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Clinical Trials Directive to be amended?

Amendments to the EU's Clinical Trials Directive (CTD) – or a replacement Directive – are expected in the summer of 2010. A public consultation on the CTD closed in January, 2010, and the European Commission is now considering the responses.

ECCO and some of its member societies – the EORTC and the European Society for Paediatric Oncology (SIOP Europe) – responded to the consultation. ECCO President, Professor Michael Bauman (University of Technology, Dresden, Germany), said, 'It is generally acknowledged that the CTD has had a catastrophic effect on the independent evaluation and comparison of drugs and other therapies by academic clinical researchers. It has greatly reduced the amount of academic clinical research in oncology in Europe in all treatment categories (surgery, radiotherapy and systemic medicinal therapy) and in their combinations'.

'Certain groups of patients have been particularly hard hit: children, patients with rare cancers, patients who would profit greatly from international trials that optimise already existing treatments and which, therefore, do not find commercial sponsorship, and elderly patients with other health problems, including secondary cancers due to earlier treatments.

The proposals put forward by ECCO, the EORTC and SIOP Europe include:

- Harmonising and refining the definitions of 'clinical trial' and 'investigational medicinal product' across all member states;

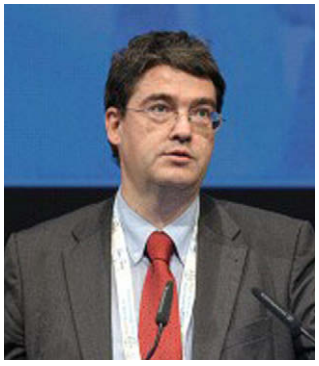


Photo: franknuerenberger.de

Professor Michael Baumann

- Harmonising rules to avoid confusion over interpretation of 'local rules' by competent authorities and ethics committees in different countries;
- Clarifying the role of the clinical trial sponsor. The need for a single pan-European sponsor is interpreted differently by national regulatory authorities and has caused severe delays to the launch of new protocols by long-established European collaborative groups;
- Simplifying the process of making amendments to trials;
- Improving and harmonising the way in which insurance for a trial is calculated \according to medically sound evaluation of risks;

The organisations said they made many other suggestions for improvement. Professor Baumann said, 'We hope the Commission's consideration of all the submissions made to its consultation on the directive will result in a reform of the Directive that really does lead to an improvement in investigators' abilities to conduct research into important questions in cancer treatment, for the benefit of patients and the competitiveness of European research.'

Ofatumumab in CLL

GlaxoSmithKline (GSK) and Genmab have announced that ofatumumab (Arzerra) has received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) for the treatment of refractory chronic lymphocytic leukaemia (CLL).

CHMP has recommended the conditional marketing authorisation of ofatumumab for CLL patients who are refractory to fludarabine and alemtuzumab. Ofatumumab is a novel human monoclonal antibody which targets the part of the CD20 molecule encompassing an epitope in the small loop. CD20 is expressed in most B cell malignancies.

Conditional marketing authorisation is granted to products with a positive benefit/risk assessment that fulfil unmet medical needs, when the benefit of immediate availability is seen to outweigh the risk inherent in the fact that additional data are still required. GSK will be required to provide further data.

EJC News is edited by
Helen Saul
Tel.: +44 1865 843340,
E-mail address: h.saul@elsevier.com

doi:10.1016/j.ejca.2010.02.001

Tobacco control in the 21st Century

A report from the American Cancer Society has outlined key challenges faced in global tobacco control, with a particular focus on low- and middle-income countries. There are now at least 1.3 billion tobacco users worldwide, the report states, of whom 14,500 are killed every day by the habit.

Support for the Framework Convention on Tobacco Control (FCTC) is 'the single most important action in the effort to eliminate tobacco-related death and disease', the report states (*Cancer J Clin 2010 doi: 10.3322/caac.20052*). All governments should be encouraged to join the 165 nations who already have ratified the treaty, and should faithfully implement it.

Raising tobacco taxes is 'perhaps the most effective intervention to reduce tobacco use' and increased access to comprehensive treatment for dependence is 'a cornerstone'.

Media-based tobacco countermarketing campaigns should be increased, along with health warnings on packaging, and regulation including basic consumer protections such as ingredient disclosure and accurate labelling. Health and economic information on tobacco should be more available, especially in low- and middle-income countries.

