Research Forum: EPAAC Work Package 8

Monday 2 July 2012, Sofitel Hotel Europe

Session One: Introductory session

The European Partnership for Action Against Cancer (EPAAC) was developed with the aim of rallying the whole of the cancer community along four themes: health promotion and early detection, dissemination of good practices in cancer care, cooperation and coordination in cancer research, and comparable information and data. The three year Joint Action between Member States and the European Union, which began in 2011, is an interactive partnership between 36 associate and 90 collaborating partners active over 10 work packages.

The Research Forum was set up in the framework of EPAAC's work package on research. Organised under the responsibility of the European CanCer Organisation (ECCO), it was an opportunity for those involved in cancer research to come together and exchange views on improving cooperation and coordination and thereby addressing the fragmentation and duplication that currently characterise the European landscape.

Work package leaders **Agnes Buzyn**, President of France's Institut National du Cancer (INCa) and **Julio Celis**, Chair of ECCO's Policy Committee, introduced the meeting, explaining that while there has been significant progress in understanding of the disease, translation of these discoveries into tangible benefits for the patient has not been equally impressive. Barriers in the innovation cycle have prevented discoveries moving into the clinic and a concerted effort is needed to improve translation through better coordination at EU, national and regional levels. Indeed there is international consensus that improved research outcomes are dependent on enhanced coordination. Currently impeding optimal coordination is lack of communication between important actors and across countries. Improved awareness of how other countries organise and prioritise their research activities, and alignment of their policies in joint orientations could dramatically improve cancer research outcomes.

Work Package 8 is entrusted with the objective of devising an approach for the coordination of one third of research from all funding sources by 2013 in selected areas and launching pilot projects in areas where commonalities exist. The work package leaders affirmed their dedication to approaching this ambitious objective in the spirit of innovativeness and inclusiveness.

Ruxandra Draghia-Akli, Health Director of the European Commission's Directorate General for Research, explained that if current trends continue, healthcare systems may well be bankrupt within the next few years. Duplication of cancer research efforts between and even within Member States is a waste of already scarce resources, and an alignment of research efforts combined with sustainable mechanisms for long term joint implementation is urgently needed. She stressed two important points in view of these trends: that EU-level research networks which have invested considerable effort in discussing coordination must now begin to deliver on their objectives; and a step-change is needed in coordination between member states. Direct funding of cancer research by the EU accounts for only 3.5% of the total spent in Europe, implying that 96.5% of the money dedicated to cancer research comes from national budgets. The supranational level funds are generally used as seed money to

kick-start and support coordination of Member States' research efforts. A new, integrated approach to health research funding will be introduced under the next research framework programme - Horizon 2020 - set to come into force in 2014, rather than the disease-specific slant that has been commonplace under the current programme, FP7.
While mutual interest and drive amongst Member States is a prerequisite to further coordinating research efforts, the scientific community may demonstrate collaborative efforts through the sharing of data and knowledge, and contribute to devising a strategic health research agenda as a basis for coordinated action at European level.

Ian Banks, Chair of the ECCO Patient Advisory Committee, whose two-year work plan for the Committee is underpinned by the theme of collaboration, cited key principals that are required for fruitful collaboration between stakeholders and countries: using the right information, asking the right questions and acting at the right time, as well as speaking the same language. Moving from research to the care-giving setting, Ian Banks emphasised the importance of open communication between doctor and patient for optimal patient outcomes. Indeed, health literacy will be a major focus of the ECCO PAC's activities in the years to come. Lastly, Ian Banks expressed the importance of investing in earlier diagnosis and behaviour-changing activities for the future health of European citizens.

