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The Clinical Trials Directive: What next?

Cancer organisations are striving to limit the potential damage to academic research caused by the European Union (EU)'s Clinical Trial Directive. The European Organisation for Research and Treatment of Cancer (EORTC) and Federation of European Cancer Societies (FECS) have produced, respectively, a petition and a position paper, and are engaged in a series of high-level meetings aimed at minimising the impact of the Directive on non-commercial clinical trials.

The Directive was introduced at European level to ensure a high level of protection for patients enrolled in clinical trials. Good Clinical Practice Guidelines existed previously but these did not have full legal power. The Directive was also intended to streamline the regulation of clinical trials.

However, as it stands, the Directive will create severe problems for international multi-centre trials run by academic networks. It introduces new administrative requirements and stipulates that a single sponsor must take overall financial and legal responsibility for trials. Academic networks do not usually have a legal body that could take on this role. The sponsor is obliged to provide the Investigational Medicinal Product (IMP) free of charge, even when the IMP might have been standard therapy for trial subjects.

Member States have until 1 May 2004, to implement national legislation. Any divergence in the requirements of each, which is almost inevitable, will further increase the administrative burden and costs associated with pan-European research.

The Directive does not distinguish between trials conducted by industry, typically investigating new agents, and those conducted by academics, often researching best medical practice with available therapies. Kathleen Vandendael, Executive Director of FECS says a distinction would have been appropriate. 'The purpose, incentives, means, and the benefits and risks for the clinical trial subjects clearly differ depending on the nature of clinical trials.'

Without modification, the Directive is likely to reduce the number of non-commercial trials and mean that a greater proportion of clinical research is carried out by industry. 'This was certainly not the intention of the authorities,' says Ms Vandendael.

Realistically, it will not be repealed at this stage, and both FECS and EORTC are now trying to find ways to reduce the negative consequences for academic research. Ms Vandendael has held meetings with the Irish Permanent Representatives and is in correspondence with Dr Philippe Brunet, Head of the Pharmaceutical Unit at DG-Enterprise. The EC will discuss the positions set out by the academic sector and the member states at the Regulatory Committee meetings.

"837 SCIENTISTS HAVE SIGNED THE EORTC PETITION"

The EORTC has drafted a petition, signed by 837 scientists from 33 countries, along with groups and individuals who have joined the Save European Cancer Research Campaign.

The annex to the petition includes 3 examples of EORTC clinical trials that have changed practice: larynx preservation in pyriform sinus cancer (*J Natl Cancer Inst* 1996, **88**, 890–899), randomised trial of 2 regimens of chemotherapy in operable osteosarcoma (*Lancet* 1997, **350**, 911–917) and effects of concomitant cisplatin and radiotherapy on inoperable non-small cell lung cancer (*N Engl J Med* 1992, **326**, 524–530). The studies illustrate 3 different situations (improvement in quality of life, reduction of costs and improvement in survival) where academic clinical research has made a substantial contribution to improvement in health care. 'It would be extremely difficult if not impossible to conduct these studies under the future legislation,' the annex notes.

"THE FDA EXEMPTS MANY ONCOLOGIC TRIALS FROM NORMAL OBLIGATIONS"

The petition states that in Belgium, there has been 'a constructive interaction' between academia and competent authorities. The Belgian proposal recognises the importance of the contribution of academic research to public health and the EORTC asks for it to be used as a basis for discussion.

'As a matter of urgency, we ask the member states to consider the Belgian proposal and adapt their own legislation accordingly to avoid a rapid blockade of academic research.'

'Since we know that this may not be sufficient to solve all the issues, we also ask for specific corrective detailed notes for guidance to be developed within the legal framework of the present Directive to address the problems raised for academic clinical research.'

(continued overleaf)

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'A milestone' in treatment for renal cell cancer

German researchers have achieved striking results with an autologous tumour vaccine for renal cell carcinoma (*Lancet* 2004, **363**, 594–599). Five-year progression-free survival among patients given the vaccine was 77%, compared with 67% in the control arm.

The study included 558 patients with a renal tumour in 55 institutions in Germany. They were scheduled for radical nephrectomy in 1997–1998 and randomised before surgery. After exclusions, 379 patients received either the autologous renal tumour cell vaccine, or no adjuvant treatment.