Health should take priority over commerce in trade agreements. The report argues that excluding tobacco from trade agreements is compatible with international law. The World Trade Organization (WTO) has said that, if necessary, governments may 'put aside WTO commitments' to protect human life. Litigation aimed at the tobacco industry needs to increase, the report states.

Basic and applied tobacco control research should be boosted, along with epidemiological and surveillance data. The other calls made by the report – the so-called 'decrease challenges' – include decreasing: tobacco use by health care providers; targeting of women, exposure to second-hand smoke; illicit trade and smuggling, duty-free and reduced-cost sales, tobacco advertising, promotion and sponsorship; youth access to tobacco.

World Cancer Day focuses on infections

The International Union Against Cancer (UICC) is calling for greater awareness of the contribution of infections to the global cancer burden.

Professor David Hill, UICC President, said, 'Of the 12 million people who are diagnosed with cancer each year, around 20% of cases can be attributed to viral and bacterial infections that either directly cause or increase the risk of cancer.

'For this reason the UICC, with over 300 member organisations in more than 100 countries will focus this year's World Cancer Day campaign on increasing awareness of the contribution of infections to the global cancer burden.'

A statement from the UICC notes the disparity between low- and high-income countries in incidence rates of cancer related to infections (26% versus 8%), access to prevention programmes and also treatment and care. For example, 80% of global cervical cancer deaths are in developing countries, and even where affordable technology is available, enormous challenges remain due to limitations in disease awareness and public health infrastructures, illustrated by the significant differences in the coverage of hepatitis B vaccination programmes worldwide.

The campaign is backed by a new report from the World Cancer Campaign, 'Protection against cancer-causing infections'. It covers the 9 infections that can lead to cancer.

Cary Adams, UICC's chief executive officer, said, 'The possibilities offered by prevention call for increased awareness of how some infections can lead to cancer. Policy-makers around the world have the opportunity and obligation to use these vaccines to save people's lives and educate their communities towards lifestyle choices and control measures that reduce their risk of cancer.'

'Cancer can be prevented too' is the theme of 2010 World Cancer Day

The '*Cancer can be prevented too*' campaign is aiming to raise awareness of six lifestyle and control measures: vaccination, regular physical activity, eating healthily, limiting alcohol consumption, reducing sun exposure and avoiding tobacco. *World Cancer Day is on 4th February every year. It is led by UICC and its member organisations with the support of the World Health organisation and key partners. To see the report, 'Protection against cancer-causing infections', visit www.worldcancercampaign.org.*

Unassisted smoking cessation is 'the most successful method'

Health authorities "should emphasise the positive message that the most successful method used by most ex-smokers is unassisted cessation," Australian researchers say.

Serious attempts at stopping need not involve using nicotine replacement therapy (NRT), other drugs or professional support. "Up to three-quarters of ex-smokers have quit without assistance," they write *(PLoS Med 2010 7(2):e1000216)*.

Unassisted cessation is seldom emphasised in advice to smokers, and clinical guidelines ignore it: "Smoking cessation is becoming increasingly pathologised, a development that risks distortion of public awareness of how most smokers quit to the obvious benefit of pharmaceutical companies."

Clinical trials show that those who use NRT have 50%–70% greater success than those using placebo. But clinical trials "typically overstate real world effectiveness" because of the free drugs and the attention paid to the participants by researchers.

The authors suggest that unassisted cessation "should be openly embraced by primary health care workers and public-health authorities" and conclude that "public sector communication should be encouraged to redress the overwhelming dominance of assisted cessation in public awareness."

EUROFILE

Towards European consensus on rare diseases

The European Commission is creating a Europe-wide committee of experts to advise and assist in formulating all legislation that affects the treatment and care of rare diseases. The move is a step forward in the Commission's strategy to tackle rare diseases, including rare and childhood cancers, on a European scale.

According to one Commission official, 'Given the wide range of stakeholders involved, we wanted a reference point where we can crystallise and pull together all the expertise and advice from across the sector with a broad enough participation that we're fairly confident it really does represent a consensus. And we wanted a formal enough mechanism so that people can see what advice is being given and how it is being used.'