Mark McCarthy, research lead for the European Public Health Association, contrasted 'earlier diagnosis' – an unclear objective which may raise 'incidence' – with true primary prevention which reduces incidence, and asserted that investing in prevention has a greater impact on mortality rates, and is more cost-efficient, than investing in treatment. Low spending on prevention and health services research suggests that policymakers do not acknowledge them as priority areas. Similarly, cancer research predominantly focuses on biomedicine, and has significantly ignored socio-medical fields. Prospective research using disease registers is needed to demonstrate the outcomes of health system interventions, and population-based studies to determine the social and environmental causes of cancer, and the measures needed for control, while at individual level, Mark McCarthy proposed that 'personalised medicine' should be balanced with investment in 'personalised behaviours'. He stressed the importance of prevention and public health research within funding programmes at EU and national level. Joint programming should link member states, while ministries of health should work with ministries of science to address national health priorities.

The **general discussion** brought to light further pertinent issues. Primary prevention will contribute to control of other major chronic diseases as well as cancer, due to shared risk factors. While lifestyle choices are a responsibility of individuals, the importance of social, economic and political factors in influencing these choices must be recognised. Health education in schools must be combined with greater health awareness throughout adulthood. While it is difficult to translate these ideas into concrete policy initiatives, especially where they challenge the commercial interests, policymakers serving the public should draw on existing evidence for interventions with known positive results, and support research for new policies in the future. These approaches could be developed through national research strategies for cancer control – which are lacking in many European countries.

Session Two: Public-Private Partnerships in early phase clinical research – Spurring access to innovative therapeutics

Fabien Calvo, Deputy General Director of INCa, explained that in recent years, France has set up a flagship coordination measure under its national cancer plan consisting of a framework between public and private partners to spur drug development through academic research. The French National Cancer Institute (INCa) has granted award of accreditation of early phase clinical trials centres in cancerology – Centres Labellisés INCa de Phase Précoce (CLIP²) - healthcare institutions authorised to treat patients and to participate in clinical trials as well as having at least one site dedicated to early phase clinical studies. The CLIP² must be able to work in close collaboration with other institutions: indeed the 16 CLIP² involved in the scheme work with 28 molecular genetic platforms for personalised medicine.

The process starts with identification of a molecule of interest between INCa and involved pharmaceutical companies. CLIP² experts provide input on the molecule and the INCa and pharma sign an agreement to work together. A competitive call for proposals is undertaken and evaluated by independent experts. Selected projects are submitted to pharma and INCa for final approval then the full protocol is submitted by the selected project team. Contracts are signed between pharma and the sponsor institution of CLIP², and between INCa and the CLIP², and the drug is then supplied free of charge by the company and the study started. Funding of the initiative is through INCa and the ARC French Foundation for Cancer Research, which support the CLIP² centres as well as the clinical studies.

The aim of the session was to assess to what extent this innovative method of coordination could be extended at European level.

Lamia Boudiaf, Medical Director of Oncology at Novartis, explained that this scheme is the first of its kind that Novartis has been involved in within Europe. The partnership with INCa benefits patients since it allows the development of innovative drugs in indications where a scientific rationale exists; where there is an unmet medical but where Novartis development plans do not cover the work. The scheme enhances current research in targeted therapies by involving academic experts from centres of excellence with molecular screening platforms accredited by INCa. It accelerates drug development in the right indications by involving INCa's accredited early phase clinical trials in the Proof of Concept (POC) studies that can guide/inform future developments. Lamia Boudiaf expressed Novartis' interest in continuing this collaboration and extending it to other molecules from Novartis' pipeline.

Asked which other European affiliates may be interested in participating in the partnership, Lamia Boudiaf explained that most European countries report to a different directorate to that which France reports to, but that there could be interest of other Member States to get involved in the initiative.

Jean-Yves Blay, Head of Department for Medical Oncology at the Centre Leon Bérard, explained that today we have a new vision of cancer. For example breast cancer is understood as a myriad of types of cancer, and treatment is based on molecular findings. Within EORTC, genomics approaches are used to respond to the new vision of the disease. Related to this, Jean-Yves Blay posed several questions for cancer research and care for the coming twenty years – Is it possible to organize healthcare systems to ensure optimal local treatments, surgery and radiotherapy, for all patients? How should we build simple academic clinical trials? Is it possible to organize annotated multinational tumour collection and storage to enable clinical research on molecular subtypes? How to recognize the driving mutations in individual patients to guide treatment? Can healthcare systems absorb the cost of targeted treatments?