There is no accepted adjuvant approach for organ-confined renal cell carcinoma, but the tumour progresses in up to 50% of patients after radical nephrectomy.

In the German study, the 5-year progression-free survival rate for patients at all tumour stages was 77.4% in the vaccine group and 67.8% in the control group (P=0.0204). Among patients with T3 tumours, the improvement associated with the vaccine was more dramatic: from 67.5% in the vaccine group to 49.7% in the control group.

Furthermore, the vaccine showed 'only few toxic effects and no negative effect on quality of life versus the control group.'

The researchers concluded that 'application of an autologous renal tumour cell vaccine can be considered in patients undergoing radical nephrectomy due to organ-confined renal-cell carcinoma of more than 2.5cm in diameter.'

An accompanying editorial (*Lancet* 2004, **363**, 583–584) was more effusive, describing the T3-subset analysis as 'striking' and 'an immunological breakthrough.' Patients with T3 disease, who may be more immunologically impaired, could be a good group in which to study determinants of meaningful vaccine response, such as tumour features or immune competence, stated Dr Mayer Fishman and Dr Scott Antonia (H Lee Moffitt Cancer Center, Tampa, Florida, USA).

"THIS IS AN IMMUNOLOGICAL BREAKTHROUGH"

They say the German work contributes towards the goal of specific anticancer immunotherapy. 'The key milestone is the suggestion of a fixed point—a non-toxic vaccine with a biological clinically relevant effect in T2-3NO renal cancer—around which innovations can be built,' they say. 'Such a milestone can serve as a concrete step towards making adjuvant treatment of renal cancer a routine and effective intervention.'

Cancer in the centenarian

How do physicians decide on treatment approaches in the very elderly? ask Japanese doctors. They report on a 104-year-old woman with advanced cervical carcinoma of the uterus (*Gynecologic Oncology* 2004, **92**, 713–715).

The woman had a foul odour and was spending an increasing amount of time sleeping. She was found to have stage IIIB cervical carcinoma of the uterus. She had a fist-sized tumour fixed to the right pelvic wall, with tumour invasion in the whole vagina.

The patient's family insisted she be given every medical treatment available, and she received external beam irradiation of the pelvis, combined with 2 sessions of high dose-rate intracavitory brachytherapy. The overall treatment time was 45 days, and on completion, the odour had disappeared.

Five years later, at the age of 109, the woman is still alive and has had no recurrent symptoms. The Japanese team say they hesitated to treat her, and may not have done, had it not been for the insistence of her family.

'Judging from these results, how do we physicians decide on radical or palliative or no treatment at all?' they ask.

Clinical Trials Directive

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'Finally a formal dialogue should be initiated between academia, industry, competent authorities and the EC for the implementation of this directive and the elaboration of new legislation.'

FECS is calling for a two-step approach. Short-term measures which could smooth the implementation of the Directive are:

- Further clarification of the definitions of Investigational Medicinal Products (IMP) and Sponsors
- Reasonable, transparent and coherent implementation measures within Member States, preferably with transitional measures, to reduce the barriers for academic research. Some Member States have exempted the Sponsor from paying for the IMP under some conditions. However, conditions differ, and may be restrictive. Adequate European guidance to facilitate exemptions would avoid further divergent approaches between Member States
- Additional funds at EU or Member State level to support non-commercial trials.

In the longer term, FECS would like to see the Directive either amended or incorporating exemptions to protect independent research. Ms Vandendael points to the situation in the States, where the Food and Drug Administration (FDA) has recognised the special character and importance of many oncologic trials, and has defined exemptions to normal obligations, under well-described conditions. 'For Europe to maintain leadership in the development of best Oncologic therapeutic regimens, such solutions should be urgently considered for improving the current legislation and/or its implementation rules,' she says.

EUROFILE

ERC—new cornerstone of European research or more of the same?

Dissatisfaction with the European Commission's framework research funding programmes has been growing for many years, but while scientists' financial need is greater than their dislike of the system, they continue to apply. Officials in DG Research have therefore had little incentive to listen to the growing clamour and consult on the future of basic research funding in the EU. New approaches to research policy have been sadly lacking.

