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Impact of EU Clinical Trial directive

The implementation of the EU directive on clinical trials will be a challenge for all concerned, according to speakers at a conference on 'The Impact of the EU Clinical Trial Directive' (Brussels, 30–31 July 2001). Delegates heard that the directive, which is designed to harmonise and streamline procedures throughout the EU, might in practice create more difficulties.

The directive must be applied in all member states by May 2004 and aims to harmonise legal and ethical procedures associated with clinical trials across Europe. It emphasises the rights, safety and well-being of patients and focuses on the importance of informed consent for children and those who are incapacitated. The directive is intended to decrease the administrative workload associated with initiating clinical trials and will increase the flow of data between the European Commission, EMEA and member states' competent authorities.

Ms An Johanna Baeyens

Whether it will achieve these objectives is unclear. The directive will need to be consistent with existing guidelines on clinical practice in order to eliminate any serious threat to ongoing transatlantic collaboration. Further, its impact will depend on how member states incorporate requirements into their national laws. Concern exists that if member states do not implement the directive consistently, operational difficulties associated with initiating a trial may actually increase. Representatives from industry fear that the new process for activating clinical trials might not be as efficient as hoped and might slow down the registration of medicines.

"LARGE PHASE III TRIALS REQUIRE AN EFFICIENT LEGAL FRAMEWORK"

Speaker Dr Denis Lacombe, assistant director at the EORTC Data Center in Brussels, stressed the importance of working within a coherent structure. "It is vital that large phase III trials which contribute to state-of-the-art treatments are conducted in an efficient legal framework," he said. Academics questionned whether practical issues relating specifically to these type of large-scale clinical trials have been carefully considered in the preparation of the directive.

Currently, researchers initiating a study across several member states need to obtain approval from the national authority of each, and deal with different procedures for reporting serious adverse events. Requirements for labels differ, as does the obligation on the sponsor to provide the medicine under investigation free of charge. Academics say questions still remain over these issues. The directive allows for "exceptional circumstances" under which the sponsor should be exempted from this latter obligation.

Insurance cover for patients participating in clinical trials also remains to be addressed. An Johanna Baeyens, EORTC Regulatory Desk Administrator, said, ''There is no harmonisation yet related to insurance coverage and indemnity for patients. Some EU countries have specific regulation relating to minimum insurance liability thus complicating international trials.''

"THERE IS NO HARMONISATION OF INDEMNITY FOR PATIENTS"

Overall, the EU directive on clinical trials sheds light on some issues but somehow its practical implementation remains a challenge for all professionals conducting clinical trials.

Samantha Christey
EORTC Communications Officer

The EU Directive on Clinical Trials can be found at: http://europa.eu.int/eur-lex/en/index.html

Speakers at the Vision in Business conference represented all sectors of clinical trials: regulatory (the Medicines Control Agency and the Irish Medicines Board, INFARMED), CRO (Quintiles Ltd, INTERCERN), ethics (Central Office for Research Ethics Committees) and academic research (the EORTC, University of Cardiff). Lovells Law firm and the EFCGP were also invited to speak.

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Adenocarcinoma of the oesophagus: rates soar

The incidence of adenocarcinoma of the oesophagus is increasing by 30% per year among white men in southern Europe (*Cancer* 2001, **92**, 549–555). Researchers say the rise is partly explained by the increasing numbers of people who are overweight.

Researchers examined 43 cancer registries covering Europe, Australia and the United States. Rates are increasing by 23.5% per year in Australia, and 20.6% per year in the US. However, the UK had the highest incidence in 2000, of up to 8.7 cases per 100 000 population. The Netherlands had 4.4 and Denmark 2.8 cases per 100 000. The incidence in Eastern Europe was low, at 1 case per 100 000.

They note that 30 years ago, less than 3.7% of oesophageal cancers worldwide were adenocarcinomas. Now, among white men in the US, up to 70% are adenocarcinomas. Obesity, alcohol consumption, tobacco use, pharmaceutical agents and diet may have contributed to this rapid increase, researchers say.

