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Clinical Trials Directive: the next step

The flexibility allowed in the interpretation and implementation of some paragraphs and articles of the Clinical Trials Directive (CTD) was intended to give Member States (MS) room for manoeuvre, say representatives of the European Commission. However, academics say it has unfortunately led to an incoherent situation, with different MS having different requirements.

The Federation of European Cancer Societies (FECS) organised a meeting together with representatives from the EC and from the 25 MS (Centre Borschette, Brussels, 24th April, 2005) to explore the boundaries of this flexibility. Delegates heard that some Member States (MS) have demonstrated considerable initiative in their interpretation of the CTD. For example, some have included definitions of the sponsor and/or of Investigational Medicinal Products (IMPs) which will be helpful for academic research.

The meeting discussed the findings of a survey conducted by FECS. It was based on a questionnaire developed by FECS in consultation with European Organization for Research and Treatment of Cancer (EORTC). The questionnaire – on the provisions made for academic research by national authorities – was sent to oncology academics and competent authorities in all 25 MS.

''SOME STATES HAVE SHOWN CONSIDERABLE INITIATIVE''

Replies have so far been received from 11 competent authorities (new information has since been received from a further 3) and from academics in 19 MS. The completed questionnaires reveal that no single question asked in the survey received the same response from all MS. Some were almost unanimous: only 2 MS have a national definition, which differentiates commercial from non-commercial trials. However, the answers to most questions were more evenly distributed: in 8 MS, it is compulsory to have a single sponsor across the EU; in 11, it is not.

''It is clear that the interpretation and implementation of the CTD has been confused and inconsistent across the European Union (EU),'' said Ms Kathleen Vandendael, Executive Director of FECS. ''This is primarily due to a lack of clear definitions in key areas of the CTD. Most authorities are supportive of academic research, but they have taken divergent approaches and had different perceptions of the administrative constraints imposed by the CTD.''

Speakers from the UK, Belgium and Spain gave concrete examples of a reduction in the number of clinical trials being activated and an increase in the bureaucracy associated with running clinical trials since the CTD came into force in May 2004. Dr. Miguel Martin (Hospital Universitario San Carlos, Madrid, Spain) said that the time taken to approve clinical trials in Spain has doubled from 60 to 120 days as a direct consequence of the CTD.

''IMPLEMENTATION OF THE CTD HAS BEEN CONFUSED AND INCONSISTENT''

The meeting discussed the definition of a sponsor. The CTD foresees only one sponsor for any clinical trial, but academics stressed that this does not reflect the reality of international academic research, which usually works through a network of local sponsors, often institutions. Under the CTD, sponsors bear a number of liabilities, which raises practical and structural issues for multicentre and multi-national academic research.

The EC's legal representative said that the guidelines were intended to clarify the single sponsor concept. He said it is foreseen that a number of parties may agree in principle to form an organisation and to distribute the sponsor's task, duties and functions between different individuals and organisations. This must be done in such a way that the collective fulfils all the required rules and responsibilities of the sponsor, because it is compulsory to be able to identify one legally responsible entity. This is outlined in an EC document, he said.

The definition of an Investigational Medicinal Product (IMP) remains confused. The CTD gives a broad definition of an IMP, and MS' interpretation could have serious implications for academic research. It could mean an increased financial burden as the IMP is supposed to be provided free of charge; and an increased bureaucratic burden as a dossier is supposed to be provided for each IMP. Of the responding countries, 12 applied a broad definition of IMP; and confusion exists between MS as to whether the

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Herceptin in early breast cancer

The addition of Herceptin (trastuzumab) to standard combination chemotherapy for early breast cancer increased disease-free and overall survival, US researchers say. The finding was due to be presented at the American Society for Clinical Oncology (ASCO) annual meeting (May 13–17, 2005, Orlando, Florida).

The results come from two large randomised clinical trials, sponsored by the US' National Cancer Institute (NCI). They were conducted by a network of researchers led by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the North Central Cancer Treatment Group (NCCTG), in collaboration with the Cancer and Leukemia Group B, the Eastern Cooperative Oncology Group and the Southwest Oncology Group.

The trials, known as NSABP-B-31 and NCCTG-N9831, included women with HER-2 positive invasive breast cancer. Those who received Herceptin had a 52% decrease in disease recurrence compared to those treated with chemotherapy alone. This difference was highly statistically significant.

The Data Monitoring Committees overseeing the trials recommended that the results of a recent combined interim analysis be made public because the studies had met the primary endpoints of increasing disease-free and overall survival.

