The EU Clinical Trials Regulation: one step forward, two steps back?

The new EU Clinical Trials Regulation has had a largely positive reception, but it leaves a lot of questions unanswered. Indeed, argues John Lisman, in some important areas it fails to improve on the legislation it is replacing.

The EU Clinical Trials Regulation was adopted on 16 April this year and entered into force on 16 June. The practical consequences of the new legislation will not become apparent for the next few years, as the use of the regulation depends on a comprehensive IT system to be built by the European Medicines Agency.

This CTR is above all a reaction to the weaknesses that were perceived in the functioning of the Clinical Trials Directive which it replaces. In conferences, on websites and in journals a lot of enthusiasm is being expressed about the new regulation. Personally, I have my doubts.

Of course it is great that the nature of the procedure will be much more European, including a modern IT platform. The fact that politicians have been able to find common ground in respect of transparency in respect of clinical trial results must be welcomed. The question is, however, whether the main problem — differences in handling procedures between member states — is actually solved with this new legislation. Will the new legislation boost pharmaceutical innovation in the EU?

After the adoption of the Clinical Trials Directive in 2001, EU member states had to implement the directive — that is, they had to adapt national legislation to the rules set out by the directive. In this process the member states took different approaches in respect of selection of the decision making bodies — medicinal ethical committees and competent authorities — and the way these authorities interact in the case of a decision for a specific clinical trial. This means that one company aiming at initiating one clinical trial with sites in different member states has to follow national, specific procedures in all the concerned member states. Each member state required — slightly — different information in its own specific format. Moreover, in many member states a site-specific approval was introduced, leading to an additional procedure that has to be completed before the trial can be initiated.

As a consequence, in the case of multicentre, multi-state trials a lot of red tape exists. Even worse is the fact that even though member states have implemented the decision terms into their national legislations, many authorities do not comply with these and take their decisions in an untimely manner. It is therefore very difficult for companies to plan a clinical trial accurately and to predict when clinical trials can be initiated. The CTD clearly did not bring industry what it had hoped for and expected.

From the side of academic researchers there has also been a fair amount of criticism with respect of the outcomes of the CTD. First of all the requirements with respect to the investigational medicinal product (IMP) dossier has been a cause for concern: it is often difficult for academic researchers to meet these requirements, even though the CTD allows that commercially available medicinal products are used with the involvement of a (hospital-) pharmacist without restrictions.

There was a general feeling that one of the reasons for the decline of clinical research in the EU was the bad functioning of the CTD.

Arriving at the Clinical Trials Regulation

The European Commission set out to evaluate the Clinical Trials Directive itself as well as how it had been implemented by the member states. It announced in December 2008 that an assessment would take place and in October 2009 the assessment was published as a public consultation. The responses and a summary of these were published on the commission website in March 2010, and a second public consultation document was issued, in February 2011. Many companies and individuals responded to the second consultation and again the responses and a summary thereof were published on the commission website.

In this second consultation document, the following “Key issues” were mentioned:

- multiple and divergent assessments of clinical trials;
- inconsistent implementation of the Clinical Trials Directive;
- regulatory framework not always adapted to the practical requirements;
- adaptation to peculiarities in trial participants and trial design; and
- ensuring compliance with good clinical practice (GCP) in trials conducted in third countries.

From the results of the consultations, it appears that many respondents were of the opinion that in practice, divergent decisions are taken in different member states. This is not only true for competent authorities but also for ethics committees. The result is that one multinational clinical trial will end up having different national “flavors” and, in doing so, there is a danger that the consistency of the protocol becomes lost.

An often-mentioned desire is streamlining the authorization procedure. Options are a mutual recognition of other authorities’ authorization or a central EU procedure. These procedures should be optional for the sponsor. As for ethics committees, suggestions have been made to strengthen the network of these bodies. Furthermore, suggestions have been made to clarify the scope of the assessment between the ethics committee and the competent authority and to combine the two decisions in a “one-stop-shop”. The commission was very clear about the proposal for a centralized EU approach: decisions about ethics are not within the remit of the EU and have to remain at the level of the individual member states.