Excess abdominal fat may be especially important since it has been linked with gastro-oesophageal reflux, which can cause Barrett oesophagus, the precursor of the adenocarcinoma. However, the role of obesity does not explain why there is a higher incidence in the UK than in the US, where obesity is 1.5 times more common. Nutritional composition may also be important since a high-fat diet reduces pressure in the lower oesophageal sphincter and may predispose people to gastro-oesophageal reflux.

Lead author Dr Elfriede Bollschweiler (University of Cologne, Germany) said the study provides hard evidence for the influence of environmental factors. "It seems quite reasonable that combining such environmental factors as nutrition and lifestyle with possible genetic factors determining tumour formation may provide an explanation for the pattern of different incidence rates," he said.

Radon and lung cancer

Risk of lung cancer among non-smokers increases in step with increased exposure to residential radon, Swedish researchers say (*Epidemiology* 2001, **12**, 396–404). They found that the relative risk among non-smokers was increased by as much as 44% where people were exposed long term to high rather than low levels of domestic radon.

The researchers followed up 436 people with lung cancer who had never smoked, and compared them with 1649 never-smoking controls. They measured radon levels in their homes going back 32 years, and on average covered 25 of each subject's 32 years.

Radon concentrations were compared with the reference level of below 50 Bq m^{-1}. Average exposure to 50 Bq m^{-1} was associated with a relative risk of 1.08; exposure to 80 Bq m^{-1} with 1.18; and exposure to 140 Bq m^{-1} with 1.44. Overall, an excess relative risk of 10% was associated with each 100 Bq m^{-1} average radon concentration.

Exposure to residential radon was also found to be more harmful for passive smokers. The researchers concluded that their work adds to the limited data on the subject: 'Overall, the radon-related excess relative risk of lung cancer among never-smokers does not appear to depart much from that in smokers (but is obviously much smaller in terms of absolute excess risk)'.

Opinion swings in favour of lung cancer screening

A more positive attitude is emerging towards screening for lung cancer, British researchers say (*Br J Radiol* 2001, **74**, 478–485), and the potential effectiveness of spiral CT is being debated.

The immense burden of lung cancer is not doubted, the researchers say, and it can be detected by conventional chest radiography in its early stages. Further, therapy can be curative in this early stage. But the question that needs to be answered is "Does screening for lung cancer produce a measurable reduction in mortality in those patients being screened?"

Previous randomised controlled trials found that use of chest radiography and sputum cytology had no beneficial effect on mortality. However, the more recent Early Lung Cancer Action Project (ELCAP) demonstrated the ability of CT to detect small non-calcified nodules in smokers (*Lancet* 1999, **354**, 99–105).

One objection to screening is that it may unearth biologically unimportant tumours. Lung cancer is aggressive but it is possible that tumours exist which do not become manifested during a life cut short by another smoking-related disease such as respiratory failure.

Another objection involves practicalities. Even with experienced operators, spiral CT misses perihilar, peripheral and lung cancers, many of which can be clearly seen in retrospect. However, outcome may still be improved across a population where nodules are missed. This, however, would have medicolegal implications. "Up to 90% of patients in whom screening detected lung cancer could sue the radiologists who identified the cancers for their earlier misses. Thankfully, this sytem does not yet operate anywhere," the researchers write.

"UP TO 90% OF PATIENTS COULD SUE FOR MISSED CANCERS"

A further question is whether screening might encourage complacency among smokers, and be regarded as a safety net to catch and cure those unlucky enough to develop lung cancer as a consequence of their smoking. The ELCAP study suggests not. It found that patients who were shown their own CT images, even when they were negative, became more likely to quit smoking than otherwise.

Any screening programme for lung cancer would have to be shown to reduce mortality and be cost effective. But the researchers say, "The tide of opinion seems to be moving against the negative attitude towards screening that has prevailed since the apparently negative randomised controlled trials."

EUROFILE

Why the EU matters in cancer

Cancer specialists may not care very much about squabbles between the European Parliament and the European Union (EU)'s Council of Ministers; or infighting among the EU's senior officials in the European Commission. They may dismiss carelessly the thousands of words that spill out of Brussels, Strasbourg and Luxembourg every day extolling the merits of the EU's policies on research, health or medicines.

And by and large, they would be right to do so, but only by and large because, like it or not, dealing with cancer means, increasingly, dealing with the EU.