Dr. Edith A. Perez (Mayo Clinic, Jacksonville) chaired the NCCTG trial. She said, ''These findings confirm that we now have a very potent weapon against the recurrence of cancer cells that overexpress HER-2.''

The analysis included information from 3300 patients with operable breast cancer, who were enrolled in the studies between February 2000, and April 2005. Many had lymph-node positive breast cancer, or breast cancer that had spread to the lymph nodes, with only a minority having lymph node-negative disease. The limited information in the node negative group did not allow for a separate analysis of this group.

The women were randomised to receive chemotherapy with doxorubicin and cyclophosphamide followed by paclitaxel, or doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab. The likelihood of congestive heart failure was increased from 3% in the former group, to 4% in the latter. Patients will continue to be followed for additional side effects.

Clinical Trials Directive *continued*...

definition of an IMP in the CTD is legally binding.

Free access to marketed drugs is another outstanding issue. Sponsors are meant to provide the IMP free of charge, but here the CTD allows national provision. However, because the definition of an IMP is so broad, academic research comparing drug regimens with commercialised products could be obliged to provide all products free of charge, even when they would have been standard therapy for the trial subjects. In the survey, 9 countries had made no special provision for the supply of IMPs free of charge.

Speakers agreed that academic clinical trials in the EU are now jeopardised by the lack of competitiveness with non-EU countries. In response, the EC representatives said that guidelines will be released in the second half of 2005 or early 2006. A further meeting will be held in 2006 to assess the progress made in the implementation of the CTD with respect to non-commercial clinical trials. Outstanding problems will be addressed then, they said.

In the meantime, the Clinical Trials Facilitation Group, (created early in 2004 and comprising representatives from MS competent authorities) is an appropriate forum for the competent authorities to discuss the issues mentioned here, and to develop a pragmatic and coherent approach for academic clinical trials across the EU.

A Million Women in HRT Study

Hormone-replacement therapy (HRT) containing either oestrogen or tibolone alone increases the risk of endometrial cancer, UK researchers say. However, the greatest increase in total cancer incidence is seen with combined oestrogen–progestagen HRT.

More than one million postmenopausal women without previous cancer or hysterectomy joined a Cancer Research UK study between 1996 and 2001. The recruitment questionnaire asked for details of sociodemographic and personal factors, including use of HRT. A further questionnaire was sent out 2–3 years later.

The current study (*Lancet* 2005, **365**, 1543–1551) included 716,738 women who were followed up for an average of 3.4 years. During this time, 1320 endometrial cancers were diagnosed.

The effect of the HRT varied according to the women's body-mass index. Among women who were not overweight, tibolone, oestrogen-only and cyclic combined HRT significantly increased the incidence of endometrial cancer. Continuous combined therapy conferred no benefit.

However, among obese women – who normally have a substantially higher incidence of endometrial cancer – use of both continuous and cyclic combined HRT significantly reduced the incidence of endometrial cancer. Use of tibolone and oestrogen-only had little additional effect on incidence. ''The progestagens in combined HRT seem to counteract the carcinogenic effects of both endogenous and exogenous oestrogens on the endometrium,'' the researchers say.

Because breast cancer is more common than endometrial cancer, the total incidence of endometrial plus breast cancer is dominated by breast cancer. Current use of combined HRT causes a greater increase in breast cancer than the other HRT preparations do, which means that the total incidence of endometrial plus breast cancer is greater with current use of combined HRT than with either tibolone or oestrogen-alone.

The conclusion applies to all women with a uterus, both obese and non-obese, but the absolute increase in total cancer incidence is greater in non-obese women.

An accompanying editorial (*Lancet* 2005, **365**, 1517–1518) points out that the follow-up was short and recent data suggest that long-term use of continuous combined therapy might carry increased risks compared with non-use. Furthermore, other evidence suggests that hormones might increase the risk of ovarian cancer, though probably decrease the risk of colorectal cancer.

It concludes, ''The important clinical question is how hormones can be prescribed in a fashion that will allow women to receive the greatest benefits without commensurate risks. To minimise cancer and other risks, clinicians should prescribe the lowest possible dose of oestrogen for short periods of time. Fortunately, recent evaluations support the idea that oestrogens prescribed at low doses are generally as effective in controlling menopausal symptoms as the traditional higher doses.''

EUROFILE

7th Framework: More of the same?

