



EPAAC WP8 Research Workshop, 13th September 2013 Instituto de Salud Carlos III, Madrid

Pilot Project 2 “A European Platform for Cancer Outcomes Research”

Parallel session Summary report

Background

Objectives of Pilot Project 2

The EPAAC WP8 Pilot Project 2 (PP2) aims at the establishment of a platform for cancer outcomes research at the European level. Generally speaking, the ultimate goal of outcomes research is to assess the end results of healthcare practices and interventions both on individual patients and populations. The specific objectives of cancer outcomes research are: to describe, interpret, and predict the impact of interventions and other factors (socio-economic, organisational, technological, and behavioural) on ‘final’ outcomes (survival, disease-free survival, quality of life, perceptions and satisfaction related to healthcare, cost-effectiveness). Therefore, cancer outcomes research can well be considered an integral part of translational research, aimed at integrating early, i.e. basic/pre-clinical, translational research, clinical research, and late (clinical) translational research in order to speed up the application of novel products, tools and approaches in healthcare systems.

The specific objectives of PP2 are: i) overcoming the lack of information in current databases; ii) integrating population-based cancer registry data with clinical data derived from clinical sets and biobanks to explain the differences in survival across areas and over time; iii) overcoming the differences in clinical treatment patterns across countries; iv) evaluating the effectiveness of new treatments as well as of treatments recommended by guidelines. The PP2 objective in the intermediate term is to test the feasibility of obtaining multicentre outcomes research measures based on a commonly standardised methodology.

Moving towards PP2: steps taken and main achievements

EPAAC WP8 questionnaires: the consultation of the scientific community and policy makers on identification and prioritisation of areas in cancer research identified the implementation of a European platform for cancer outcomes research as a priority.

Interaction between EPAAC WP8 - Research and WP9 – Information: elaboration of a concept paper for PP2.

EPAAC WP8 Research Forum (Brussels, July 2012): the PP2 concept paper was presented in a panel discussion with funders, researchers, clinicians, patients, industry, public health experts and policy makers. A general agreement was reached on the importance of pursuing the PP2.

Follow-up workshop (Paris, October 2012): the concept behind PP2 was further elaborated between experts, by discussing concrete steps towards the implementation and design of a tentative roadmap. A *consensus* opinion was expressed on the following considerations:

- Currently, despite the development and validation of outcome measures in the context of the health services research area, standardised tools or methodologies for assessing the impact of interventions and other factors (socio-economic, organisational, technological, and behavioural) on final cancer outcomes are not applied at a pan-European level.



- This gap represents an obstacle to the: i) decision-making process, impeding the objective evaluation (benefit for the subjects/patients and cost-effectiveness) especially of new agents and strategies for cancer prevention, diagnosis/early detection, treatment and palliation; and ii) definition of a cancer research agenda intended to generate better scientific products and information, as well as to optimise the quality of cancer care through an evidence-based decision-making process.

It was therefore decided to proceed with the definition of PP2 specific objectives, tasks, and activities. To this end, a draft document was then elaborated in preparation of the follow-up meeting planned to be held in Valencia in April 2013. In parallel, the above mentioned concept paper was further refined and distributed in preparation of the Valencia meeting (see document “EPAAC WP8 Pilot Project 2_Concept Paper”).

Follow-up meeting (Valencia, April 2013): in this restricted meeting of the PP2 “core” group, represented by the Istituto Superiore di Sanità, the National Cancer Institute in Milan, Italy and the EurocanPlatform Network of Excellence (funded by the European Commission under the 7th Framework Programme), the above mentioned draft document focused on the definition of objectives, tasks, activities, and possible implementation measures for PP2 was discussed and further refined. As a result, a proposal was elaborated for the PP2 strategy (objectives, main tasks and related activities) and methodology, and identification of potential leaders for the various tasks (see document “European Cancer Research Outcomes Platform_strategy and methodology”).

Presentation of PP2 at the TRANSCAN meetings (Athens, June 2013): the state of PP2 development, as of the Valencia meeting, was presented to the funding organisations partnering in the ERA-NET on Translational Cancer Research TRANSCAN.

EPAAC WP8 Research workshop (Madrid, September 2013): The PP2 parallel session in the EPAAC WP8 workshop held in Madrid had the main objective of consolidating the PP2 proposal by defining the details, in terms of structure, objectives and activities and delineating the steps needed for PP2 implementation, through the discussion with selected experts, previously identified as potential participants in the different activities. The main outcomes are reported in the following section.