Brussels has a growing influence on healthcare: on how medicines are tested, what sort of preventive policies are developed, how far research is funded, or whether European healthcare companies can survive growing global competition.

This column is not going to wade through EU swamps of procedures, institutions and preliminary draft directives, but it will explore some of the efforts Brussels is making towards fighting cancer—and to reveal where it has been successful, and where, wittingly or unwittingly, it has not.

It's the right time for such a review. Cancer is being driven further up the EU agenda by demographics, by the reaction to remorselessly grim mortality and morbidity figures, by a new level of EU interest in exploiting research openings and even by the personal convictions of some of the leading players at EU level.

For instance, the member of the European Commission now responsible for research, Philippe Busquin, has backed cancer research energetically. Busquin is a Belgian former health minister who was on the board of a number of hospitals—including the Institut Jules Bordet in Brussels—before he came to the job. In May, he brought together 45 cancer researchers, clinicians and cancer research managers from 30 European countries in a bid to improve co-ordination.

Busquin is long on rhetoric: "The whole subject of cancer research requires a European approach because a large, cooperative effort is needed to ensure that every European citizen will rapidly profit from the revolution of knowledge in cancer management," but he is also trying to steer the EU towards the most effective use of the funds available.

And this isn't an agenda dreamt up uniquely by cloistered bureaucrats. Professor Harald Zur Hausen, head of the Deutsches Krebsforschungszentrum, publicly backed the initiative: coordination could "lead to wider understanding of mechanisms of cancer development and to a higher quality in assessment, prevention, diagnosis and therapy. This should have an impact on clinical practitioners and contribute in general to improved scientific quality of European medical research," he announced.

The Commission is proposing that its next 4-year research support programme—with a budget of €4 billion per year—should put cancer among the priorities, particularly integrating new genomics-based tools with more conventional cancer therapy.

The range of EU involvement in cancer is vast. In June alone:

- An expert EU scientific committee for cosmetic products declared that the potential bladder cancer risk from permanent hair dyes ''is of concern'', and it wants new regulatory controls;
- EU ministers backed a new public health programme being pushed by the Commissioner responsible for health, Irishman David Byrne, which will subsume the current EU cancer support activities, and could lead to an EU ''rapid reaction capability'' to counter serious health threats;
- EU ministers formally recorded their concerns on tobacco, stating explicitly that ''tobacco-related diseases are now responsible for one in 10 adult deaths worldwide, including one third of cancer deaths''; and they backed tougher action to combat smoking and control advertising;
- Busquin signed an agreement with the European Investment Bank aimed at boosting research in Europe through complementary loans to researchers and start-up companies—to back initiatives such as the European Mutant Mouse Archive, or the French bio-imaging systems company Imstar;
- The European Medicines Evaluation Agency in London granted authorisation for exceptional use of temoporfin for palliative treatment of advanced head and neck squamous cell carcinoma.

But the EU picture is not only complex: it is often confused. Ministers cut the proposed budget for the public health programme—from an already sparse €300 million to €280 million. The EU fights tobacco—but continues to provide heavy subsidies to tobacco farmers. Tobacco advertising controls were introduced in 1998—but were ruled invalid by the EU's own Court of Justice only last year. And the EMEA endorsed temoporfin only on appeal, and only by a majority vote.

"COORDINATION COULD CONTRIBUTE TO IMPROVED SCIENTIFIC QUALITY OF RESEARCH"

A coherent EU approach has still to emerge. As Dr Bill Baig, a senior Commission official who has been involved in EU policy on cancer for 10 years, complains: "We waste half our money by pure duplication by everyone working in the same field". But even if the EU has a long way to go—and the perception of the EU is often as low in the research community as it is among the public—he is optimistic that a new era is opening in the EU fight against cancer. This column will be watching closely.

Peter O'Donnell
Brussels

Longer interval in prostate cancer screening?

A screening interval of 4 years is short enough to constrain the development of large tumours, say researchers in The Netherlands (*J Natl Cancer Inst* 2001, **93**, 1153–1158). Few advanced tumours were found after the 4-year interval.

The study included 4491 men aged between 55 and 75 years, who received an initial PSA screening and were invited back 4 years later. Findings from needle biopsy cores were compared for men in both rounds.