A second point that was raised from different sides is the inconsistent implementation of the CTD. Differences that cause problems are different classification of amendments as “substantial”; the rules for reporting adverse events; the classification of trials as clinical trial or non-interventional study; and the borderline between IMP on non-IMP.

To solve the perceived lack of harmonization the suggestion was made to change the legal context from a directive — a European law that has to be implemented into national legislations to have its legal effect — into a regulation. Regulations bind all natural and legal persons directly, without any national step.

The third issue addressed involves (risk-based) differentiation in requirements. The one-size-fits-all approach is found to be too rigid. In fact, this is also at the basis of the long-heard criticism from academia regarding the heavy regime of the CTD.

The new consultation document that was issued in February 2011 gave an appraisal of all suggestions that had been made in the first consultation round. On the basis of all input received during the evaluation process, the commission adopted and issued a draft regulation. This draft regulation was heavily amended during the legislative procedure.

These amendments mainly concern the role of the ethics committees in the national and European approval procedure for clinical trials and the requirement that the results of all clinical trials should be made assessable for the general public and for the academic world one year after the end of the trial at the latest.
The regulation
The Clinical Trials Regulation was finally adopted, in April this year. The essence of the regulation can be summarized as follows. A clinical trial may be conducted only if the rights, safety and dignity of the trial subjects are protected and prevail over all interests and if the trial is designed in such a way that it will generate reliable and robust data. For each clinical trial prior authorization is required involving a scientific and an ethics review. The ethics review shall be performed by a (national) ethics committee in each concerned member state based on the national legislation, the scientific review is undertaken in a European procedure. The application for a clinical trial authorization is submitted through an EU portal in electronic format. For each application a reporting member state is chosen, the other member states in which the clinical trial will take place are the concerned member states. The reporting member state is responsible for the drafting of Part I of the assessment report, each concerned member states for the national Part II. The topics of the two parts are summarized in Table 1 below.

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<th>Part I of the assessment report</th>
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Part I of the assessment report is drafted by the reporting member state within a timeframe of 45 days counted from the validation date. Part II of the assessment report is drafted by the concerned member states during the same timeframe. Within these 45 days, the ethics committees in all concerned member states, including the reporting member state have to deliver their opinion on both the Part I and the Part II issues. These opinions have to be incorporated in the Part II assessment reports. In the event that the reporting member state is positive, the concerned member states have to accept this opinion unless:
- the subjects would receive an inferior treatment than in normal clinical practice;
- the trial would infringe national legislation, eg in respect of abortion;
- they disagree with the reporting member state in respect of data reliability and robustness of data to be expected.

Furthermore, a concerned member state may refuse to authorize a clinical trial if it finds that the requirements of Part II are not met.

Low-intervention trials
The CTR introduces the so-called low-intervention trial: a trial in which the investigational medicinal product is used in accordance with the approved use in a marketing authorization or the use is evidence-based and in which subjects taking part in the trial are not subject to additional risks and burdens in comparison with normal clinical standards. If a trial meets the criteria for a low-intervention trial, those clinical trials should be subject to less stringent rules as regards monitoring, requirements for the contents of the master file and traceability of investigational medicinal products.

The main problems
With respect to solving the main problems with the CTD, the following changes that the new legislation brings about seem to be the most important: (i) from directive to regulation; (ii) an EU wide procedure with limited room for national deviation; and (iii) the introduction of the low-intervention clinical trial to stimulate non-industry sponsored (academic) research. This sounds great, but will it deliver? Furthermore, the CTR brings a few new issues to the surface: (i) can ethical standards be met; and (ii) problems in respect of legal protection.