Asked whether there should be a list of all cancers at European level, similar to the one for paediatric cancers by the EMA, Jean-Yves Blay responded that this is a crucial point, and the fact that individual countries do this is causing fragmentation whereas such a list should be explored at European level.

The evolution of standard randomised clinical trials was brought up in light of personalised medicine. While it has still been possible at European level to randomise in certain subsets of patients, randomised clinical trials are being carried out with fewer patients. The difficulty in changing the procedure stems from the fact that the EMA continues to require randomised clinical trials to be undertaken before authorisation is given.

Christelle David-Basei, Scientific Director of the ARC French Foundation for Cancer Research, described the activities of her organisation, a major French cancer charity, and what motivated the organisation to be part of the INCa initiative. The charity has six objectives: to discover causes and mechanisms of cancer development, to improve prevention and screening, to accelerate early cancer diagnosis, to improve existing treatments, to develop new therapeutics and to inform on advances and perspectives. The ARC French Foundation for Cancer Research's involvement in the partnership partnership allows unique access to innovative compounds and is grounded in excellence due to the INCa accreditation system.

Discussion with the audience

Michel Goldman, Executive Director of the Innovative Medicines Initiative, chaired a discussion with the audience. Asked what stage of drug development the partnership focuses on, Fabien Calvo explained that experience has shown that phase 2 trials are the norm for this type of initiative but the programme will also allow the development of phase 1 trials in association with other drugs. Potentially in the future the programme will even extend to phase 0. In terms of intellectual property (IP), the company is the owner of the developed drug and pre-existing related IP. The agreement signed between the sponsor of the trial and the company defines the conditions for access to the data generated during the trial. Comments from the floor included the suggestion to invite social security into the partnership. One way of extending the model throughout Europe could also involve the EORTC network. Asked whether there is any overlap between what the partnership is doing and what the International Rare Cancers Initiative is carrying out, Fabien Calvo replied that there is no overlap so far but rather they are complementary programmes. However, there is interest in working with the centres in the International Rare Cancers Initiative to develop innovation. Links with ECRIN are being explored and could be considered with EATRIS too. Partnerships with technology partners may be considered in the future – indeed a priority of INCa is to put technology at the heart of the organisation's mission.

The partnership can be seen as a unique approach driven by academics which has led France to set up a network of centres which are quality assured. If this model could be expanded and extended at European level it could profoundly change the way Europe implements high quality early phase clinical trials. A similar endeavour is being carried out in the UK, which, together with the INCa initiative could become part of a broader effort at European level. Italy also expressed potential interest. Michel Goldman recommended further discussion about the partnership with other pharmaceutical companies and to assess to what extent the Innovative Medicines Initiative could help extend it outwards. Michel Goldman added that it is sometimes difficult to involve charities in this type of initiative and asked Christelle David-Basei how they could be attracted to participating. What is important for charities is visibility and quality. The INCa accreditation of centres in the present partnership is a proof of quality that is highly regarded by the Fondation ARC. Lastly, the involvement of patients in all stages of the initiative is important.

Session Three: Towards a European platform for outcomes research - Needs, challenges and opportunities

Outcomes research is used to understand the results of particular healthcare interventions and practices on individual patients and populations. The impacts of interventions include not only survival and disease-free survival but also important non-biomedical patient-reported outcomes. As such, it is a valuable means of assessing the value of particular interventions and an important discipline for guiding policymaking.

In Europe, outcomes research is sorely lacking in the oncology field, due in part to a lack of standardised tools and methodologies for assessing the impact of interventions on outcomes. This gap is all the more problematic in an era of personalised medicine.