As any scientist will tell you, the reality of applying for funding under Framework Programmes is far removed from the rather grandiose visions the schemes espouse. Changes in emphasis every four years, increasing numbers of forms to complete, the political correctness expected in every application—and the low success rates—have made many despair of ever getting it right.

"THE PRESENT FRAMEWORK PROGRAMMES ARE A TRAGEDY"

Will the proposed European Research Council (ERC) make a difference? Or will it become yet another adjunct of Commission policy, forced to implement its bureaucratic structures and labyrinthine application procedures?

The expert group charged with advising the Council of Ministers on the need for an ERC calls it a 'cornerstone in the European Research Area' and clearly believes it is badly needed. Their report, published late 2003, calls for an ERC to "support investigator-driven research of the highest quality selected through European competition", which it says is essential in order to achieve a "new, forward-looking definition of European added value."

The European Science Foundation (ESF) has welcomed the proposals. "The establishment of an ERC is badly needed", said ESF Secretary General Eric Banda. "But an ERC working in isolation will not have the desired effect. Europe already has a considerable number of excellent researchers. Now the time has come for them to join efforts through competition and collaboration to reach the European dimension we lack."

However, big questions remain about funding of the ERC and its relationship both with national research councils and Commission framework programmes. The expert group recommends that the ERC should be a specific item in the budget in the next framework programme (FP7). The major increase in research funding foreseen by the Commission in the next round of funding should pay for it. Others would prefer to see the ERC receive money from national research councils, fearing that too close a relationship with the Commission will lead to more of the same in the long run. But some national research councils have already expressed opposition to this idea, unwilling to lose part of their already restricted budgets, along with the freedom to choose what they fund.

"POLITICIANS BASICALLY TELL SCIENTISTS WHAT TO DISCOVER"

The expert group identified the following reasons for needing to strengthen European research: long term economic development and growth; harmonious cultural and social development; and the future of the great European scientific and intellectual potential. "We do not believe that a European Research Council could or should take up all these issues at once", they say, "but its work has to be seen in the light of the full spectrum of tasks which has to be undertaken by the Union and its member states in order to strengthen the knowledge base in Europe."

European research is not strong enough, say the experts, and citation rates reflect this. They say that 1.64% of science papers published by US researchers are highly cited, as are 0.59% of those published by Japanese researchers, but only 0.25% of those from EU-based researchers.

"When European countries collaborate in research they can achieve the highest international quality and are able to take the lead", they say, citing CERN, ESA, EMBL, and ESO as examples of successful European collaboration operating at the highest level of international excellence.

The European Science Foundation has been running an Internet consultation on this issue for the past few months. The responses make interesting reading. "A unique Council would increase the intellectual liberty of scientists and give them the responsibility for innovative thinking and propositions. Compare this to the present aberrant situation with EU programmes where politicians basically tell scientists what they should discover! The same nonsense exists at many national levels," writes a scientist from France.

Achilleas Mitsos, Director General of DG Research, sees no conflict between Commission funding of an ERC and its complete independence. The European Research Council, he says, would distribute money simply on the basis of scientific excellence, as judged by peer review. The new European Constitution, which should be finalized before the end of the year, is likely to give the Commission more power to try new research policies, and Mitsos makes it clear that that they will take this opportunity to advance support of basic research.

But there is much suspicion to be overcome. "I consider the present Framework Programmes to be a tragedy and an insult to Europe's science", said Gottfried Schatz, President of the Swiss Science and Technology Council. "Letting the same people run the ERC would doom it from the start."

Mary Rice
Brussels

Virotherapy paves the way for new cancer treatment

In recent years, experimental methods designed to treat cancer with viral-based therapy have produced results hinting at the technique's potential. Self-replicating viruses that selectively lyse and destroy tumour cells without affecting healthy cells could complement, or even replace, treatment with chemotherapy or radiotherapy.

According to David Kirn (Oxford University Medical School, UK), oncolytic viruses hold "great potential as a new biological therapeutic platform". He adds, "The key advantages are high selectivity, so fewer toxic effects, and multiple methods of killing tumour cells". Previous phase I and II trials with adenovirus and herpesvirus, as well as preclinical studies with poliovirus, have shown that in addition to tumour-cell lysis, oncolytic viruses can cause apoptosis, trigger induction of antivascular cytokines, and act as vectors for gene therapy.