Chaired by the Commission, the EU Committee of Experts on Rare Diseases will comprise 51 members:

- One representative from the department responsible for rare diseases in each member state;
- Four representatives from patients' organisations;
- Four pharmaceutical industry representatives;
- Nine representatives of ongoing and/or past rare diseases projects financed by the EU Health programmes, including three members of the pilot European Reference Networks on rare diseases;
- Six representatives of the ongoing and/or past rare diseases projects financed by the EU Framework research programmes;
- One representative of the European Centre for Disease Prevention and Control.

The remit of the committee will include advising on the EU laws governing clinical trials, cross-border patient healthcare, pharmaceuticals and orphan drugs. 'In the future if there is any revision of legislative framework in these areas, we would use the committee to make an input into those,' the official says.

The clinical trials directive may be one of the committee's first ports of call. The Commission is currently engaged in a stakeholder consultation on the directive, for which the cancer community in particular, is calling for revisions to the rules governing non-commercial trials *(see page one)*.

Another role involves evaluating areas being considered for legislation, such as screening for rare diseases. 'Screening raises sensitive scientific, medical and financial issues about cost-effectiveness. Before we went too far down that road, we'd want the opportunity to make sure we knew what the balance of opinion was across the community by putting it through the rare diseases committee,' adds the official.

'*MANY MEDICAL FIELDS ARE INVOLVED AND THE CANCER COMMUNITY SOMETIMES DISCONNECTS*'

The experts will also make annual recommendations for funding research activities through the EU's Framework research programme.

In addition, the Commission envisages the committee taking on a number of non-legislative tasks that would benefit member states. 'We have unfortunately all too many years of experience of projects under the health programme and many other community programmes, where they have very good results, but it's not easy to find them and their uptake is always an issue. Here, the committee can act as a reference point in translating results into opinions that can be a source of reference for the wider rare diseases community,' explains the official.

This could include the Europlan project to support member states developing their national rare disease plans. 'As the project comes to an end, some of the recommendations could be formulated through the EU committee on rare diseases as lessons we've learned,' he says.

'Wider issues of standards and approaches to healthcare are not a matter for EU competence but there's still enormous scope for sharing expertise. Everything from the technical side of registries and information gathering, to how better to evaluate new products and how they are going to be used,' he continues.

The Committee succeeds the 36-member Rare Diseases Task Force which ran from 2004 to 2008. The work of the Task Force has helped shape orphan drug legislation, the coding for rare diseases, the development of indicators and the dissemination of information.

One member of the task force who has applied to serve on the new committee is Jan Geissler, Director of the European Cancer Patients Coalition (ECPC) and the founder of the CML Advocates Network – a group of 42 chronic myeloid leukaemia patient groups worldwide. He said the attention on rare diseases is helpful. 'Because there are so many different medical fields involved, there is sometimes a disconnect by the cancer community. This is improper,' he says. 'The ECPC is convinced that we need to work closely with other groups on rare diseases to make sure we are not advocating for subdivisions instead of joining forces to do what would be beneficial for both groups.'

Access to clinical trials and treatment are major concerns to Geissler and to another ex-task force member who has also applied to serve on the committee - Gemma Gatta, leader of the EU Rarecare project on the surveillance of rare cancers in Europe. 'It will be very important for the committee to make population based evaluations of the outcomes of national rare disease plans, and come up with ways to improve access to treatment everywhere in Europe' she says.

Gatta also recommends an assessment of the pricing and re-imbursement of orphan drugs for rare diseases. 'Their cost is very high and prices differ across Europe,' she explains.

'Other rare diseases can learn from the experience of childhood cancers,' says Gatta. 'Many can be treated effectively, but sadly there is not the same access to treatments across the EU.

Saffina Rana
Brussels

Appropriate feeding balances risk and quality of life

Health-care professionals should establish multidisciplinary support teams to assess the nutritional needs of patients, concludes a Working Party report published by the UK Royal College of Physicians (RCP) on Jan 6, 2010.

The report, entitled *Oral Feeding* Difficulties, addresses the spectrum of cases for which artificial nutrition might be considered, and delineates the ethical and legal considerations that underpin this decision. It was occasioned, explains John Saunders (RCF London, UK)—one of the coauthors—by "widespread uncertainty over when gastrostomy feeding is appropriate and when it should be avoided". This uncertainty is restricted to patients with cognitive impairment, a situation that is not usually a factor for cancer patients. But there are several unresolved issues associated with artificial nutrition and cancer.