Of adenocarcinomas detected in the first round, 25% had adverse prognostic features, compared with only 6% of those detected in the second round. This suggests that an interval of 4 years is not long enough for most large tumours to develop. In total, only 12 out of a total of 316 cancers were detected between screening rounds.

The study did not prove that screening for prostate cancer has a survival benefit, but it did address one of the major criticisms of such a programme: that it may lead to overtreatment for clinically unimportant tumours. The researchers found only a moderate increase in the fraction of category A tumours in the second screen.

The American Cancer Society has recommended annual PSA screening for prostate cancer since 1993, but the researchers say that no study has yet demonstrated that this is the optimum interval. Further, they found that baseline PSA levels did not predict the occurrence of prostate cancer and would not help select men who would benefit from more frequent screening.

The researchers conclude: "Our results strongly suggest that, even over an interval of 4 years between screening rounds, there was no evidence of unfavourable changes in the characteristics of detected carcinomas in the subsequent rounds of prostate cancer screening".

Patients say yes to chemotherapy

Many women with early-stage breast cancer would accept adjuvant chemotherapy even if it had no clinical benefit at all, say researchers in The Netherlands (*Br J Cancer* 2001, **84**, 1577–1585). They found that 39% of those receiving chemotherapy, along with 8% of those not eligible for it, would accept the treatment regardless of whether it would improve their outcome.

The study included 38 women with early-stage breast cancer who were scheduled to receive chemotherapy. They were matched with patients who were not going to receive it, on the basis of their experience with radiotherapy and the type of surgery they received. All were interviewed three times.

On average, 94% of the chemotherapy patients said they were willing to accept adjuvant chemotherapy for an improvement of 15% or less in 5-year disease-free survival, the mean benefit for those under 50 with positive lymph nodes. They concluded that the prescription of chemotherapy in this group was largely in accordance with patients' preferences.

In the no-chemotherapy group, patients were generally older and more likely to have negative lymph nodes, so their absolute benefit from chemotherapy was less, at an estimated 6.7% increase in 5-year disease-free survival. However, the study found that 26% of patients in this group said they would accept adjuvant chemotherapy for a benefit of 7% or less. The researchers say that the most likely reason why they were not receiving it was their physician's recommendation. "Most likely they were not offered chemotherapy and did not ask for it," they said.

Adjuvant chemotherapy may have hidden benefits for patients, such as providing women with a sense of control over their lives and with a feeling that they are doing something active to deal with the disease. The researchers say this raises questions: "If we adhere to patient autonomy and shared decision-making, are we willing to give burdening treatments to patients for cognitive and affective reasons?"

"ARE WE WILLING TO GIVE BURDENING TREATMENTS FOR COGNITIVE REASONS?"

"If we define a rational decision as one that complies with the priniciples of expected utility, it is clear that accepting a potential aggressive treatment without expected benefit is not a rational choice. To what extent should a health care system or society, tolerate such 'irrational' choices by well-informed and autonomous patients? Subsequently, if there are limits to the 'irrationality" that society tolerates, and is willing to pay for, who is going to set those limits?" they ask.

Care during last week of life

Almost one third of patients with acute myeloid leukaemia (AML) were receiving intensive treatment when they died, say Swedish researchers (Leukemia Research 2001, **25**, 673–680). They stress the importance of considering palliative care, especially for elderly patients.

The researchers analysed the medical and nursing records of 106 patients with AML who died between 1995 and 1997. They determined the phase of the disease at death and the extent of palliative care received by the patients. Overall, they considered 658 days of care.

Almost two-thirds of all the patients died in their home district hospital. Three-quarters had palliative care during the last week which, researchers say, "points to a certain restraint from curative treatment." However, patients aged 60 to 69 were likely to be referred to specialised hospitals and half of this group died far from home.

"The decision to give curative treatment in elderly patients is a question which needs careful consideration," they write, and suggest that people over 70, who have limited survival after aggressive treatment, "might prefer palliative care in order to have the best possible quality of life towards the end of life."