The so-called 'Lisbon agenda', which aims to raise industrial competitiveness in Europe up to the levels in the USA, has clearly been influential in the proposals presented by the European Commission for the 7th Framework research programme (FP7). On the money side, at least: an overall funding increase from nearly €18bn to €73bn has been called for. MEPs have expressed enthusiasm for a large increase, so the chances are good that, if national governments do not object, this could become a reality. National governments are notoriously reluctant to hand over more money than they have to, though, so the final budget may be much lower. ''The Commission can count on the Parliament in case the Council is a bit strict'', says Pia Locatelli, the Italian MEP who composed the Parliament's opinion on the draft proposal earlier this year.

So far, so good. But how will FP7 differ from the much-criticised FP6, apart from having more money? The answer would seem to be: not much. The nine ''co-operative themes'' proposed in FP7 do not look very different to FP6's ''thematic priorities''. Under the health theme, the 'activities' are: biotechnology for human health; translational research; and optimising health care delivery. No big change there. And taking into account that FP7 will run for 7 years, as opposed to FP6's 4, even the large funding increase looks rather less impressive. Also included this time round is nearly €12bn for the European Research Council (ERC), which previously did not exist. Taking this into account, the overall budget is about double that of FP6.

Funding initiatives will fall under four ''programmes'' – Co-operation, Ideas, People, and Capacities – striking a balance, according to the Commission, between collaboration and competition, Europe-wide initiatives and regional funding. Health research will get a decent increase from €2.5bn to €8.3bn (90%). This is the largest rise for any sector apart from nanotechnology, which gets 95%, probably due to the fact that it started from a low FP6 baseline. This is encouraging, but other factors are causing concern among medical researchers.

''Under FP6, I really wasn't sure whether those who make money out of translating the forms had also written them from scratch'', says Professor Gordon McVie of the European Institute of Oncology, Milan. ''The administrative load needs to be lightened and simplified if scientists are going to bother to apply for money from the EC. We are talking about taxpayers' money here, and it cannot be right that so many first class scientists are put off from using it in the interests of European citizens by the Byzantine application procedures and onerous reporting requirements.''

The Commission is aware of the disquiet among researchers over the huge administrative burden which both applying for and complying with the terms of a grant imposes on scientists. A Working Paper has been published setting out an agenda for simplifying FP7, and which includes fewer demands for reports and greater autonomy for consortia. Ramon Marimon, author of a critical report of FP6 administration published last year, welcomed the new proposals as ''very good. But the current state of affairs, as reflected in the simplification document, is still immature in some important details. It may be better to have a reduced menu of grant forms and, in those activities where it is not obvious which form is better, let the users choose''. Some national governments and MEPs have also said that they would like things to be even simpler. Simplification of administration would not need new legislation and the final version is expected in the autumn of 2005.

''THE ADMINISTRATIVE LOAD NEEDS TO BE LIGHTENED''

With the Lisbon agenda such a hot issue for Commissioners, is it likely that researchers will see the changes they want? Gunther Verheugen, vice-president of the Commission and head of enterprise and industry, said in April 2005 that he was to hold talks with pharmaceutical companies in order to strengthen the industry in Europe and to stem the loss of R&D centres to the US. ''We need to preserve a strong industrial base in Europe by means of modern industrial policy'', he said. ''A further relocation of development centres of the pharmaceutical industry to the US bioscience clusters will most certainly lead to a decline of the European biotechnology industry.''

This is vitally important, says Professor McVie. ''A major priority under FP7 should be applied research, right through to technology transfer – this is currently a real gap for Europe… A spate of mergers has meant that, increasingly, research facilities have moved to the US, and this is a big threat to the European critical mass. This is an area where the EC could make considerable strides, but up till now it seems that the Commission is much more interested in funding basic research.''

''WE NEED TO PRESERVE EUROPE'S INDUSTRIAL BASE''

Prevention is another under-supported area, he says. ''Where is the new generation of epidemiologists? There is little serious prevention research being carried out at present. This should be a win–win situation for the EU, and I do not understand why they are not putting more effort into encouraging it.''

Good marks for trying, then, but we will have to wait and see whether this programme brings about real improvements in the funding and direction of European science.

Mary Rice
Brussels

New brain tumour advocacy group

The International Brain Tumour Alliance (IBTA) has been set up by a group of brain tumour patients, carers and health professionals. It seeks to achieve a wider public understanding of the specific challenges faced by those living with a central nervous system tumour, their families and carers.

IBTA was formed at the joint conference of the World Federation of Neuro Oncology and the European Association for Neuro Oncology (Edinburgh, UK, 5–8 May, 2005). At the inaugural meeting, Mr. Denis Strangman of Canberra, Australia, whose wife Margaret died from a malignant brain tumour in 2001, was appointed chair of IBTA. Mrs Kathy Oliver of Surrey, UK, is to be secretary.