Maria Ferrantini from the Italian Ministry of Health and Istituto Superiore di Sanita, explained that a platform for outcomes research at European level would provide much-needed evidence for further cancer research, health economics and clinical practice as well as research and healthcare policies. Much relevant data exists but the challenge is to build an information platform for the collection, aggregation, linking and analysis of data from quality assured patient registries and population based registries. Such a concept is tightly linked to the current proposal by work package 9 of EPAAC for a European Cancer Information System.

Paolo Baili from the Fondazione IRCCS Istituto Nazionale Tumori in Italy explained that setting up such a platform is more realistic in cancer than in some other diseases due to the existence of population based registries for cancer. The European Cancer Information System, which would provide a coordinated structure of knowledge and thereby serve as a basis for outcomes research, aims to bring together the currently existing networks, projects and institutions to set up a system for the provision of the knowledge needed to optimise cancer control activities. The proposal for such a system is grounded in the fact that cancer information does exist in Europe but is under-used due to fragmentation of data sources, barriers in data access and insufficient interaction between specialities within the cancer community, as well as difficulties in keeping information up-to-date and the lack of coordination between existing activities.

Jan-Willem Coebergh, coordinator of the EUROCOURSE project, highlighted the role of the European Network of Cancer Registries in improving population-based clinical evaluation of cancer care in Europe. EUROCOURSE is developing infrastructure in terms of context, content, working methods, funding, governance, coordination and legal framework, for over 150 cancer registries throughout Europe. A major issue for cancer registration is data protection, and Eurocourse, through its work package 2, is active in the discussions on the revision of the EU Data Protection Directive. An important fact to remember in the context of cancer information systems is that oncology is a constantly evolving discipline, and registries must be able to deal with the challenges of molecular medicine, increasing prevalence and survivorship amongst other aspects.

Cancer information being a building block of outcomes research, much more attention needs to be paid to the process of data collection in Member States. Furthermore, outcome indicators can be of prime importance. Finally, findings will only be translated into effective policy if there is the will and ability to present the findings in the form of compelling information for medical decision-makers and policy makers through the involvement of patient groups.

Ulrik Ringborg, coordinator of the EurocanPlatform, positioned outcomes research as an integral part of translational research. Translational cancer research represents the integration of the cancer research continuum, with early translational research bridging basic/preclinical and clinical research and late translational research bridging clinical research and implementation/evaluation of innovations in healthcare systems.

Ulrik Ringborg reinforced the view that in most European countries, information is lacking on the impact of anti-cancer therapies on outcome. Assumptions on their effects are usually based on results from clinical trials (i.e. clinical efficacy) but detailed data on clinical effectiveness (i.e. effects on population- based patient cohorts) is required for reliable assessments on outcomes.

The crucial importance of a complete infrastructure for outcomes research was framed within the assertion that personalised cancer medicine will be difficult, and probably impossible to develop and implement without it. Furthermore, detailed and quality-assured clinical cancer registries will create added value to population-based cancer registries. The EurocanPlatform is hoping to establish a platform of clinical cancer registries for outcomes research and clinical epidemiology and Professor Ringborg added that collaboration with EPAAC will provide value for both organisations.

Maria Ferrantini explained that a European platform for outcomes research would aim to create a system for assessing the dissemination and effects in clinical practice of health procedures of proven efficacy, on samples of unselected patients and in the general population. Proposed starting points include evaluating procedures to link data from population-based and clinical registries, and developing criteria and methods to ensure adequate sampling and statistical power of High Resolution studies in order to ensure representativeness. For practical reasons, as a starting point, a small number of selected areas in which both population based registries and clinical registries are present, would be dealt with. Possible pilot areas of study include:

- Evaluation of outcome (survival) after the introduction of new treatments for haematological malignancies (Imatinib for chronic myeloid leukaemia, rituximab for lymphoma, multiple myeloma)
- Sustainability and outcomes of personalized medicine
- Evaluation of overtime changes in survival for advanced stage disease.

