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## Report of the workshop on the use of registries in the monitoring of cancer therapies based on tumours' genetic and molecular features - 29 November 2019

Patient registries initiative

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# 1. Executive summary

New cancer therapies targeting tumours' genetic and molecular features instead of the sites of origin in the body are being developed. Regulators have raised the need to explore the possible data sources that could be used to gather long-term data on the safety and effectiveness of these innovative treatments for which only limited information is available at the time of authorisation. In November 2019, the European Medicines Agency (EMA) hosted a multi stakeholder workshop including participants from regulatory agencies, registries groups, academia, industry, health technology agencies (HTA), health care professionals (HCP) and patients. The workshop explored the opportunities and challenges of using registries in the context of regulator assessments and post-authorisation follow-up of patients treated with these products. The expected outcomes of the workshop were to understand the landscape of cancer registries currently existing in Europe, to understand challenges and opportunities for their contribution to the evaluation of the new cancer therapies, and to start a brainstorming across stakeholders on which data elements, quality measures and governance aspects would be considered important to ensure confidence in the registries' data for regulatory use. The workshop did not aim at discussing the authorisation of specific products or the development of a centralised EU cancer registry to monitor new cancer therapies.

Prior to the meeting, participants provided information on their experience in working with and within registries: on their requirements in relation to monitoring the safety and effectiveness of cancer therapies targeting tumours defined by genetic and molecular features (as opposed to tumours defined by histology and location), on registry quality assurance and governance matters, as well as on data elements considered important to be collected. The information served as a basis for discussions held during the breakout sessions.

This report summarises the observations made by the participants on the use of registry data to support regulatory benefit-risk evaluation of these cancer therapies. It highlights aspects that should be considered by all stakeholders to facilitate the use of data collected by cancer registries, including the systematic collection of commonly defined data elements, the collection of data with an appropriate degree of quality, and the need for arrangements to permit data sharing between registry holders, regulators, marketing authorisation holders (MAH) and applicants (MAA). The workshop report is without influence on any EMA committee opinion on any products under evaluation or authorised in the European Union.

**Table: Summary of main actions and recommendations for the main stakeholder groups**

Group	Actions	Topic
<b>Regulators</b>	<ul style="list-style-type: none"> <li>Should seek information from registry holders regarding the challenges of collecting specific data elements that may not be part of the information routinely recorded.</li> </ul>	<b>Communication</b>
	<ul style="list-style-type: none"> <li>Need to clearly outline which data are required when requesting a study based on registry data (e.g. data on treatments, genetic and molecular tests, follow-ups, AE/SADR).</li> <li>Should indicate when they expect to receive the data required to make a decision.</li> </ul>	<b>Regulatory requirements on data elements and governance</b>
	<ul style="list-style-type: none"> <li>Should recommend a set of quality standards that should be applied (e.g. minimum quality requirements and standard terminologies).</li> </ul>	<b>Data Quality</b>
	<ul style="list-style-type: none"> <li>Should support registry holders to optimise data collection and quality of the data, e.g. through the EMA <a href="#">qualification</a> procedure.</li> </ul>	<b>General Guidance and workshop report</b>
<b>Registry holders</b>	<ul style="list-style-type: none"> <li>Should inform MAH/MAA and regulators about the data elements that are routinely collected, as well as other data elements that can be collected and shared, specifying the timeframes.</li> <li>Should inform HCPs and patients about the rationale for data collection, data sharing with relevant stakeholders and participation in registry-based studies; emphasise on the benefits it can bring to public health.</li> <li>Should provide adequate training programs to integrate the data collection process into the daily routine of care.</li> </ul>	<b>Communication</b>
	<ul style="list-style-type: none"> <li>Should involve patients in the review of their own data and facilitate dialogue with patients' associations if needed.</li> <li>Should collaborate with other registry holders to share experience on data collection and to increase harmonised processes for quality assurance of data.</li> <li>Should provide feedback to the centres on how they perform based on (nationally) established quality indicators, publication of periodic reports on registries data.</li> <li>Should provide transparent information on the data process flow.</li> <li>Should register their registry in the ENCePP Resources database.</li> </ul>	<b>Governance</b>

