect on academic research as it reduces the number of training opportunities for junior researchers.

The future

The ECTD, and the UK legislation that flows from it, are dynamic documents under review and subject to change. Already the Medicines for Human Use legislation in the UK has been amended three times and a major review of the Directive is currently underway. In preparation for this a consultation process has just been completed to collect and collate the opinions of stakeholders.[5] A number of options are on the table. Repeal of the legislation is one (unlikely) option, while a major overhaul or redrafting of the law as a European Regulation rather than a Directive may be possibilities. The latter would force all member EU states to adopt a common piece of legislation unaltered by national influences. While this may satisfy the original aim of the Directive, of harmonising the approach across Europe, the imposition of such a European law may not be welcome in every member state, including the UK.

Conclusions

Without the regulation of clinical trials, patient safety is not assured. History has shown us that, at times, vulnerable subjects can be put at risk in the name of science. With clinical trials being conducted throughout Europe in accordance with national regulations, the ECTD was conceived in a bid to ensure that patient safety is the primary concern of investigators across the board. Despite this, many feel that the administrative and financial burdens imposed upon researchers by the Directive discourages investigators from participating in research and could have a subsequent effect on the development of novel therapies vital in the fight against disease. Fundamentally, the Directive has failed to meet its primary aim of harmonising regulation throughout the EU. Vague directions and definitions mean that the Directive has been adopted with slight, but significant, legislative differences by individual member states across the EU. Further guidelines should be more explicit and member states should be supported in their implementation to help achieve this goal in the future.

Finally, in spite of the concern raised by academic researchers, there is little hard evidence to support the notion that academic clinical trials are in marked decline. Indeed, in some studies no change has been reported, but this has been attributed to the provision of an adequate infrastructure to support academics through the regulatory process. In the UK, we already have a network of clinical research facilities, which, through their concentration of expertise, experience of GCP and the regulatory environment, and through the provision of dedicated space and equipment, can greatly ease the difficulties experienced by investigators and appease fears that tight regulatory control could bring an end to academic clinical research in the UK

Conflict of interest

None declared.

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