INTERVIEW

Professor Edith Oláh is president of the European Association for Cancer Research (EACR). She is a trustee for the Alliance of World Cancer Research Organizations and a member of several American Association for Cancer Research committees. A molecular geneticist, she co-ordinates the Eastern and Central European Cancer Genetics Network and has won numerous awards for her work. She is head of molecular biology at the National Institute of Oncology, Budapest, Hungary.

Professor Edith Oláh

Where did you train?
My first degree in biology and chemistry, and my Ph.D. in cancer genetics, are from the Eötvös Loránd University in Budapest. I spent 2 years at Indiana University in Indianapolis before returning to the National Institute of Oncology, Budapest in 1978. I have been here ever since.

Who inspired you?
My mother and an excellent biology teacher at my secondary school, István Kerényi, first directed my attention towards the life sciences. Then, Professor Sándor Eckhardt, who was director of the National Institute of Oncology, and president of UICC. He is a visionary, exciting to work with and he enthuses all those around him. We worked together to organise a UICC Congress in Budapest in 1986, and through this I met leading cancer investigators from around the world. In Indiana, Professor George Weber, who has pioneered work on the metabolism of cancer cells, introduced me to high quality cancer research and we have collaborated now for more than 20 years.

Like other Hungarian scientists of my generation, I was influenced by the so-called *genius loci*: an improbable number of scientific greats born in Hungary at the turn of the 20th century and afterwards. They include Albert Szent-Györgyi and later George Oláh, creative talents with high personal values.

Why did you choose to work in the field of cancer?
I didn't. After graduation, a job I had been promised did not materialise, and my genetics professor suggested I take a Ph.D. at the Research Institute of Oncopathology, Budapest. In the end, I was grateful for the experience because the position at the Institute was far better than I could have expected. The challenge of understanding the origin and nature of cancer has remained attractive.

Might you have done something else altogether?
I originally wanted to be a teacher and qualified to teach biology and chemistry. This wish was fulfilled eventually, through my teaching at Eötvös and Semmelweis Universities.

What has been the highlight of your career to date?
The last decade has been wonderful for genome research, and my group has made original contributions to understanding the molecular mechanisms of genetic susceptibility to cancer. But specifically, the highlight was being elected president of EACR, an extraordinary honour. In the 33 years since EACR was established, I am not only the first president from a non-western European country, but also the first woman.

. . .and your greatest regret?
Battles lost against cancer. In the year 2000, two very painful events were the death of Professor Mike Price, who—as Secretary General for 21 years—established the excellence of EACR, and that of Professor György Liszka, a great supporter of my group's work. Both devoted their lifetime's work to conquering the cancer which finally killed them, and both were my very best friends.

If you could complete only one more task before you retire, what would it be?
To explain why central Europeans, particularly Hungarians, top the world cancer mortality lists.

What is your greatest fear?
That commercial pressure from the biotech industry is driving the application of information generated by genome research. The discoveries are very new and scientists need time to digest the information, to identify priorites for future research and to select the areas most likely to be beneficial. The Alliance of World Cancer Research Organisations was formed in response to this and many other ongoing challenges and opportunities in cancer research worldwide.

What impact has the Internet had on your working life?
I enjoy the benefits of easy communication, getting important information in a short time, but try not to be dependent on it.

How do you relax?
Good company and chatting with my family and friends; listening to classical music and reading poetry. I like to spend my summer holidays by the lakes where I can watch the amazing changes in a myriad of blue shadows in the interplay of water and sky. That's when I regenerate.

Who is your favourite author?
In this region of Europe we live in historic times and I like to read about the historic and scientific milestones of the 20th century. Essays by Sir Peter Medawar, who won the Nobel prize in 1960 for his work on tissue transplantation, are a particular intellectual and literary delight. I also make sure I take a book of English and American idioms on holiday with me.

What do you wish you had known before you embarked on your career?
I was not prepared for the negative and deliberately harmful aspects of human nature. I am not so sensitive now. I can accept people as they are, and just be pleased when I meet someone helpful!

What advice would you give someone starting out now?
Discovery is your business, accomplish extraordinary things, and work only on important problems. Always remember that cancer research is a cooperative enterprise in which we all lean upon and sustain each other.

What is your greatest vice?
The sunshine, but from under an umbrella.