Group	Actions	Topic
	<ul style="list-style-type: none"> <li>• Should consider the use of common international standards on core data elements.</li> <li>• Should implement the collection of additional data elements as needed.</li> <li>• Should consider the possibility to routinely collect data on treatments, genetic/molecular tests, and AE/SADR to allow the registry to be considered as a potentially suitable data source for regulatory studies on cancer therapies.</li> <li>• They should also explore possibilities for later access to raw data on testing and to samples to address new developments in the concepts of diagnosis and management of disease.</li> <li>• Should consider opportunities such as the EMA <a href="#">qualification</a> procedure that may provide reassurance on the suitability of the data to support regulatory decision making.</li> </ul>	<p><b>Data elements, data quality and sustainability aspects</b></p>
<p><b>MAH/MAA</b></p>	<ul style="list-style-type: none"> <li>• Should anticipate the regulatory data requests that are likely to arise in the event of a successful marketing authorisation application, especially for post-authorisation surveillance.</li> <li>• Should engage at an early stage with registry holders to understand the feasibility of data collection (of common and additional data elements) by the registries and possibility of data sharing with other stakeholders.</li> <li>• Should consider using the Scientific Advice procedures to discuss the design and analytical plan of registry-based studies at an early stage in regulatory procedures.</li> <li>• Could provide funding in the frame of registry-based studies.</li> </ul>	<p><b>Governance</b></p>
<p><b>Patients</b></p>	<ul style="list-style-type: none"> <li>• May facilitate the use of their own data by consenting on their use and sharing with other stakeholders for regulatory purposes.</li> <li>• Could get involved in the quality of their data by peer-reviewing the information recorded in the databases (as applicable).</li> <li>• Could help promote data collection and sharing through registries via engagement with relevant stakeholders (importance of patients' initiatives, patients' associations).</li> </ul>	<p><b>Governance, data quality</b></p>

## 2. Background

There has been an important shift in oncology treatment towards new possibilities of treating cancers based on tumour genetics rather than the site of origin in the body. The first contemporary example is the treatment of adult and paediatric patients with solid tumours that display a neurotrophic tyrosine receptor kinase (NTRK) gene fusion, independent of tumour type/histology. Larotrectinib is an adenosine triphosphate competitive and selective tropomyosin receptor kinase (TRK) inhibitor which targets the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by NTRK1,

NTRK2 and NTRK3 genes, respectively. It was approved in September 2019 under conditional marketing authorisation in the EU. Another NTRK inhibitor agent, entrectinib, is currently under evaluation in the EU for the treatment of adult and paediatric patients with solid tumours that show an NTRK gene fusion as well as for the treatment of adult patients with ROS1-positive, advanced non-small cell lung cancer not previously treated with ROS1 inhibitors. Both larotrectinib and entrectinib were granted accelerated approvals in 2018 and 2019 respectively by the US Food and Drug Administration.

The evolving field of cancer treatment has implications on existing and future collection of pre- and post-authorisation data on cancer therapies.

### **Limitations of evidence supporting authorisation**

The efficacy and safety of larotrectinib were studied in three multicentre, open-label, single-arm clinical studies in adult and paediatric cancer patients. Due to the small sample size of the clinical trials for larotrectinib (e.g. up to 102 patients across 15 different histology types enrolled in 3 clinical studies with larotrectinib), the confidence intervals around the point estimates for efficacy are mostly wide, making estimates generally imprecise and hampering the possibility to draw conclusions regarding efficacy in subgroups with regard to age groups and gene fusion type. Comprehensive data on the product was therefore not available at the time of the marketing authorisation, hence the necessity for post-authorisation monitoring of the effectiveness and safety of such new cancer treatments under real world conditions in order to provide insight on clinical outcomes over time. In these cases, the preferred regulatory approach favours the use of disease registries owned by healthcare / public health / academic bodies over product registries, due to the small number of patients taking part in the pre-authorisation studies and their spread into a variety of subgroups, the need to recruit several histological sub-types, the need to collect comparative data and the possible introduction of new treatments for other genetically driven cancers.