Caregivers in the UK have tended not to widely use parenteral nutrition in palliative care. According to British Artificial Nutrition Survey (BANS) in 2008, patients with cancer accounted for 15.3% of those receiving home parenteral nutrition. This is a much lower proportion than in Europe— particularly Italy and Scandinavia— and in the USA. It is tricky drawing conclusions from the USA, but it is reasonable to assume that insured patients face a much better chance of being offered home parenteral nutrition.

Barry Jones (BANS, Worcestershire, UK) admits that there are no comprehensive European statistics on this subject, but notes that "the data do suggest a very high representation of cancer as a primary indication for home parenteral nutrition, even up to 80% in some countries". Around half of these patients have obstruction of the bowel, usually caused by inoperable ovarian or colonic cancer. A combination of parenteral nutrition and a drainage tube allows such patients to spend time at home.

'*SOME PEOPLE MAY SEE IT AS EUTHANASIA ON THE SLY*'

Jones believes that poorly coordinated services have resulted in too few patients being sent home in England (he does not claim this for Scotland and Wales). "Patients in England are not being referred because oncologists don't know about the service or they think it's not possible or appropriate to provide this expensive treatment." He hopes that establishment of a home parenteral nutrition and intestinal failure clinical network will go some way to changing this situation.

By contrast, patients with cancer form an increasing proportion of the new UK cases of community-based enteral feeding: 36% in 2008, up from 25% in 2000. Most of these are cancers of the head and neck, oesophagus, and oropharynx. In some cases—eg, where the oesophagus is totally blocked—a gastrostomy is unavoidable. In fact, points out Jones, part of the reason the UK feeds so few people by parenteral routes is that so many are fed by enteral routes, and for head and neck cancers this is appropriate. "1n some European countries we think there is not sufficient emphasis on gastrostomies for these patients" he told *The Lancet Oncology*.

Nonetheless, there are occasions when oral feeding is not done for fear of spillage into the lungs. Saunders believes that this is overcautious. "It's a legitimate risk to take in order to preserv equality of life", he said, "feeding is not just a question of calories; it's part of a living experience and to deprive someone of that on the grounds of some small risk is not acceptable".

The RCP report is predicated on the notion that medical considerations are not the sole determinant of a patient's best interests. These issues are particularly knotty when it comes to end-of-life decisions. In the UK, withdrawal of nutrition is widely misunderstood, "some people may even see it as euthanasia on the sly", concedes Saunders. Part of the function of the prospective nutritional support team would be to outline to patients and families the sharp loss of appetite that attends the final stages of terminal cancer; and the scant difference that maintaining nutrition makes to life expectancy in such cases. The team might suggest that sufficient intake be provided to satisify' a patient's residual appetite, but not so much so as to meet nutritional requirements. There is a rough parallel with chemotherapy: patients might already have wrestled with the cost and benefits of continuing such treatment. "The object of therapy at that point may be to secure good symptom control and reasonable quali of life" Saunders adds.

"We have to think about nutrition in cancer" urges Jones, "It's terribly important that there are proper links between oncology centres, dietetics services, and multidisciplinary teams within each hospital". Nutritional teams, for example, are only operating in 60—65% of acute hospitals in the UK.

Jones cites occasions in which patients with cancer have died of malnutrition. 'We cannot separate the nutritional consequences of cancer from the treatment of that cancer', he told *The Lancet Oncology*.

Talha Burki

This story originally appeared in Lancet Oncol 2010; 11:117

Vitamin D levels linked to risk of colon cancer

High blood levels of vitamin D were associated with a reduced risk of colon cancer in a large European study. The risk was cut by 40% in people with the highest levels, compared to those in the lowest.

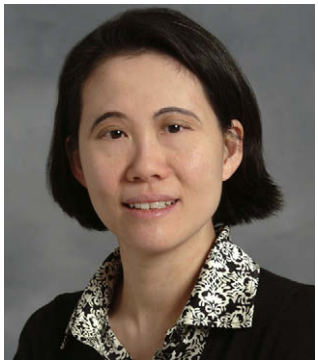
The findings are based on the European Prospective Investigation into Cancer Study (EPIC), which included 520,000 people from 10 western European countries. Between 1992 and 1998, participants completed detailed dietary and lifestyle questionnaires, and gave blood samples. They were tracked for several years, during which 1,248 cases of colorectal cancer were diagnosed, and they were matched to 1,248 healthy controls.

