EUROPEAN CANCER ORGANISATION

Oncopolicy Forum 2011: Boosting Cancer Clinical Trials in Europe - Session 1

According to former ECCO President **Michael Baumann**, the scientific community needs to learn to "speak the same language" as policy-makers in the upcoming revision of the EU Clinical Trials Directive (2001/20/EC) to avoid making the same mistakes that occurred in the original legislation. Welcoming delegates, Chair of this first session of the Oncopolicy Forum Michael Baumann explained the Forum's goal of promoting multidisciplinary discussions between health professionals, patient advocates and policy-makers to determine the best ways to improve the care of cancer patients and the organisation of research.

The Clinical Trials Directive, which came into force in 2004, has attracted widespread criticism from both the medical and scientific community. One key problem at the time, said Baumann, was the failure of the scientific oncology community to foresee the impact that the Directive would have on their work. Since then ECCO, together with its Member Societies the European Organisation for Research and Treatment of Cancer (EORTC) and the European Society for Paediatric Oncology (SIOPE), has acted as an umbrella organisation for their 24 Member Organisations to coordinate statements and activities.
He provided an overview of the discussions on the Directive to date and the revision process and noted that a key finding of the 2011 'Concept Paper' by the European Commission, which attracted 143 responses, was that clinical trials conducted by academic non-commercial sponsors should continue to be included in the scope of the Directive.

The way forward to counter the bureaucracy of clinical trials in Europe, said Director-General of EORTC **Françoise Meunier**, is to "streamline, simplify and harmonise". Setting the background of the EORTC, created in 1962 to conduct independent, international clinical trials, Meunier explained that this dynamic organisation includes a network of 300 institutions across 29 countries. Indeed, each year the EORTC enrols around 6000 patients to clinical trials and maintains a database of more than 180,000 patients. With less than 5% of patients currently entered into clinical trials in Europe, there is an urgent need to boost the participation of patients in order to maintain medical excellence and ensure both competitiveness and innovation.
Exploring the impact that the Clinical Trials Directive had on the EORTC, Meunier said that there had been a decrease in the number of studies undertaken between 2003 and 2010, but an increase in the number of staff employed and resultant costs.
The advent of personalised medicine has resulted in a new requirement in oncology trials to screen large numbers of patients to find subgroups with appropriate markers. Consequently large-scale international collaborations have been promoted and small-scale trials have been discouraged.
EORTC proposes a "one-stop-shop" procedure for the authorisation of international clinical trials, and the creation of a single electronic submission portal, which would be in English, encompassing both competent authorities and ethics committees.
Clinical trials in the 21st century need to involve collaborations between patient organisations, charities, academia, policymakers and the pharmaceutical industry. There is a need, said Meunier, to establish stronger partnerships with industry, while at the same timing maintaining the all-important academic independence.

For personalised medicine with affordable costs a completely different model is needed for conducting cancer clinical trials, argued **Martine Piccart**, President-Elect of the European Society for Medical Oncology (ESMO).
In her presentation, Piccart, President of the European Society for Medical Oncology (ESMO), provided the benefit of her experience as principle investigator of the BIG01-01 HERA trial of trastuzumab in breast cancer. In the pivotal adjuvant trial investigators found that among HER2+ women given trastuzumab the cancer returned in a significant proportion of patients, although less than in the chemotherapy alone arm. What trialists failed to take into account,

commented Piccart, was that not all HER2 positive tumours are addicted to HER2 and that a proportion of them rely for their survival on compensatory pathways.
The experience emphasises the need for greater efforts in the identification of biomarkers to predict efficacy. But despite publication between 1999 and 2009 of over 1700 papers exploring preclinical resistance to antiHER2 therapy, no single biomarker has been validated to identify the subgroup, in which trastuzumab works.
Another issue, said Piccart, is that it may not be necessary to give trastuzumab for the customary duration of one year. The study never explored whether patients might have done just as well with three months treatment. Calculations suggest that a combination of "tailored oncology" (where trastuzumab is only prescribed to the 50% of patients who benefit) with a reduced three months duration of treatment would allow costs in the EU to fall from €2 billion to €250 million per year.
With many trials conducted exclusively by the pharmaceutical industry (who pay around $1.8 million for bringing each drug to market), funding the translational aspects of clinical trials can prove challenging. Piccart concluded her presentation with a suggestion for how translational research might be funded by changing the current system in Europe where pharmaceutical companies pay for procedures and 'standard of care' drugs included in trials. In the recent ALTTO trial, for example, where trastuzumab was compared to lapatinib, only 3 out of 18 participating countries funded trastuzumab (the current standard of care). A possible way forward that can free up budgets and allow the pharmaceutical industry to invest in translational research, suggested Piccart, would be to enforce national healthcare systems and insurance companies to fund the medical procedures and 'standard of care' treatments involved in trials.

Introducing the roundtable discussion, **Ingrid Klingmann**, a clinical pharmacologist involved in clinical trials, said the focus would be around three main issues: whether there should be a process of more central ethical review in multinational clinical trials; the definition of risk in clinical trial legislation, and whether insurance indemnisation should be covered by national health care systems.

"The current shift to personalised medicine", said **Elena Colajori**, the Clinical Development Head for Pfizer Oncology, "creates the need for studies to be conducted in multiple countries to allow for adequate accrual of subsets of molecularly-identified patients".

