



EUROFILE

New EU rules for clinical trials: are they right this time?

The European Commission has come up with a new set of rules intended to remove some of the regulatory burdens on clinical trials in the EU, and cut the cost of clinical research. Although the proposal has been welcomed across the board by the cancer community and medical community, concerns persist that some of the changes could further impede clinical cancer research.

The new legislation will eventually replace the much maligned clinical trials directive (2001/20/EC), in effect since 2004. Presenting the draft proposal in Brussels on 17 July 2012, EU commissioner for health and consumer protection, John Dalli, acknowledged the failings of the existing law. "Clinical trials conducted in the EU have declined by 25% in recent years. One factor [responsible] is the current regulatory environment, which has led to high administrative burdens. The staff needed to run a clinical trial has doubled, mostly needed for paperwork, and the insurance costs have increased by 800 per cent," he said. The Commission estimates the associated cost of the regulatory failings at around 800 million Euros a year. The new rules aim to "turn these trends around," he said. "We have to get it right this time."

One of the most prominent reforms involves streamlining the application and assessment procedures for multi-national trials. Instead of investigators having to grapple with differing application procedures in each country earmarked for the trial, just one standardised application would be sent electronically to a portal managed by the Commission.

A co-ordinated two-part assessment of the trial would then take place. Part I would be conducted jointly by all member states in which trial sites are located. It would include the assessment of anticipated benefits; the risks and inconveniences imposed on participants; and compliance with manufacturing, importation, and labelling requirements.

Part II would cover all ethical and local considerations and would be left to individual member states to conduct, as before. The Part II assessment would include compliance with the requirements for informed consent; data protection; suitability of the site and those conducting the trial, and damage compensation.

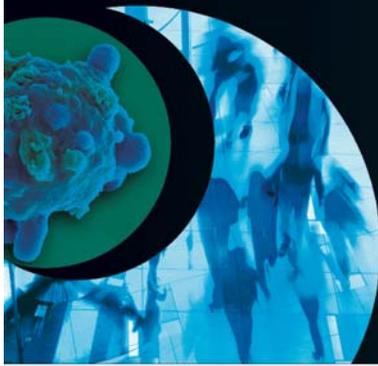
'The draft proposal is an encouraging first step in addressing the problems created by the current legislation. We will be scrutinising the text in greater detail'

Julio Celis
ECCO policy committee

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Member states would be responsible for choosing which national bodies conduct the assessments and ensuring their expertise and independence.

Both parts of the assessment would be channelled through a single "reporting member state," chosen by the investigator. For the Part I assessment, this country would draw up a report stating whether the trial is acceptable, acceptable subject to conditions or not acceptable. Other countries involved would only be able to opt out of the overall conclusion if the trial were shown to lead to participants receiving an inferior treatment than in normal national clinical practice or if national laws restricting the use of specific types of human or animal cells were infringed.

The Commission proposes strict time deadlines for each assessment. Member States are being asked to submit Part I assessment within 10 to 30 days depending on the type of trial, and Part II assessments within 10 days. These periods could be suspended for specified amounts of time to allow for member state requests for additional explanation and sponsor amendments.

However, as with the current law, the trial would be tacitly approved if the deadlines are exceeded.

A Commission body would be set up to oversee the implementation, enforcement and smooth running of the system, and deal with any problems. A second new Commission body would inspect trial sites in non-EU countries to ensure they comply with EU standards.

The Commission proposes specific help for non-commercial sponsors to cover the obligatory insurance and compensation requirements introduced by the current law. It is asking each member state to set up a national indemnity mechanism for damage compensation on a not-for-profit basis.

Another prominent change to the current law is that the insurance and indemnity compensation would not be required for "low intervention trials." These are trials using authorised drugs within the approved indication or consistent with standard treatment, where the additional diagnostic or monitoring procedures pose a minimal risk to the safety of the participant when compared to standard clinical practice. "In these cases, the insurance coverage of the medical practitioner, the institution, or product liability insurance provides sufficient coverage," says the Commission.

Shorter authorisation procedures would also apply for these trials. In addition, multi-centre trials would be permitted to have more than one sponsor.

The Commission also proposes to simplify the reporting of suspected unexpected serious adverse reactions (SUSARs). Currently, national competent authorities, ethics committees and the EU's own EudraVigilance database all require different processes for reporting SUSARs, which involves significant additional work but with no evident benefit for patients. The Commission proposes that all SUSARs be reported directly to the EU EudraVigilance database by the sponsor.

