
Editorial: Are clinical trial authorisations truly being harmonised?

As is stated by Graeme Ladds in his paper in this issue, 'the aim of the EU [European Union] Clinical Trials Directive was to unify the various processes for conduct of clinical trials in Europe.' He concludes that, 'National implementation of the Directive relies on all member states *only* implementing what is in the Directive and not adding on top additional national requirements.' Without such restraint at the member state level, 'all the Directive will do is set a minimum standard for all member states to achieve and not the consistency it was intended' to accomplish.

Pharmaceutical companies operate on a global level and need global approaches to clinical trials. Instead, pharmaceutical companies face heavy and ever-changing regulatory burdens from the variant clinical trial requirements around the world. More than a decade of effort by the International Conference for the Harmonization of the Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) has aimed at reducing disparities in good clinical practices (GCPs) for clinical trials.¹ The EU Clinical Trial Directive,² which became operational on 1st May, 2004, represents an improvement over the completely unharmonised national laws it replaced. However, disparate implementation at the member state level could prevent it from fulfilling its original promise.

As Ladds notes, another difficulty is that many EU member states have been late implementing the Directive. To complicate matters still further, on 1st July, 2004, the European Commission published a draft Directive specifying detailed requirements for GCP for clinical trials of medicinal products for human use. This new draft in some respects merely restates what has already been required, but it also adds details on a range of topics and bows to concerns from universities and other sponsors of 'non-commercial research' by empowering member states to grant them more flexibility in non-commercial trials. This latest draft law no doubt has laudable purposes, but it joins a long list of recent medicinal products initiatives that must be taken on board, including burgeoning clinical trial-implementing laws, regulations, guidelines and forms *and* the new pharmaceutical regulations published on 30th April, 2004. These included a new version of the EU Regulation on the European Medicines Agency (EMA), replacing the Regulation 2309/93,³ along with an amendment to Directive 2001/83/EC, the Community code for medicinal products for human use.⁴

Regulatory affairs officials in companies give mixed reviews to the EU Clinical Trials Directive. Some believe it enhances harmonisation while others are dismayed by the continued national disparities. It should be noted that the Directive did not introduce mutual recognition of approval of clinical trials among EU member states, so applications must be filed in multiple countries, in the case of a multi-centre trial, where more than one EU country is involved.

My own view of the Directive is that it represents two steps forward, one step back. It is progress, but not enough, and it now stands as a symbol of a missed opportunity to do more. The choice of an EU regulation, rather than an EU directive, would be a major advance that would more effectively achieve harmonisation, patient safety, and EU

competitiveness than any EU directive ever could. However, an EU regulation can be used if, and only if, the member states permit its use for clinical trials.

Already the sheer heterogeneity of member state implementation and other costs associated with EU trials – including the general difficulty in affluent countries of enrolling patients – has reportedly already driven certain clinical research out of the EU. Such a trend should be worrisome to those concerned about EU patients' access to the latest therapies, as well as EU competitiveness. Clinical trial activity has increased in non-EU European nations such as Russia and Ukraine, as well as in countries in the Americas and Asia viewed as friendly to clinical trials.

Even large-company sponsors with the best legal counsel and regulatory affairs professionals to decipher their way through the morass of EU regulation may find it impractical to conduct the EU component of a 'global clinical trial' under a Food and Drug Administration (FDA) Notice of Claimed Exemption for an Investigational New Drug (IND). Quite simply, the combination of the application of EU and FDA requirements may result in more complexity than any one clinical trial can accommodate. Sponsors may run the EU study as a non-IND study, striving in its dealings with ethics committees and EU regulators to maintain a protocol similar to that in its IND study, so that FDA and European Medical Association (EMA) (or EU member state) reviewers are willing to allow data pooling and meta-analysis to show clinically significant efficacy.

WHAT CAN BE DONE?

An EU Community Code Regulation on clinical trials

If the necessary political will can be found among the member states, the EU lawmakers could use a 'regulation' rather than a 'directive' to enact a Community Code *Regulation* on clinical trials. The Regulation could pull into one text the current Directive, the new amendments, the ICH GCPs, and the best practices from member state legislation. Much of the continuing divergence among EU member states in implementing the Directive stems from the form of EU legislation used, ie it is a 'directive'. While an EU 'regulation' is a self-executing form of legislation that speaks directly to private parties such as drug companies operating in the EU, as well as to the EU member states, the 'Directive' has as its target audience the member states themselves. In response to a directive, each EU member state must take the necessary steps to adopt the requirements imposed by the directive, but it enjoys considerable latitude. A related and also achievable objective would be to reflect any local variations (eg in clinical trial liability arrangements at the national level) in Annexes to the Community Code Regulation on Clinical Trials.