Discussion with the audience

In the general discussion, the question was raised of whether less curable diseases such as glioblastoma and pancreatic cancer should be focused on, or more curable cancers such as breast, haematological, kidney, colorectal or lung, the argument for the latter being that it is much more difficult to show increases in curable cancers. The issue of patient confidentiality was cited as of central significance to the discussion. Security of patient data has to be guaranteed as a matter of priority. In some countries observational studies are very difficult since informed consent is required. The variations between countries in this respect may be due to different interpretations of the EU Data Protection Directive by Member States.

On a side note, the PARENT joint action was cited as a means to collaborate on joint approaches to cross-border registry data exchange for research purposes.

In terms of practical next steps, a word of caution was given that the quality and comparability of data is of prime importance and should be dealt with before large ambitions are set upon. Another suggestion is that information and infrastructure already exists in the field of breast cancer, and therefore this could be a point of departure for the platform. How the platform could be funded is a critical issue and the instruments and funding sources for realising the project need to be carefully considered. It might be timely to involve finance ministers in the discussion since the need for investing in such an infrastructure should be supported at a high political level.

Session Four: Improving coordination and collaboration in cancer research- New ways forward

The objective of the last session was to cast a light on various models of cancer research coordination ongoing in Europe – at national, regional and European levels - and to understand to what extent these models could be adapted, extended or duplicated to further enhance coordination at European level.

Jane Cope, Director of the UK's National Cancer Research Institute (NCRI) explained that the role of the NRCI is to facilitate communication, coordination and collaboration amongst its members. Although coordination and collaboration are not always easy, they are means of optimising scarce resources. As well as identifying synergies between members and proposing consortia, the NCRI boasts a cancer intelligence network merging cancer registration data with other health data such as hospital statistics, networks for all phases of clinical trials and community-led collaborations such as clinical studies groups and a confederation of cancer bio banks.

However, the challenges that are inherent in such coordination actions include lack of awareness amongst the different players of each others' activities, the fact that investigators are, to an extent, conditioned to compete for resources rather than to collaborate, lack of understanding between researchers and funders as well as different agendas of funding organisations.

Jane Cope explained that the first step to improving cooperation is to share information. In the UK, data showed that research was scarce in areas such as prevention, outcomes research and cancer control which then led to the creation of specific research agendas in some of these areas.

Some key ideas for effective collaboration include the setting up of research databases, development of funding consortia through a bottom-up approach, identification of synergies amongst funders or between countries, identifying common ground between researchers and funders, increasing strategic funding of research, making funding conditional on collaboration and bringing research and health ministries together. Finally the fact that different funders or countries have different levels of readiness to collaborate should be respected.

Liisa Pylkkanen, Medical Director of the Cancer Society of Finland, explained the coordination model embodied by the Nordic Cancer Union (NCU). The NCU dedicates 1 million Euros per year to strategic collaborative cancer research carried out between at least two Nordic countries across a broad spectrum of topics in basic science, epidemiology and clinical research.

Nordcan is a tool for cancer information, planning, quality control and research that is financially supported by the Nordic Cancer Union. It sets out incidence, mortality, prevalence and survival statistics from 41 major cancers in the Nordic countries.

Nordforsk is an organisation under the Nordic Council of Ministers that provides funding for Nordic research cooperation as well as advice and input on Nordic research policy. It uses a strategic approach to add value to existing research activities in the Nordic countries, thereby strengthening the position and influence of Nordic research, both in Europe and internationally. With the purpose of promoting excellence in research, the organization launches strategic initiatives which bring together national research groups in large-scale Nordic programs based on a common pot of funding.

The success of collaboration and coordination at Nordic level is due to long-term experience working together and to mutual trust between the partners. Further collaboration at European level is much needed and whether the Nordic model could be extended is a consideration for the future.

Fabien Calvo described French efforts to encourage collaboration and coordination at national level. Development of CLIP^2 (see above) and facilitation of collaboration between the eight French Comprehensive Cancer Centres has been a major focus. Further European instruments could include

the development of bio banks, cohorts and molecular genetics platforms. An example of a highly successful ongoing European coordination initiative, in which France partakes, is TRANSCAN (see below). Lastly, Fabien Calvo underlined the importance of maintaining a creative stance with regard to coordination methodologies within EPAAC. He also added that EPAAC is an opportunity to demonstrate that personalised medicine is a practical concept, and not just an intellectual one.