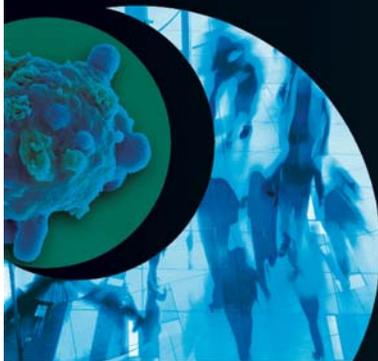
'The assessment timelines proposed are tough. This is positive, but will it be realistic? Trial sponsors will only have 10 days to address important comments'

Anastassia Negrouk
EORTC

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A key criticism of the current clinical trials law is that member states were left to their own devices to incorporate the rules into their national laws, which has led to divergent national procedures across Europe. This time around, the Commission wants to push through the reform as a regulation rather than a directive, which would legally remove this freedom.

Europe's cancer community is encouraged by the new proposal. "The Commission has taken our concerns into consideration and at first glance, the draft proposal is an encouraging first step in addressing the problems created by the current legislation," says Julio Celis, chair of ECCO's policy committee. "ECCO and our member organisations are pleased that the eventual text will be adopted as a regulation, serving to standardise practices governing clinical trials in member states. However, we will be scrutinising the text in greater detail with our member organisations before consulting further with the Commission in September," he adds.

The EORTC is "extremely pleased" with the proposal but has uncovered several potential problems on closer scrutiny of the text. "The single portal is a major achievement. However, the Commission has allowed the language of documents to be determined by member states. Currently many countries only ask for patient information sheets in their national language, which is entirely reasonable. Translating many more documents into several different languages could reintroduce delays," says Anastassia Negrouk, head of international regulatory affairs at EORTC.

EORTC will ask the Commission to further specify the rules here. "Except for the patient information sheet, for international trials all documents should be in English," says Françoise Meunier, EORTC director general.

EORTC will also ask the Commission to clarify how the rules would apply to oncology trials investigating the effect of drugs and radiotherapy, and combinations of drugs.

"These may be blocked by the draft rules as the definitions of clinical trials and clinical studies only mention drugs. The specificity in oncology trials to use drugs with radiotherapy needs to be taken into account. The study of the combination of drugs also needs to be conducted in oncology. It is also unclear how this will be affected and whether it will be allowed," she says.

EORTC feels the assessment deadlines need rethinking. "The assessment timelines proposed are quite tough and shorter than those we discussed with other stakeholders and the Commission in spring," says Negrouk. "Working it out, it seems that we will have a green light for a trial in a country in 40-70 days depending on the type of the trial. This is extremely positive, but the question is, will it be realistic? Trial sponsors frequently receive important comments on the patient information and informed consent part of the dossier. In the new proposal, the sponsor only has 10 days to address them which will be very tough for everybody," she says.

A national indemnity scheme for non-commercial sponsors "would really boost non-commercial clinical trials in Europe," according to Meunier. However, she feels it will be difficult for member states to agree on. "It puts a lot [of responsibility] on the shoulders of the member states, and

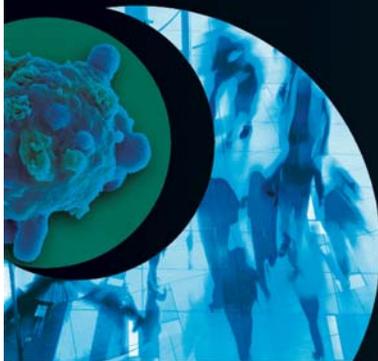
'We call on the European Parliament and Member States to take a responsible, ambitious and pragmatic approach when debating the Commission's proposal'

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EFPIA

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unless they are all agreed on a single mechanism, there'll be a lot of heterogeneity amongst national schemes which will put us back at square one, where we have to face 27 separate laws," she says.

The proposal also states that trial participants should not pay for the trial drugs. EORTC is concerned over how this would translate into practice when in certain countries cancer drugs are currently only partly reimbursed, and patients foot the rest of the bill. "This poses a potentially huge problem for academic sponsors, especially in developing countries, if they need to provide or pay for the trial drugs. It's a potentially a huge problem, even for commercial research," says Meunier.

There is only one solution to this problem, according to Eric Briers, executive director of the European Cancer Patient's Coalition (ECPC). "If the trial patient does not qualify for the reimbursement scheme the company should supply the drug for free completely. I don't think any cancer patient, unless they are rather wealthy, could afford to pay for some of these novel medical products. If companies are not willing to supply the drug for free I think the trial will not proceed."