Apparently some believe that clinical trials represent a peculiarly local issue in which national culture, laws and norms come into play. Such a view is, in my opinion, easily challenged. After all, for more than a half century the Declaration of Helsinki has stood as an international norm for clinical trials, and the recent arrival of the ICH GCP fills in the details. Since 1962 the FDA has had just a single IND regulation for a diverse country with a population now exceeding 293 million. In any case, it is through the Ethics Committee that local values should be applied, eg a clinical trial site's committee could decline to participate in a multi-centre trial, not through disparate regulatory rules.

Indeed, it is difficult to see what national differences require the EU to have 25 investigational drug product regulations for its 455 million people. Indeed, the 25 laws are similar in many respects, but the process of locating, reading and digesting each is laborious and wasteful, and inevitably there are local idiosyncrasies, eg on clinical trial insurance, that must be tracked and met.

EU privacy laws, also called 'data protection' laws, likewise impede achievement of the legislative goals for the Clinical Trials Directive. Here again, the use of a 'directive'

to deal with personal privacy resulted in divergent national laws that, in the case of clinical trials, add nothing in terms of patient protection and harmonisation. The Clinical Trials Directive, its guidance, and the 25 member state laws are perceived as impenetrable by some – and further confusion is added by the need to meet the EU ‘Data Protection’ Privacy Directive, *its* guidance and *its* 25 member state laws.

Ideally, the future Community Code Regulation on Clinical Trials would include all provisions necessary for adequate protection of personal privacy in this field as well as an amendment to the EU Privacy Directive exempting such trials from the Privacy Directive and all member state implementing legislation on personal ‘data protection’. This would be appropriate since the clinical trial legislation already being put in place includes adequate safeguards of the privacy of clinical trial subjects, and was also written in cognisance of the necessity of international movement of clinical trial data to permit regulatory filings and to avoid undue repetition of clinical trials, consistent with ICH objectives. Thus, the Community Code Regulation on Clinical Trials would represent truly comprehensive and self-contained legislation.

We need to keep in mind that, for clinical trials and privacy, it is not simply 25 laws that need to be found and met but more like 33: in addition to the EU 25, we have the European Economic Area partners (Iceland, Liechtenstein and Norway), Switzerland, and future possible accession candidates (Bulgaria, Croatia, Romania and Turkey).

Better use of the internet

National drug regulatory bodies do not consistently post on their websites all requirements, guidance documents and forms. Lack of transparency undermines compliance with clinical trial requirements. The resulting cost and delay hurt patients awaiting new therapies. Regulators should make compliance easy. No interest is served by making it difficult to find the law that one is supposed to obey. Including English translations of documents would also significantly aid compliance, not only by those in English-speaking countries but also by the hosts of people who speak English as a second language.

Restraint in adding member state requirements

Steps taken today at the member state level will determine whether the Directive is successful. Will the member states allow applications for ethics committee review, and will they themselves accept clinical trial applications that have been prepared in accordance with EU-level guidelines?⁵ While a number of member state agencies, including the UK Medicines and Healthcare Products Regulatory Agency (MHRA),⁶ have stepped forward with helpful guidance to promote compliance with national laws implementing the Directive, this kind of assistance will be useful only if it supports use of the EU guidance for format and content of ethics committee, and competent authority, applications that may be filed in all member states. One-off guidance for a single national authority is less helpful.

Web-based clinical authorisations

ICH should spearhead web-based clinical trial authorisations. Sponsors could upload to a secure website the relevant documents such as the clinical investigator’s brochure, the clinical trial agreement, the protocol, the application for the ethics committee and the regulatory application – and with a few keystrokes grant access to the appropriate documents to newly enrolled investigators, ethics committees and regulatory bodies. Cost-recovery user fees could at the same time be paid to ethics committees’ and agencies’ official accounts. The impediments to this web-based and completely harmonised approach are not technological, and the legal hurdles can be overcome. This approach is very much within reach if – and this is a very big if – there is the will to

move in this direction. Many drug companies and clinical research organisations are already using internal websites to manage their clinical trial development activities. Also, various ICH initiatives relating to encryption and standards for electronic transmission of regulatory information are the building blocks for future web-based submissions.

The 1st July draft Directive as a draft regulation?

The international product development community affected by the current Tower of Babel of clinical trial requirements – the industry, clinical research organisations, the researchers, their institutions, ethics committees, and first and foremost the patients – need to insist that their governments commit to global clinical trial approaches. The pharmaceutical industry and others who care about both patients' health and the EU's economic health could seek to persuade the EU authorities, and particularly the member state authorities, that the new 1st July draft Directive on GCPs ought to be transformed into a draft regulation. In that way, regulators, drug companies around the world, and others will be spared the task of multiplying by 25 (or 33) the number of national laws that might be required to implement its provisions.

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References

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6. See the summary at URLs: <http://www.mca.gov.uk/ourwork/licensingmeds/types/clintrialdir.htm>, <http://www.mca.gov.uk/ourwork/licensingmeds/types/revisedbrief.pdf> and <http://www.corec.org.uk/PDF/Guidance%20for%20applicants%20to%20RECs.pdf>