PP2 developments during and following the EPAAC WP8 Workshop in Madrid

The participants in the PP2 parallel session held during the workshop in Madrid (see document “PP2_parallel_session_draft agenda”) commonly agreed that, at the light of recent improvements in cancer diagnosis and treatment, the establishment of an European Platform for Cancer Outcomes Research would allow to investigate and compare the adherence to clinical recommendations, as well as the dissemination and impact of novel treatments in population-based set of patients, in relation to internationally agreed guidelines. As an example, those which are now being developed for breast cancer in the JRC initiative “*Voluntary accreditation scheme for breast cancer services and further development of European breast cancer guidelines*”. Similar JRC initiatives are envisaged for colorectal and other cancers. In this context, an important contribution will be provided also by the future European Union joint action (2014-2017) “Development of a European guide on quality improvement in comprehensive cancer control” (CanCon).

The key objectives and activities for the PP2 implementation, as outlined in the document “European Cancer Research Outcomes Platform_strategy and methodology”, were illustrated by the task leaders and discussed with the audience, as summarised below.

Clinical Cancer Registries (see presentation < EPAAC WP8 PP2_Task 1_Ringborg_Madrid_13092013 >. This task refers to the development of a methodology for: i) collecting information on the impact of diagnostic tools, treatment and intensity of follow-up on outcome, based on effectiveness (i.e. effects on population-based patient cohorts) and definition of outcome indicators; ii) obtaining comprehensive clinical cancer registries, including treatment of recurrent disease. These activities and objectives are of crucial



importance to overcome the current lack of information on the impact of anti-cancer therapies on the outcome in most countries. Currently, assumptions on the effects of anti-cancer therapies are usually based on results from clinical trials i.e. on the clinical efficacy. In contrast, detailed data on clinical effectiveness are needed, i.e. effects of therapeutic interventions on a population based patient cohort, particularly in the case of new therapies, to demonstrate effects of innovations for the patients: cure, survival and quality of life. In addition, data on clinical effectiveness are a prerequisite for assessment of cost-effectiveness.

The establishment of a platform of clinical cancer registries for outcomes research and clinical epidemiology is the ultimate goal of the EurocanPlatform WP11, (<http://eurocanplatform.eu>) chaired by Hermann Brenner, Cornelia Ulrich, Adam Gondos and Petra Schrotz-King (DKFZ and NCT, Heidelberg, Germany). The WP11 is currently focused on the compilation of comprehensive clinical cancer registries in selected cancer types, by collecting detailed information on the patient's characteristics, tumour data, primary treatment, treatment of recurrent disease, outcomes of treatments (individual treatments as well as integration of the complete clinical pathway), and follow-up.

The operational and functional link of these WP11 activities with the PP2 task aimed at linking population-based and clinical cancer registries is a pre-requisite and a cornerstone for the building of a European cancer outcomes research platform.

Linking Population-based and Clinical Registries (see presentation < EPAAC WP8 PP2_Task 2_Capocaccia_Madrid_13092013 >). This task refers to the development of a methodology for optimising and harmonising/standardising the process of collection, linking, sharing and analysis of cancer data between quality assured patient registries and population based registries, with particular attention to assuring quality and comparability of data. The rationale of this task is based on the need of optimising the use of data collected in population-based and clinical cancer registries to allow the evaluation of the impact of cancer care activities on public health impact and measurement of their outcome. The task activities will be implemented by building on the previous experience, such as that developed in the EURO CARE, EURO COURSE, EurocanPlatform, ENCR projects, among others. Possible procedures to be adopted, as well as indicators and outcomes to be selected and further defined, were presented and discussed. Their detailed definition as well as a roadmap for the next steps is currently under preparation in close interaction with the EurocanPlatform WP11.

High Resolution Studies (see presentation < EPAAC WP8 PP2_Task 3_Sant_Madrid_13092013 >. This task aims at the design, based on clinical sets of data, of new High Resolution Studies (HRS) in selected cancers, collecting specific clinical data in addition to those routinely available in cancer registries, for representative samples of patients. The importance of HRS for the assessment of cancer care outcomes has been already demonstrated by the EURO CARE project, that has repeatedly documented large inequalities in cancer survival across European countries and highlighted many inter-country variations. As an outcome of the EURO CARE studies, actions aimed at reducing disparities and improving the outcome of care for cancer patients have been already implemented in some countries. To better understand the functional importance of HRS in the context of a European platform for cancer outcomes research, it should be noted that different approaches can be adopted to evaluate the outcome of cancer care, and namely:

- **National vs international studies:** standardized tools or methodologies on cancer outcomes for assessing the impact of interventions and other factors (socioeconomic, organizational, technological, and behavioral) are applied mainly at national level, and their impact is difficult to interpret across countries due to the scarce comparability of data collected by different institutions.
- **Population vs hospital-based studies:** clinical registries are useful to identify outcomes of clinical relevance in the group of patients cured in an hospital (or in a group of hospitals). However databases based on all the patients cured in a specific hospital not always can be generalized to the whole patient population, as patients referring to a specific hospital may be selected, for example, according to socioeconomic conditions or disease characteristics, or other confounders. To avoid these selection



biases, it is necessary to perform studies on patients (or samples of patients) representative of the whole incidence set, for instance random samples from population-based cancer registries, as in HRS. Past experiences of HRS proved that a networking of European cancer registries represent an effective outcome research tool at a European level. Through the collection of information on patterns of care and follow-up data, in more detail than in the usual registry activity, HRS can contribute to implement a system for timely monitoring the adherence to clinical guidelines (for instance the European guidelines now being developed). While the short time objective of new HRS is to monitor timely adherence to clinical guidelines, a long term objective is to study survival and disease-free survival and the influence of patterns of care or comorbidity on prognosis. This action should however be based on a systematic and continuous collection of data by the population cancer registries included in the network. Beside conventional outcomes, such as survival or disease-free survival, other types of outcomes as quality of life (QoL) and health economy-related issues can be investigated. Of note, a number of European population-based cancer registries have already expressed their interest in carrying out HRS, aimed to investigate: i) the dissemination and the impact of new treatments in population-based set of patients; ii) frequency of and variation in adherence to standard care; iii) the reasons for differences in survival; iv) the reasons for overtime changes in survival for advanced stage disease. (*Note: the EPAAC WP9 organised on 25-26th September 2013 the 2nd European High Resolution Workshop at the JRC premises in Ispra with cancer registries and clinicians from 11 EU countries to define a protocol for a New European HRS on Breast, Colorectal, Lung, Melanoma to investigate and compare patterns of care, comorbidity and adherence to internationally agreed clinical guidelines for diagnosis and treatment for these cancers, and set the basis for updating follow-up and diagnosis of relapses or subsequent tumors, if any, to estimate survival and disease-free survival. As a result, a protocol has now been circulated and data collection for the new HRS will start in January 2014.*)

In the light of the rationale and objectives of PP2, the implementation of HRS in the context of this pilot project would represent a strong added value. In particular, HRS would guarantee:

- correct methodology for evaluating survival differences and adherence to guidelines at population level at international level;
- implementation of the same methodology also with hospital registry data;
- comparative analysis between the cases of clinical registries and population-based cases with respect to adherence to guidelines for diagnosis and treatment, frequency and type of pathological events occurred during follow-up in the long term, with mutual validation of the information contained in the respective series
- data collection and data organization also for the QoL and health-economy studies.

Stage Coding (see presentation < EPAAC WP8 PP2_Task 4_Van Eycken_Madrid_13092013 >. With the major objective of increasing the quality of stage-specific treatments, this task aims at the development of a methodology for consensus coding and categorising of cancer stage at diagnosis, and consistent stage recording for transmission to registries. The importance of performing these activities in the context of a cancer outcomes research platform was strongly underlined in the previous discussions on PP2. The main reasons being that, based on previous studies (Eurocare, HRS, Concord, among others), differences in cancer outcome appear to be dependent, among other factors, also on diagnostic imprecision and differences in stage distribution and stage-specific comparisons. As demonstrated by EURO COURSE (EUROpe against Cancer: Optimisation of the Use of Registries for Scientific Excellence in research), cancer registries serve 50-55% of the EU populations, of which only 60% record stage, because of lack of staff and/or finances and/or access to data. In addition, a concerted effort between EUROCHIP (European Cancer Health Indicators Project), ENCR (European Network of Cancer Registries) and EURO COURSE, demonstrated that only 15% of all the population-based cancer registries (PBCR) in EU had available all the three most important indicators for understanding inequalities in the cancer burden, care and survival, i.e. "stage at diagnosis," "cancer treatment delay" and "compliance with cancer guidelines" (Siesling S. et al, Int J Cancer. 2013 Jun 15;132(12):2910-7). Future work is needed to optimize the staging systems currently used in cancer registries, and HRS can be of high value to reach this objective. Based on the most critical



issues to be addressed, as presented in the PP2 parallel session, a roadmap for the next steps to be taken is under preparation.