The specificity of oncolytic viruses has again been highlighted in a recent Australian study by Darren Shafren and colleagues at the University of Newcastle, NSW (*Clin Cancer Res* 2004, **10**, 53–63). The researchers showed that coxsackievirus A21 (CVA21, an enterovirus that causes the common cold) caused complete lytic destruction and tumour-mass fragmentation in melanoma cell-lines and primary cultures of human melanoma cells derived from clinical biopsy samples.

When melanoma cells were xenografted into immunodeficient mice, tumour burden started to decrease within 14 days after viral treatment, and had disappeared by day 30. Furthermore, a single dose of 200–500 L of CVA21 administered directly into the tumours caused the xenografts to lyse away from the site of CVA21 infection.

The sensitive viral response in melanoma cells is thought to be a consequence of upregulated expression of the cellular receptors necessary for CVA21 entry into cells, a combination of intracellular adhesion molecule 1 (ICAM1) and decay accelerating factor (DAF), leading to rapid production of viral progeny.

John Bell (Ottawa Regional Cancer Centre, Ontario, Canada) is interested by the Australian finding, particularly that low doses of virus can replicate and spread in mice to distant tumour growths. "This is probably the lowest dose of virus administered that has had therapeutic benefit in an animal model that I have seen published", he says.

Shafren and co-workers believe that oncolytic viruses will work best for early-stage disease, but "whether CVA21-mediated oncolysis of metastatic tumours of late-stage melanoma patients will translate into improve-ments in survival and quality-of-life remains to be answered in the clinical environment", cautions Shafren.

Yet CVA21 is a welcome addition to a growing repertoire of oncolytic viruses, and one whose consequences of recombination would be more favourable than an oncolytic poliovirus. And, moreover, high con-centrations of DAF expression on cancer cells of the colon and stomach clearly mark these types of malignancy as potential targets for CVA21 therapy. Clinical trials with CVA21 are planned for 2005. Enrolment, in the first instance, will involve a small number of late-stage melanoma patients.

The main question for researchers is to what extent pre-existing viral immunity affects systemic spread of the virus and its resultant ability to target metastatic cells with repeated doses. Shafren postulates that CVA21 infection only produces a local mucosal immune response. "Our pilot investigations have shown that in normal laboratory staff and late-stage melanoma patients, about 10% have some level of CVA21-neutralising serum antibody", he explains.

But Stephen Russell (Mayo Clinic, Rochester, NY, USA) cautions that this figure should be, "rigorously confirmed because, if true, it may be the major advantage of this new agent".

With their potential to specifically infect a variety of tumour cells, initiate tumour-cell lysis, deliver therapeutic genes, and be used in combination with conventional treatment regimens, the translational push for oncolytic viruses into clinical trials seems warranted. "The bigger story", concludes Russell, "is that viruses are 'druggable' and are rapidly emerging as a new class of anticancer drug".

ClaireTilstone

This is an extract from a story originally published in Lancet Oncol 2004, **5**, 136.

'Inadequate' teaching on smoking cessation

Teaching on smoking cessation in UK medical schools is inadequate, researchers say (*Tobacco Control* 2004, **13**, 74–77). Only 17% of newly qualified doctors feel well prepared to deliver advice on nicotine replacement therapy, they found.

The researchers conducted a survey of all medical school deans and all qualified pre-registration house officers in the UK. They found no mention of smoking or smoking cessation in the published curriculum of 10 out of the total 24 medical schools.

Training in clinical aspects of smoking cessation was particularly neglected. While the majority of newly qualified doctors felt well prepared to deliver advice on the health risks of smoking, 60% said they were unable to deliver smoking cessation interventions in accordance with national guidelines. Only 5% felt ready to deliver advice on use of bupropion.

The researchers said their findings are 'surprising given the public health importance of the topic and the highly cost effective nature of smoking cessation interventions, particularly in relation to other interventions (for example, thrombolysis in the treatment of myocardial infarction) that are widely taught.'