Bertrand Coiffier, President of the European Lymphoma Institute, gave the example of LYSA (Lymphoma Study Association) - formerly GELA (Groupe d'Etudes des Lymphomes de l'Adulte) - as a model of cooperation at European level in a single disease. LYSA, a European structure from the outset, now boasts over 130 centres from France, Belgium, Switzerland, Portugal and Luxembourg, and carries out large randomised studies.

The European Lymphoma Institute (ELI) complements the LYSA structure by promoting collaboration between European groups in Lymphoma and supporting patients' associations. The exceptional success of the European infrastructure for lymphoma is due to the focus on one particular cancer and the willingness of European physicians to cooperate. It is questionable whether such success would be seen if the model was extended to other cancers or diseases. However, such cooperation could be induced by European actions leading to the same efficacy.

Maria Ferrantini presented the TRANSCAN ERA-Net, the first example of a collaborative effort involving over 25 funding organisations, all of which are fully willing to coordinate cancer research activities. The project, born from the conclusions of the Eurocan+Plus project, maps the nature and extent of cancer research funding in Europe by using the CSO coding of individual projects. This will deliver information on the current extent of translational cancer research in Europe, and will enable identification of opportunities for coordinated funding, thereby reducing fragmentation in the future. There will be three joint transnational calls over 4 years, leading to the funding of multinational translational cancer research projects integrating basic, clinical and epidemiological cancer research. The forthcoming joint call will focus on cancer prevention, incorporating primary, secondary and tertiary prevention. The commitment of major European funding organisations to launch programmes on prevention is an important signal to politicians that prevention research is a real need and should be invested in.

Carlos Segovia, in charge of International Research Programmes and Institutional Relations at Spain's Instituto de Salud Carlos III, and who was chairing the session, concluded by affirming that excellence in science and the will of Member States to work together are important criteria for mobilising cooperation. He added that leadership is needed in order to mobilise actors and move cooperation forward. Specific instruments for use at EU level may include Article 185 initiatives[1] as well as Joint Programming.

In the general discussion, **Mark McCarthy** brought attention to the fact that the Structural Funds have an allocation for 'research and innovation' of €50 billion over seven years, which equals the funding available for the whole of FP7 programme. At present there is very little awareness of how these funds are being used, and particularly their integration with current European and national research programmes. Mark McCarthy asserted his wish for the European Commission to create a clearer integration between these two sources of funding through Horizon 2020.

[1] Article 185 TFEU (ex Article 169 TEC) states that:
"In implementing the multiannual framework programme, the Union may make provision, in agreement with the Member States concerned, for participation in research and development programmes undertaken by several Member States, including participation in the structures created for the execution of those programmes."

Conclusions and forthcoming activities

Agnès Buzyn concluded the meeting with some final thoughts on the next steps in the work package.

Increased cooperation is not an option but rather a necessity for the future, given the pressures on healthcare systems and the need to avoid dispersion of resources. There will be challenges and limitations inherent in the process, and ambitious, yet realistic goals which provide sustainable solutions, should be sought whilst respecting the priorities and readiness of each country. A bottom-up process of coordination should be developed through two pilot projects which will be further developed at a meeting in Paris on 18-19 October.

Julio Celis closed the meeting saying that in order for the work package to go forward, support from Member States is needed, in particular through participation in the pilot projects. Two possible pilot projects were discussed during the meeting, but the work package is not closed to further ideas. A strong consensus on the need for further research in prevention was reached so this could be a topic for a third pilot project. The European CanCer Organisation will reach out to Member States who were not present at the meeting to inform them of the discussions and invite them to be part of the process.

For further information regarding EPAAC Work Package 8 please contact **Anna Rouillard** at anna.rouillard@ecco-org.eu or on + 32 2 775 02 01