The results support a role for vitamin D in the aetiology of colorectal cancer, but the authors caution that little is known about its association with other cancers, and that the long term health effects of high circulating concentrations, potentially obtained by taking supplements and/or widespread fortification of some foods, have not been well-studied.

(*http://www.bmj.com/cgi/doi/10.1136/bmj.b5500*).

PODIUM

A window of opportunity in drug development



Professor Lilian Siu (University of Toronto, Canada) divides her time between drug development – in particular, phase I trials of new anticancer agents – and the care and treatment of patients with head and neck cancer. Her interests overlap in early testing of novel agents targeting head and neck cancers. Professor Siu recently joined EJC's editorial board as clinical oncology editor; and here she discusses the potential advantages of evaluating compounds in the pre-operative 'window'.

How significant are the problems associated with testing novel agents in the recurrent or metastatic setting?
They can be profound. Most of these patients will have had radiation and/or chemotherapy; their tumours are likely to have developed resistance which can prevent response to a new agent. Further, it can be technically and ethically difficult to take tumour biopsies for research among these patients: we need pre- and post-treatment samples in order to study mechanism of action, and it's not uncommon for one or both of the samples to be insufficient.

What is the alternative?
An attractive strategy is to evaluate new compounds in the preoperative setting. These tumours are fresh – the patients are newly-diagnosed and have never been treated – so there is a lower risk of treatment resistance that can confound results in the advanced cancer setting. The first, pre-treatment, biopsy is taken at the time of diagnosis and the post-treatment biopsy could be taken during surgery. We're much more likely to get 2 good samples.

In order to avoid delaying patients' curative surgery, the study drug is typically only given for a short interval, so it's unlikely to shrink the tumour, but this sort of study could provide insights into the pharmacodynamic effects of an agent and give us proof of mechanism.

Couldn't the drug be given for longer?
No. We're cognisant that these patients have a curable disease and we can't delay their definitive treatment. We're proposing to test new agents while patients are waiting for their surgery, hence the term 'window of opportunity'. But even after a few days' of treatment, we should be able to see the drug's effects on the tumour tissue.

Is this approach being used?
In my institution and some others, this approach has been used in lung and breast cancers but there is not a lot of published work. We're finalising the protocol for a study testing a Pan-HER inhibitor in oral cavity cancer in this 'window'. The study design will allow us to look at the biomechanics of Pan-HER blockade, including those tumours which harbour the EGFRvIII variant.

We're hoping to get the study up and running this spring, and to have results by the end of 2011. That's an ambitious target; we'll need 45 patients in all but Princess Margaret Hospital (Toronto, Canada) is a high volume centre.

The concept of the pre-operative window goes beyond this drug; if this trial is successful it could be a model for many others.

Will the patients themselves benefit?
We're not expecting differences in outcomes. A drug taken for such a short period of time is unlikely to help too much in down-staging, although we're expecting some to respond. Taking part won't necessarily benefit the individual and, as with phase I trials, we won't describe it to patients as a therapeutic trial. This also means that we have to be confident of a drug's safety profile; we couldn't use this window for first-in-human trials. The drug we'll be testing is already being tested in phase II trials.

Have there been ethical barriers to setting up this study?
Surprisingly, no. As mentioned, breast and lung cancer groups in our centre have already gone through this approach with the Independent Review Board (IRB), and our design is similar. We find that most well-informed patients are interested to take part in research studies, when there is a strong scientific rationale to conduct these studies.

As an aside, my group has studied patients' willingness to undergo biopsies which are solely performed for research purposes. We found that the most willing partner is the patient, while medical oncologists and IRB members tend to be more conservative. Patients are often much more open to participating in research protocols than we think.

Will the drugs ever be used in the way they're being tested?
I suspect these drugs will never be used for such a short time unless there's a very dramatic downsizing of tumour. Ultimately, they're likely to be combined with radiotherapy or chemoradiotherapy or used in the adjunct setting. The purpose of the study is to improve our understanding of the molecular mechanism.

Finally, what do you hope to achieve as an editor at EJC?
As the only non-European on the Board, I hope to help the journal expand its authorship and reviewership on this side of the Atlantic. EJC has been moving in that direction already, and becoming more international, so this is an important step for both of us. From my own point of view, I'm enjoying working with the editorial board on this multidisciplinary journal. It's meant that I'm reading more than ever before and it's broadening my horizons!

Helen Saul