Quality of Life. This task focuses on the development of a methodology for improving the collection of data concerning quality of life and functional status of survivors, through a cross-disciplinary approach and integration of the different data sources.

Lonneke van de Poll-Franse (IKZ Eindhoven Cancer Registry, The Netherlands), leader of the task, unfortunately could not attend the workshop. The specific task activities will be defined, taking into consideration all possible contributors, with particular reference to the OEI working group on survivorship.

Linking health economy to a platform for cancer outcomes research (see presentation < EPAAC WP8 PP2_Task_6_Jonsson_Madrid_13092013 >). Main objectives of the health care systems are: i) improvements in outcome (population health), including equity aspects; ii) evidence on cost-effectiveness, i.e. identifying the patients which will benefit most from any given intervention; and iii) well constructed evidence base, i.e. clear definition of which patients that should be treated. With specific regard to personalised medicine, definition of a target population is important for assessment of cost-effectiveness. Thus, to maximize the impact on population health, decisions about access and use of new cancer therapies by patients, payers and providers should be based on relevant evidence on effectiveness and cost-effectiveness. This means to address the following critical issues: i) development of evidence on outcome in clinical practice; ii) development of evidence for health technology assessment (HTA) and decisions about reimbursement; iii) equity and variations in patients access to treatments, including new treatments, between and within countries; iv) pricing and affordability. The data needed to be collected as well as the critical issues to be addressed were illustrated. A methodology for implementing the task activities is currently in preparation under the lead of Prof. Bengt Jönsson, Professor in Health Economics at the Stockholm School of Economics and leader of the “Taskforce on evidence based cancer medicine and cost-effectiveness” of the European Academy of Cancer Sciences.

Feedback from the participants.

A strong interest in PP2 was represented by ENCCA, the European Network for Cancer research in Children and Adolescents project (www.encca.eu) (see presentation < EPAAC WP8 PP2 - ENCCA_Cañete_Madrid_13092013 >). ENCCA aims to accelerate clinical and translational research in paediatric and adolescent oncology and to promote evaluation of and access to innovative therapies. In the context of ENCCA: i) the WP 11 aims to establish methods to work with cancer registries and linkage to other forms of routine health care data, in order to conduct prospective research in childhood cancers where the overall population has a good prognosis; ii) the WP 10 aims to develop risk-adapted therapies in solid tumors, mainly neuroblastoma. Based on these specific objectives, ENCCA expressed a strong interest in interacting with PP2 for establishing a cancer registry-wide study of survival from infant neuroblastoma, as an exemplar of this approach in childhood cancer. The aim is to include as much information as it is possible to obtain from either HRS or by linking to health records, to document the nature of the treatment received [surgery, chemotherapy, radiotherapy, MIBG (metaiodobenzyl guanidine)] and the date of progression or relapse. Clinical treatment decision making is complex in this very rare and heterogeneous disease entity and there is evidence that overall survival has decreased in the last decade when no standard treatment guidelines or clinical trials were available in many countries (see document “NBL worse survival in infants off trial Scientific report2010-NBL charts”). Of equal importance, survivors may suffer long term adverse health consequences from treatments that may not have been indicated in this cancer that has an overall very favourable prognosis.

The importance of the implementation of PP2 was also underlined by Prof. Giorgio Stanta, Chairman of the OEI (Organisation of European Cancer Institutes) Working Group on Biobanks and Molecular Pathobiology and coordinator of the IMPACTS group (www.impactsnetwork.eu) which, since 2005, has developed



validation and standardization of molecular methods in fixed and paraffin embedded tissues. These methods represent a unique tool for investigating, in tissues available in all the cancer centres and hospitals, the real clinical heterogeneity of cancer and for performing molecular analyses aimed at the clinical validation of biomarkers in archive tissues by multi-centric retrospective studies. The importance of applying said methods/approaches for the discovery of new biomarkers on a population basis, by linking the ensuing results to high-quality clinical data and population-based cancer registries in prospective studies, was underlined by Ulrik Ringborg and a general agreement was expressed by the participants. It was generally agreed that the operational link of the above-mentioned activities with those foreseen in PP2 appears of utmost importance for a “holistic” approach to biomarkers discovery and validation leading to an evidence-based prediction of biomarkers value for clinical cancer outcomes.

In consideration of the outcome of the PP2 parallel session, the envisaged and desirable functional and operational interactions between the EPAAC WP8 PP2 and other initiatives currently ongoing at the European level are illustrated in Figure 1.