One of the authors, Professor John Britton (University of Nottingham, UK), chairs the Royal College of Physician's Tobacco Advisory Group. He said, 'This study shows that most medical schools in the UK are failing to train doctors to deliver the simple but effective help that smokers need.'

The report concluded that the situation needs to change. 'Until the importance of this topic is recognised at undergraduate level, doctors will not perceive it as a priority,' they wrote.

PODIUM

The Undue Importance of the Impact Factor

Dr Riccardo Ponzone (Gynaecological Oncology, University of Turin, Italy) trained in Turin, at the Wistar Institute of Philadelphia, USA, and the Royal Marsden Hospital, London. He is a co-investigator on national and international breast cancer studies, including both basic and clinical research projects.

Dr Riccardo Ponzone

How important are Impact Factors?
They are becoming ever more important in the assessment of the quality of work carried out by individuals seeking a new post, and for research teams applying for grants. It is widely recognised that this approach has many limitations, but the impact factor is being used blindly, and taken as an exact measure of the worth of someone's, or a group's output. The value of the research itself is not considered and this is a major omission.

What sort of questions should be asked?
Clinical research has to meet ethical requirements, be practically relevant and have sufficient statistical power to get a result. Basic research does not have the same limitations. Obviously it is difficult to foresee the practical relevance of work going on in the laboratory today, but we must make the greatest efforts to make the acquisition of useful results more likely. A lot of research is contemplative, and without clinical implications.

Does the use of impact factors disproportionately affect clinical research?
Yes, clinical trials are usually lengthy and multicentric so that only a minority of those involved can be listed in the authorship. Furthermore, basic research papers tend to cite articles on basic research only, whereas clinical papers cite both. Clinical journals have lower impact factors than basic research journals but that does not make them less important; we need both. Decisions based only on impact factors will favour basic researchers.

The impact factor is at least an objective measure?
It may eliminate the need for human judgement, but we *should* be using judgement in making these decisions. The question of whether a research strand is likely to lead to a clinical application and benefit humankind is important.

Does this problem exist in isolation?
It's only the tip of the iceberg. It's generally acknowledged that translational research represents the way ahead, but it requires collaboration between lab and clinic. Traditionally a gulf has separated the two groups and recent progress is progressively enlarging it; the clinician without a minimal understanding of genetic principles now cannot even communicate with a basic scientist. Conversely, basic scientists may not have sufficient experience of the clinical behaviour of tumours and the priorities for research in terms of prevention, screening and treatment.

The role of the clinician is of paramount importance in providing the link between the patient and the scientist and to help prioritise the most relevant research.

What if nothing changes?
Increasing costs and bureaucracy are making clinical research exceedingly difficult and prohibitively expensive. If clinical research becomes limited to that funded by drug companies, the flame of progress will be extinguished. The selection of people and ideas most likely to lead to practical benefits is of paramount importance.

Is the situation universal?
It is most pronounced in countries where resources are most limited. In an ideal world, all areas of research would be funded, but in the real world, resources are finite.

Wouldn't your framework prevent out-of-the-box thinking?
New ideas on treatment or our understanding of diseases are welcome, but they are most likely to come from people with experience of the disease. If things continue getting more technical, more analytical, we could lose sight of the bigger picture. It is not happening yet, and in breast cancer, a new paradigm emerges every 20 to 30 years. But we must strive to improve things as quickly as possible.

What steps should be taken now, in your view?
Priorities need to be set. We need some way of objectively measuring the relevance of work that people are doing. Impact factors should never be the only or even the main measure that qualifies someone to sit on a committee or take important decisions on funding. We need to use judgement.

In the Anglo-Saxon world, the UK and US, letters of recommendation are used quite successfully in making appointments. It would be difficult to suggest this in Italy where, historically, recommendations have been given without merit; we need some other, more objective measure.

Could the impact factor be weighted in favour of clinical research?
This is done in Italy, and it's a start because otherwise clinical research would never get funding. But it doesn't take the relevance of the work into account. We must find a way through this; effective research requires interplay among competences from many different disciplines. The translation of the benefits from genomics, transcriptomics and proteomics into medicine will require large concerted interdisciplinary efforts to be successful. Let us never forget that people are dying while we struggle with this and the only measure that counts is how many of them we are able to save.