Regulation versus directive
There is a general trend, supported by the commission, to change the format of EU legislation from directive to regulation. A directive is directed to the member states; a regulation works directly. This trend is motivated by the idea that in case of a regulation it is completely clear what the rules of law are in all member states and there is no room of deviation by the member states. This was perceived as one of the problems with the CTD: all member states gave their own national interpretation of the provisions. I do not agree with this preference. First of all, the way a member state “implements” the provisions of a directive is under strict scrutiny from different sides. The commission needs to approve national legislation intended to implement a directive. Furthermore, any interested party that does not agree with the national implementation may request a court to take a decision based on the text of the directive if this differs from the national law. In case of a directly binding act such as a regulation, the commission is not involved in the practical use of the provisions.

The problems industry had with the CTD were not caused by the actual provisions in the directive and the way these were implemented into national law, but by the practical operation by the competent authorities in the member states. The authorities did not comply with the rules in their national legislation and the directive. This problem is not addressed by the change from directive to regulation. Furthermore, the commission loses an important instrument if it is no longer able to check and approve national implementing legislation.

Finally, there is another issue that is more of a legal nature. Because the regulation acts directly, its provisions do not require implementation into national legislation, but this is only true for clinical research that falls within the scope of the CTR. This means that member states will have to keep their national legislation for all other clinical research and also keep their national administrative system.

At the end of the day, each EU member state will have two pieces of legislation in different systems to deal with the single issue of clinical research. Furthermore, the CTR – even as a regulation – requires quite a lot of implementation, because of the way it is drafted. In many of its provisions, reference is made to “a member state”, “the member state”, “the concerned Member State”, “the reporting Member State”, the “competent authority” or “the national contact point”, but these references should have been made to a particular agency, committee or other body in that member state.

Therefore, all member states need to adopt legislation that explains which body is implicated in each provision of the CTR where the terms “member state”, “competent authority” or “national contact point” are used. In addition, member states have to ensure that persons that assess the applications are in accordance with the requirements as mentioned in Article 9. This also requires additional legislation. National legislation will...
need to be drafted or revised to clarify which persons may act as legal representative have to draft or amend legislation to clarify participating in a clinical trial, member states obtaining informed consent from those participating in a clinical trial, member states discussing the scientific and ethical principles in respect of the trial subjects, infringement of national law the trial subjects, infringement of national law the trial would lead to inferior treatment of the trial subjects, infringement of national law the trial would lead to inferior treatment of the trial subjects. In respect to monitoring, requirements for the contents of the master file and traceability of investigational medicinal products, the CTR only states that the competent authorities should take the status of low-intervention clinical trial in account when assessing the file.

National measures under the CTR

Another problem caused by the system of the CTR is that there is a lack of clarity for the applicant of an authorization for a clinical trial, but not the national procedure. This means that in 31 countries in Europe – 28 member states plus three EFTA countries participating in the EU systems for medicinal products – national procedures have to be developed to create the input for the European legal framework.

First of all, member states need to establish a system that allows them to adequately assess the draft assessment report from the reporting member state in case the member state is concerned. Even though a concerned member state can only disagree with the assessment made by the reporting member state in case it demonstrates that authorization of the trial would lead to inferior treatment of the trial subjects, infringement of national law or issues relating to trial subjects’ safety or data robustness, a national assessment has to be made in every concerned member state within a period of 38 to 45 days. It seems to me that within this period an evaluation by the nationally involved ethics committee has to take, because otherwise there is no positive opinion of this committee. Each member state will also have to establish an evaluation procedure in respect of Part II of the assessment report. This assessment deals with national and international issues of both a scientific and an ethical nature. Each member state concerned will have to establish a procedure to deliver an assessment within five days from the date the Part I assessment was finalized. An opinion of the nationally involved ethics committee has to be part of the national assessment of the application. This opinion should regard both Part I and Part II of the assessment report.

I would not be surprised if these national procedures turn out to show many differences and also differ in respect of the quality of the output, and that the situation that was found undesirable under the CTD does not improve.

Promotion of academic research/low-intervention clinical trial

Based on the requests of the academic research world, the concept of a low-intervention clinical trial is introduced. Unfortunately, the scope for using this concept is rather limited: a low-intervention clinical trial is only accepted as such in case the IMP is authorized and is used either in accordance with the summary of product characteristics or if the use is evidence-based and the evidence is in the peer reviewed scientific literature. This type of clinical research should be rare, because it would look for scientific data which are already available.