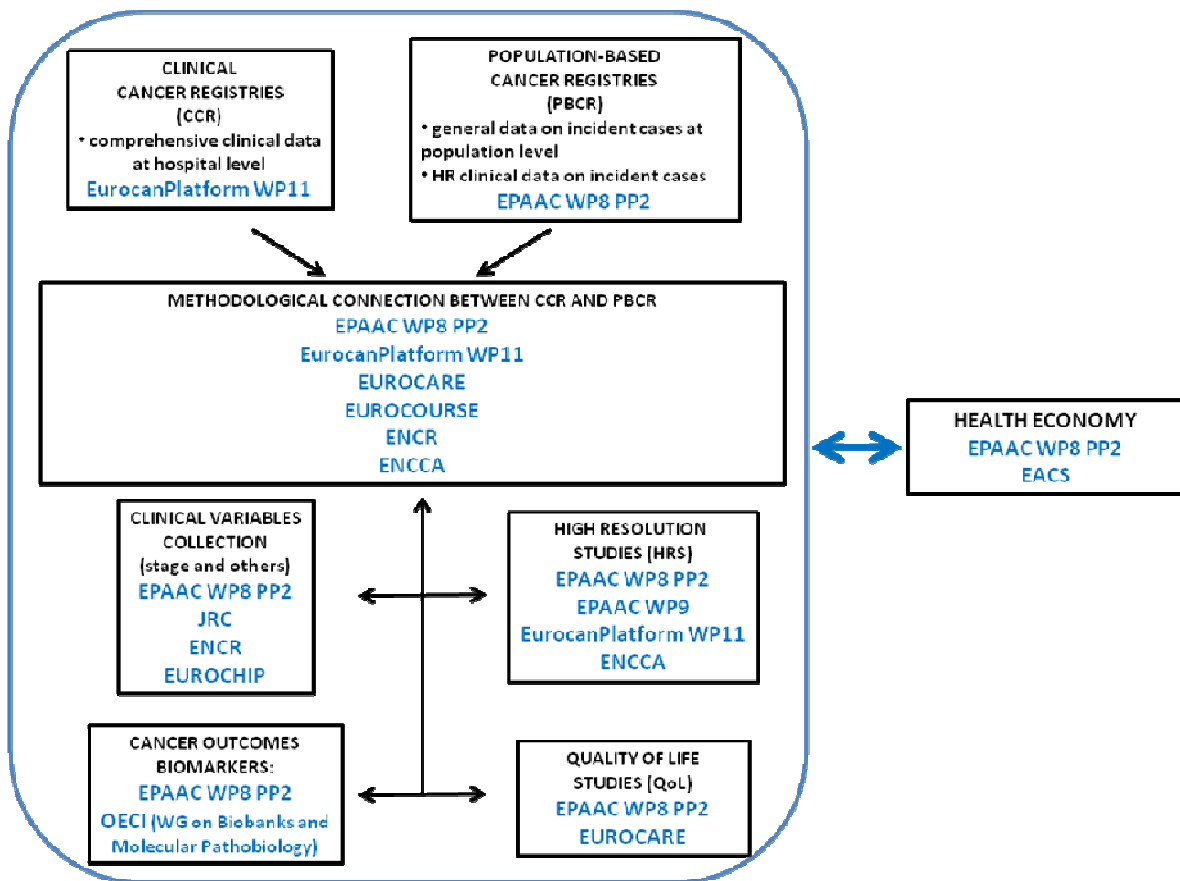


Figure 1: Possible functional organisation of a European Cancer Outcomes Research Platform.

Future steps

- A roadmap for the implementation of the above-mentioned activities as well as their detailed definition will be developed with all the interested actors, involving those indicated in Figure 1 but also including possible additional ones with whom initial contacts are ongoing or will be established



soon. As mentioned under the preceding section, the definition of such a roadmap is currently ongoing as for the tasks “Linking Population-based and Clinical Registries”, in close interaction with the EurocanPlatform WP11, and “High Resolution Studies”, in collaboration with the cancer registries and clinical centres already involved in these studies.

- Specific advice will be requested to the European Commission concerning options for the implementation of PP2, in terms of instrument/funding scheme, possibly to be started under the first Work Programme of Horizon 2020.
- In parallel, the issue of sustainability of a European Cancer Outcomes Research Platform will be addressed with all interested funding organisations, those partnering in TRANSCAN in the first place, with the aim of establishing a network willing to commit financially in said initiative.