'Clinical trials declined by 25%; the number of staff doubled; insurance costs increased by 800%. We have to get it right this time.'

John Dalli
EU commissioner for health

The ECPC will ask for further clarification on how national ethics procedures would be integrated with the new assessment system. "If national ethics committees drag their feet and don't comply with the new timelines proposed by the Commission, there will be no clearance for the trial in that country, and that would be bad for the patients. For many cancer patients, clinical trials are a last resort," says Briers. "We would like to see some sort of EU standards for ethics committees added in the future - something like an ISO [International Organization for Standardization] standard where if one ethics committee gives the go ahead, others that follow the same procedure would also accept the decision."

The Association of Clinical Research Organisations (ACRO) has earmarked other areas for clarification. "We look forward to working with the Commission to further clarify the roles and responsibilities of ethics committees, the implementation of a clear risk-based approach

to quality clinical trial management, the adoption of sound data privacy standards and guidelines for insurance verification requirements," says ACRO executive director, Doug Peddicord.

The onus now lies on member states to cooperate over the legislation says Richard Bergström, director general of the European Federation of Pharmaceutical Industries and Associations (EFPIA). "A workable administrative and scientific cooperation for large scale clinical trials is the key to make the new system effective. We call on the European Parliament and Member States to take a responsible, ambitious and pragmatic approach when debating the Commission's proposal. They need to make sure that the new Clinical Trials Regulation provides a legal framework that is fit for the future so that all European patients have an equal chance to swiftly access the latest medical research," he says.

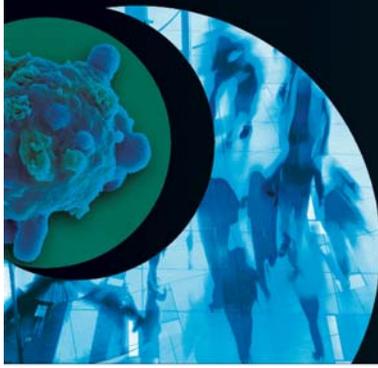
The draft will now be scrutinised and amended by the Council of Ministers, the European Parliament, and the Commission in an iterative process which is expected to reach a final agreement by 2014. The regulation will then run in parallel with the existing legislation and is not expected to come into force on its own until 2016.

Saffina Rana,
Brussels

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INTERVIEW

Predictive marker changes practice in brain cancer

Long term follow-up of an EORTC study in patients with anaplastic oligodendroglioma (AOD) found that those whose tumours showed a deletion of both the 1p and 19q arms of respective chromosomes were 44% more likely to live longer if they received PCV chemotherapy (CT) plus radiotherapy (RT), rather than RT alone. Median follow up was 140 months. The results contrast with findings of the same study (EORTC 26951) in 2006 when there was little difference in outcomes whether or not patients had received CT.

*At a plenary session at the ASCO Annual Meeting (June 1-5, 2012; Chicago, Illinois), lead author **Martin van den Bent** presented the new data (Abstract #2). The findings are backed by similar results from the US' RTOG 9402 study, also presented at the meeting (Abstract 2008b).*



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Are these findings robust enough to change practice?

Yes, absolutely. The two trials, although somewhat different in design, gave exactly the same result. Each includes only a subset of patients with 1p 19q codeleted tumours because at the time they were initiated we didn't know about this marker so neither was powered to answer questions about it. The American RTOG study includes 120 patients with 1p 19q codeleted tumours and is a retrospective analysis of this group. Our study (EORTC 26951), which includes 80 of these patients, was amended after it had started so that it has more or less a prospective design. Together, the studies show convincingly that combining RT and CT makes a huge difference in long term survival in these patients (median progression-free survival with RT alone is 50 months, compared to 157 months with RT/CT. Median overall survival is 112 months in the RT group but has not yet been reached in the RT/CT group).

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We started the study knowing that we were looking at a CT-sensitive population. But we would never have anticipated the hazard ratio of 0.56 which we saw at 140 months in this particular subgroup, especially because both our results, and the Americans', were negative in 2006. We were all stunned to see this outcome.

How did the significance of the 1p 19q codeletion come to light mid-study?

Guido and Julia Reifenberger showed back in 1994 that 1p19q codeletion is a typical chromosomal abnormality in ODAs. David Lewis and Greg Cairncross then showed a 90-100% response rate to PCV chemotherapy where tumours have this codeletion; we amended our study in 2000. The American group simply did their analysis retrospectively. It was later, in 2004/5 that Bob Jenkins and Peter Burger showed that 1p19q is not just a codeletion but a translocation. There is a translocation from 1p to 19q and the other chromosomal translocation is kicked out of the cell. This balanced translocation explains why this codeletion is a typical feature in these tumours.