Even more importantly, it seems to me that the CTR itself offers hardly any benefits for low-intervention clinical trials. The only requirement that’s waived in case of a low-intervention clinical trial is the mandatory system of damage compensation for the trial subjects. In respect to monitoring, requirements for the contents of the master file and traceability of investigational medicinal products, the CTR only states that the competent authorities should take the status of low-intervention clinical trial in account when assessing the file.

Ethical standards – compliance with Helsinki Declaration

Of course all clinical research needs to comply with the Helsinki Declaration. This is acknowledged in the CTR, but it remains to be seen if the system it introduces actually allows the appropriate input of ethics committees. First of all, there is the issue of timing: member states have to deliver their opinion within 45 days from the notification of the validation and within this period of time the opinion of the ethics committee has to be given and incorporated. In accordance with the Helsinki Declaration and with the CTR, this opinion should be based on a full evaluation of scientific and ethical principles in respect of the concerned trial.

A second issue regards the monitoring of ongoing studies. From paragraph 23 of the Helsinki Declaration, it follows that it is the task of ethics committees to monitor ongoing studies. The CTR does not offer a mechanism for all concerned ethics committees to be able to do this. More important, ethics committees should be able to withdraw their positive opinion at any time in case the monitoring of the trial shows that the assumptions made before the trial began are not met. The CTR does not provide for a mechanism that allows an ethics committee to monitor, revoke a positive opinion for, or end a clinical trial.

Legal protection under the CTR

Authorization of clinical trials under the CTR takes place in a legal vacuum: there are roles for administrative bodies in the reporting member state and in the concerned member states and their interaction. The regulation does not specify how legal protection of the applicant is implemented.

If the applicant of an authorization for a clinical trial does not agree with the outcome of the process, for example because at the end of the day no authorization is granted or if the member states do not agree that the clinical trial is a low-intervention clinical trial, it is totally unclear how to appeal such a decision. The only guidance in this respect is given in Article 8(4), providing that a member state has to establish an appeal procedure regarding the national conclusion of Part II of the assessment report or the negative opinion of the national ethics committee. What can an applicant do if it is of the opinion that the assessment of the reporting member state is flawed? To which court or judge can it turn? It seems to me that one of the principles of the EU, as well as the human rights legislation applicable in the EU, is that interested parties should always be able to ask a court or judge for its or his decision.

Conclusion

The newly adopted CTR leaves a lot of questions unanswered, for example in respect of the relationship of the EU authorization procedure with the Helsinki Declaration and in respect of legal protection. Taking into account the fact that these legal problems did not occur in the system based on the CTD, the CTR is not an improvement at all.

An even more important consequence of the chosen system is that the CTR is like a car without a motor: at first glance the car looks efficient and powerful, but there is not yet anything under the hood. Each member state must develop its own motor within the specifications the EU has given. The motors, developed in the 31 EU and EFTA member states, will all differ in respect of necessary information, terms for decision making and ways the national ethics committees are involved in the authorization procedure. It is to be expected that these differences will lead to a range of different characteristics. I expect that the harmonization of the practices of the
member states dealing with applications for the authorization of a clinical trial will not improve through the introduction of the CTR, but instead decline. The objectives of the legal review of the CTD would therefore not be met.

The desire of the academic researchers, to be able to conduct clinical research in a less heavily regulated framework than under the CTD, is also not met in the CTR because it offers hardly any advantage in case of a low-intervention clinical trial.

In my opinion the CTR is not an improvement in respect of the promotion of innovation and bringing clinical research back to Europe.

Of course, the CTR addresses other issues which are outside the scope of this article and may be very important from a political viewpoint, for example the stronger focus on transparency. But a solution for the problems that were assumed to be caused by the system of the CTD has not been achieved.

To address these problems, the EU member states are of the essence: it is up to them to work together and deliver their scientific and ethical assessment of high quality in a timely manner. This was also the case under the CTD.

References


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