Representatives from brain tumour support advocacy and information groups in the UK, US, Canada and Australia attended the meeting. Support for IBTA has also come from brain tumour groups in Italy, Germany, India and Ireland. The group is particularly keen to encourage the establishment of support groups in countries where they do not already exist.

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Earlier access to bortezomib

The European Commission (EC) has approved the use of bortezomib (Velcade) for injection as second-line treatment of patients with multiple myeloma. It is now indicated as monotherapy in patients who have already undergone or are unsuitable for bone marrow transplantation.

The approval is based on the results of the Phase III APEX trial (*Proc Am Soc Hematology 2004 # 336.5*) comparing bortezomib with high-dose dexamethasone in relapse multiple myeloma. Patients in the bortezomib arm had a significant survival advantage.

Bortezomib was previously approved in Europe for the treatment of multiple myeloma patients who had received at least two prior therapies. It is approved in the US for second-line use in patients who have received at least one prior line of therapy.

Missing link in tumour-prone disorders

Abnormal DNA damage response is the cause of neuronal defects in chromosome instability and tumour-prone disorders, say scientists from the International Agency for Research on Cancer (IARC). Their work may have found the missing link in a group of genetic disorders.

Nijmegen Breakage Syndrome (NBS) is a rare autosomal recessive disease characterised by microcephaly, chromosomal instability, radiosensitivity, immunodeficiency and cancer predisposition. NBS, Ataxia Telangiectasia (A-T) and AT-Like Disorder (A-TLD) constitute a sub-group of chromosome instability syndromes, which exhibit similar clinical and cellular characteristics but have distinct neurological anomalies. Distinct genes are responsible for each of the disorders.

Extensive molecular and cellular studies have shown that molecules encoded by the responsible genes play a central role in DNA damage response. If this response is disrupted, more severe degenerative diseases characterised by cancer predisposition may result. However, the link between these genetic disorders had not previously been elucidated.

Dr. Zhao-Qi Wang and his colleagues at IARC showed for the first time that the neurological anomalies in these syndromes are due to abnormal DNA damage response. They used specific gene disruption technology to demonstrate that depleting the DNA double strand break repair molecule NBS1 in the mouse neural lineage overactivates the tumour suppressor p53 and results in a combination of the neurological anomalies of NBS, A-T, and A-TLD (*Nature Medicine* 2005 DOI: 10.1038/nm1228).

Epidemiological work has suggested that NBS1 deficiency represents an important risk factor in the development of malignancies both in NBS patients and in heterozygous carriers. The average carrier frequency of the NBS1 founder mutation is one in 177 among Slav newborns in Central and Eastern Europe.

''Even a moderately elevated cancer risk in heterozygous carriers could potentially result in several hundreds of new cancer cases in these populations,'' the researchers say. ''Therefore it is important to note that any genotoxic treatment of the patients suffering from chromosome instability syndromes may well increase the risk of developing neuronal degeneration symptoms.'' They stress that more work is needed on these potential effects.

Screening for the Lynch Syndrome

Screening for the Lynch syndrome among patients with colorectal adenocarcinoma can be effectively conducted with relatively simple immunohistochemical analysis, say researchers in Ohio, US. The method gives similar results to the more complex strategy of genotyping for microsatellite instability, they found (*New Eng J Med* 2005, **352**, 1851–1860).

The Lynch syndrome, or hereditary nonpolyposis colorectal cancer, develops where there are germ-line mutations in the mismatch-repair genes *MLH1, MSH2, MSH6* and *PMS2*. It confers a strong susceptibility to cancer. Such syndromes represent important models and ''their contribution to the understanding of mechanisms of carcinogenesis is out of proportion to their frequency,'' according to an accompanying editorial (*New Eng J Med* 2005, **352**, 1920–1922).

The Ohio study included 1066 patients with a new diagnosis of colorectal adenocarcinoma, of whom 208 (19.5%) had microsatellite instability. Of these, 23 had a mutation causing the Lynch syndrome (2.2%). Genotyping for microsatellite instability alone failed to identify two probands; as did immunohistochemical analysis alone.

Another striking finding was that of the 23 probands, 10 were more than 50 years old and only three fulfilled the Amsterdam criteria for the syndrome. This ''emphasises the need to search for the Lynch syndrome outside the typical 'high-risk' situation''.