Progression free survival is improved from the beginning of the study among patients who received RT/RCV (compared to those treated with RT alone). But the benefit in overall survival doesn't kick in for years. Why is that?

Someone at ASCO said they could not remember ever seeing anything like this in oncology. The improvement in progression-free survival is not difficult to explain: many of these patients simply benefit from receiving initial CT and RT. But why we don't see an effect on overall survival until much later is puzzling. Also, the multivariate analysis shows benefit associated with extensive resection. So typically the best treatment you can give to a patient is extensive resection, first, then radiation therapy followed by chemotherapy or the other way around.

The overall survival curve looks as if it's flattening. Is it too optimistic to think that some patients might have been cured?

It's intriguing. We have only a few observations, but we intend to continue to follow these patients. I have a few patients in my hospital who, after more than 12 years still show no signs of progression and that's remarkable in this disease.

Did you take biological samples from beginning of your study?

Yes. We collected tissue samples even though at the time, we had no clear idea what we were going to do with them. But because we have them we are still able to continue translational research within this trial – we think we are discovering new markers right now. It's only possible where we have tissue blocks, rather than slides, but they have made it possible to continue this research. Institutional Review Boards must be made fully aware of this point: it is completely unethical to conduct a study like this without collecting tissue samples for future research. If we want to improve the outcome of our patients, this is the way to go. Any study which does not include mandatory collection of tissues samples should be considered unethical. We are wasting resources, we are wasting the efforts of patients and doctors alike, and we are not benefitting humanity if we don't do these trials correctly.

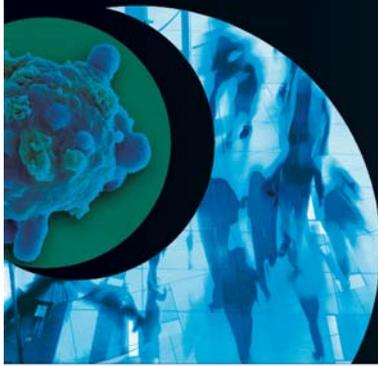
And are the tissue blocks for every single patient in the study?

For some we had only slides. We were able to do the 1p19q analysis for about 320 patients; the other tests we were able to do are on a decreasing number of patients.

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We are currently looking at the subgroup with CpG island hypermethylation phenotype (CIMP+) which seems to be another population that benefits from RT/CT. But we can only do this type of research where we have tissue blocks, not slides, and many centres are reluctant to send blocks – even where they have signed patient consent forms. We are currently conducting a trial on grade III tumours and we need the blocks but often we receive slides. It is impeding the progress we could make and jeopardising improvements in medicine. And most of the time nobody will ever do any research on many of those tissue samples; they will just sit in archives. .

How difficult has it been to follow patients for such a long time?

It's a challenge for academic institutions to follow these patients for so many years without support. But the effect would not have been seen if the follow-up had not continued beyond 2006. No pharma company would ever do a study like this on a disease like this. But these trials have helped us understand this tumour better. At the start, based on retrospective surveys, we thought we were looking at a patient population with a likely median survival of 2- 4 years. We didn't know then that the histological diagnosis consisted of a variety of subgroups which looked more or less the same under a microscope but were completely different at a molecular and clinical level. We now have a much better understanding of what is behind the diagnosis, that there is a multitude of tumours behind one histological diagnosis. We're teasing these patients into different subsets, and we have learnt that there is one very favourable subset of patients in there. They have a median survival of 10-15 years so researchers setting up the study know that it will not have concluded when they retire. But that's the only way to go if we want to study this kind of diseases. There's no alternative.

What studies are ongoing?

We also have two big randomised phase III studies ongoing, both are international multi-group collaborations. The first, the CATNON study, is on grade III tumours which lack the 1p19q codeletions. In this study we are collaborating closely with American and Australian groups to tease out subgroups other than the 1p19q codeleted tumours which also benefit from the addition of CT. The other, the CODEL study, a US-led initiative is specifically on the co-deleted tumours. If we want to be successful in studying these patients, we need to collaborate across continents in order to answer questions in a reasonable amount of time. Legal and regulatory frameworks and research environments are different in Europe, Australia and North America, so setting up the collaborations is a huge challenge. But when it works – and it does work – it is extremely rewarding. We look forward to further improvements in care for brain tumour patients.

Interview by Helen Saul

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