"While the principal of the Central Ethical Review should be positively welcomed", said **Roger Wilson**, patient advocate and Founder of Sarcoma UK, "different standards currently applied across EU countries." In the UK, for example, studies involve patients in the scientific peer review process, giving rise to concerns that multinational studies might no longer include such requirements. Any central review process introduced would need to adopt the highest of standards identified in Europe, rather than opting for "the lowest common denominator". "A centralised system", commented Wilson, "might benefit some countries in Europe, but hold back others." He underlined the importance of an impact assessment of a centralised system that can gauge its success and identify any adverse effects for individual countries.
Wilson also pointed out that currently in the UK there are more clinical trials running than ever before and it would be detrimental to our common aim of improving patient outcome if any change to the current legislation was to impact negatively on the number of trials being run.

Europe has a choice to make, stated **Martin Seychell**, Deputy Director of the European Commission's Directorate for Health and Consumers, over whether the region remains a key player in health research or becomes sidelined. Until there is true harmonisation of legislation between countries, Europe will not be able to function effectively, and there is a danger Europe could be far less competitive if this issue is not urgently addressed. The European Commission is dedicated to ensuring this legislation is amended but it is a significant challenge. Problematic issues include foreseeing how legislation would be implemented in

practice at both national and local levels, and ensuring all stakeholders are involved, such as the legal profession being involved in discussions on ethics.

Implementation of the Directive at national level, stated Fellow of the European Academy of Cancer Sciences **Jacek Jassem**, could prove more restrictive than the actual Directive itself. In particular, there is an important need to achieve a balance between safety on the one hand and feasibility on the other. Jassem provided the example of his home country Poland, where the academic community has fallen victim to significant regulatory barriers, resulting in the disappearance of most academic trials since the implementation of the Directive. Polish investigators are still facing significant challenges to participate in EORTC studies.

The only way for Europe to become truly competitive, stated **Otmar Wiestler** of the German Consortium for Translational Cancer Research, is for the widespread introduction of large-scale clinical trials. He raised concern about whether more specialised trials, like the use of viruses, should actually be covered by a central European authority. In such specialist situations, trials may function more efficiently if covered by national agencies, or at expert branches of national agencies. What needs to be avoided on the other hand, stressed Wiestler, is a fall back to national solutions, since this would create significant problems for the large number of patients required for personalised oncology trials, which are likely to be more common in the long-term.

Outlining the three proposed categories of risk in clinical trials, **Ingrid Klingmann** explained the concept of studies where drugs without marketing authorisation are used; studies where drugs with marketing authorisation are investigated outside their authorisation; and studies where drugs with marketing authorisation are used within their label.
From the patient perspective, **Wilson** reacted positively to the solution for a more simplified and straightforward approach; the one-stop-shop concept could make it easier for patients to understand the clinical trial procedure and even encourage greater patient participation. He thought the “simple delineation” being proposed was easy to follow. Colajori also welcomed the more simplistic approach being considered, but was keen to point out that high safety standards and reliability need to be retained.

For drugs with lower risk, commented **Martin Seychell**, greater simplification is needed, but this should not mean that standards for subject right safety and reliability and robustness of trial data are lowered.
The current system, said **Jassem**, lacks pragmatism and common sense, and any approach that can simplify the system without jeopardising patient safety should be welcomed.
In addition to the pharmaceutical agent risk categories outlined, suggested **Otmar Wiestler**, quality control procedures for participating research centres need to be established.

On the subject of ethics committees, **Klingmann** posed the question of whether a single vote per country involved in clinical trial might be achievable.
According to **Jassem**, creating one ethics committee at the international level would certainly help to increase the quality of decision-making. Of course, certain cultural features in different countries would still need to be taken into account.
While legislation can establish a framework, said **Seychell** of the European Commission, it is unable to change the way people view issues.
Ethical decisions, felt **Roger Wilson**, should be made as culturally close to the patient as possible. He also makes the point that information alone is not the key to better patient accrual to clinical trials. He believes that a lot of the UK’s current success (19% of all cancer patients in clinical studies and 8% in RCTs) is due to trained nurses taking consent. They can spend more time giving information, they often have a better empathy with patients, and they are more accessible by phone to answer questions.

On the suggestion that clinical trial insurance liability should be reimbursed by national health systems, Mr. **Seychell** raised the point that the current financial crisis is affecting some

European countries to a greater extent than others. While the need for long-term sustainability is recognised, due to economic difficulties facing several countries, this will not be easily resolved.
New joint initiatives are required with partnership between, industry, private parties and national organisations in order to fund clinical trials, said **Otmar Wiestler**, with special recognition of the funding needs of early clinical trials, rare tumours and lower-income countries required.

Summarising the discussion Session Moderator **Ingrid Klingmann** said there had been agreement on the need for a more centralised approach to multinational trials. After hearing the debate, 61.8% of the audience voted to support the introduction of three risk-related drug categories for clinical trials; 80% felt that a more central ethical review of multinational clinical trials should be introduced and 66.7% supported the concept that insurance indemnisation should be covered by the healthcare systems of different countries.

If you have any comments about any of the issues raised in this report or would like further information, please contact ECCO Public Affairs: EccoPublicAffairs@ecco-org.eu