Patients with tumours with high-frequency microsatellite instability have a better prognosis than those whose tumours lack it, and may not benefit from fluorouracil-based adjuvant chemotherapy. Determining the mismatch-repair status of all patients with colorectal cancer ''has prognostic implications and may serve as a guide to optimal chemotherapy'', the researchers conclude.

PODIUM

Let's halt the brain drain!

Professor Jacques Bernier (Oncology Institute of Southern Switzerland, Bellinzona) specialises in chemoradiation for locally advanced head and neck cancers. He chairs the EORTC's Head and Neck Group, the European Intergroup of Head and Neck Oncology (EINHO) and the International Conferences on Translational Research in Radio-Oncology (ICTR).

Professor Jacques Bernier

How pronounced is the brain drain from Europe?

It is difficult to quantify because it varies, but over R&D as a whole – not just medicine – by 2010, the EU will have to recruit 700,000 scientists to meet its own requirements. Of the 400,000 European science and technology graduates now living in the US, only about one in three intend to return. If things did not change, Western Europe will have a deficit of about 300,000 scientists, which is worse than 5–10 years ago.

Why do scientists leave Europe?

Scientists in the US may earn three times more than those in the UK. Further, the imbalance between temporary and permanent positions in some countries leads to precarious employment. In Italy for instance, the number of permanent jobs has been drastically reduced, and researchers face unemployment if their contract is not renewed. The working environment in the US is also better, and research teams have a critical mass. In Europe, staff shortages mean that teams are small and fragmented. It's rare to find a true collaboration among laboratories.

How can the situation be reversed?

Most laboratory chiefs tell students and post-docs they need to spend 2–4 years in the States in order to get the platform they deserve in Europe. But whenever they go, there is a risk that they would not return. We need to increase the quality of training in Europe and reduce the need for our students to leave.

We also need to create clusters of excellence to co-ordinate a broad range of research. The clusters should not have exclusively private or public funding, and new funding sources should support academic clinical trials, the most endangered type of research. The new French cancéropoles are an important model and they require co-ordination and synergism between labs and clinics. But clusters should not be confined to a single country, they should operate between countries.

Is translational research better managed in the States?

Screening for new drugs and molecules is conducted efficiently in the States and new discoveries are moved into development rapidly. In Europe, we are too cautious when we have a new discovery; and the latency between discovery and implementation is an increasing problem.

Does the "American Dream" apply to researchers?

We can't match the financial conditions and working environment in the States. But the American Dream is not all positive; many scientists who have returned were disappointed by excessive competitiveness and pressure. Even as things stand, one in three Europeans are willing to come back; if the working conditions improve here, that would increase.

Do we need changes within the European scientific community?

The system in many laboratories is too rigid. Contracts are inflexible and exchanges between laboratories are not sufficiently encouraged. We need to improve researchers' mobility to keep up the fresh blood in laboratories. At present, too many people are on temporary contracts.

What changes are necessary at a political level?

At the pan European level, the European Research Area (ERA), has been discussed by the European Commission (EC) and would be a common market for researchers: someone in France could apply more easily for a job in Germany, and so on. The ERA would co-ordinate research at a pan European level. Within each country, governments should give more direction to research, and define their own priorities. Researchers should then evaluate specific research projects within their government's criteria, and the end result should be evaluated by an independent monitoring committee.

Should priorities be defined at national level?

It depends on the scientific area. CERN in Geneva is a wonderful example of the pan European approach in physics. The EC's biomedical programmes fund important projects involving many different countries. In translational cancer research, we need a network of national cancer institutes, such as the NCRI in the UK and INCa in France. This would create a pan-European programme and – why not? – pave the way for a European Cancer Institute.

Doesn't the brain drain come down to a lack of funding?

Lack of investment is a problem and it varies from country to country but investment per capita here is about half that in the States. There is also a lack of return on investment: bigger tax breaks would encourage more investment from industry. At present only a few percent can be deducted from companies' pre-tax revenue, and this needs to be increased.

Is it realistic to think Europe can compete with the States?

We have to increase our scientific creativity and reverse the current climate but even with all these measures in place it would take 3–4 decades before there is some sort of equilibrium. It depends on the political willingness. The EU could offer tax incentives for biotech companies. Pharma scientists add to the critical mass, and there is a drift to the US: every recent Pharma merger (except Sanofi-Aventis) has seen a closure of European research labs.

What do you think will happen?

Many states are trying to shift the financial input into biomedical research from the State to the pharmaceutical industry. This might be acceptable financially, but there is a loss of independence. We must find new incentives for funders.