### **Data sources for long-term monitoring**

Successful completion of the post-marketing requirements relies on the availability of data sources capable of supporting long term follow-up of these new products. In June 2019, the Committee for Medicinal Products for Human Use (CHMP) and Scientific Advice Working Party (SAWP) discussed the need to define data standards for tumour histology-independent cancer registry(-ies). It was therefore proposed that EMA would host a multi stakeholders' workshop to better understand the landscape of existing registries in Europe, as well as their capacity to collect and share data that could be used to support regulatory assessment of therapies based on tumours' genetic and molecular features of solid cancers. The workshop was organised in the frame of the [EMA Patients registries initiative](#) and took place on the 29<sup>th</sup> November 2019.

## **3. Workshop objectives, participants and methods**

### **3.1. Objectives**

The aim of the workshop was to provide a forum whereby experts from various stakeholders would brainstorm on the feasibility of using disease registries for regulatory purposes linked to cancer therapies based on tumours' genetic and molecular features.

The objectives were to start a dialogue on the following aspects:

- core data elements that should be collected in cancer registries to support regulatory assessment of long-term safety and effectiveness of new cancer treatments;

- quality assurance measures necessary to ensure registry data are of suitable quality to support regulatory evaluation and to permit registries interoperability;
- practical considerations for accessing and sharing data to be used for regulatory purposes.

### **3.2. Participants**

Sixty representatives from regulatory agencies including the EMA, registry groups, academia, industry, HTA, health care professionals and patients were present at the meeting, while members from the EU regulatory network could listen remotely.

Most workshop participants had experience with cancer therapies from a scientific, clinical or regulatory perspective. The workshop agenda and participants' list are included as Appendices 1 and 2.

### **3.3. Method**

#### **Pre-work package**

A few weeks before the workshop, the EMA sent participants a pre-work package with questions tailored to each stakeholder's type to seek their views on proposed core data elements to be collected by cancer registries, as well as on quality measures and governance aspects that should be put in place to ensure the registries can support the monitoring of the safety and effectiveness of cancer therapies based on genetic and molecular features, through appropriate data collection.

The EMA collated the responses and provided these as background information to the attendees prior to the workshop. The intention was that participants had a good understanding of each other's perspectives in advance of the meeting in order to facilitate group work on the day.

#### **Proceedings of the day – Morning plenary**

The meeting started with an introduction on the expected outcomes of the workshop by the Chair, Dr. Peter Mol (Dutch College ter Beoordeling van Geneesmiddelen - Medicines Evaluation Board). Dr Filip Josephson (Läkemedelsverket - Medical Products Agency, Sweden) gave an overview of the role of registries for generating data on cancer therapies from the regulators' perspective. Examples on how registries could contribute as a source of information to regulatory assessments were provided, e.g. to help describe the prevalence and prognosis of biomarker selected populations, to help define comparator cohorts for single arm trials, or to use in the context of post authorisation efficacy studies (e.g. informing on outcomes achieved overall or in subgroups or special populations), and in the context of post authorisation safety studies (e.g. addressing drug specific safety issues, or safety in special populations). The potential use of building comparator cohorts for single arm trials was discussed particularly critical. Dr Otto Visser, Chair of the Dutch cancer registry (Integraal Kankercentrum Nederland (IKNL), gave a presentation on the European Network of Cancer Registries (ENCR), highlighting the data elements that cancer registries currently collect and discussing the challenges of cancer registration in Europe. Hélène Le Borgne from the Directorate General for Health & Food Safety (DG SANTE) of the European Commission (EC) introduced the registries for the 24 European Reference Networks (ERNs), in particular the 4 ERNs dealing with paediatric and rare cancers, emphasizing on the importance of creating a network to exchange expertise and clinical data on cancer patients' cases through registries. This approach is currently facilitated by the EC through financial grants allocated under the EU Health Programme to support the development/use of registries for rare diseases (RD) and through collective efforts. The aim is to align approaches and data elements across ERNs thanks to tools such as the "common data elements" agreed upon in the field of RD with the support of the EC Joint Research Centre (JRC) and the EU RD platform. Finally, Alice Turnbull gave a very detailed overview of the National Cancer Registration and Analysis Service (NCRAS)

administered by Public Health England with a focus on how data collection on cancer including tumour agnostic treatments is organised, data quality is assured, and data sharing is allowed in line with applicable legislation.

All the presentations have been published on the [workshop webpage](#) of the EMA website.

### **Breakout sessions**

The participants were divided evenly into three working groups composed of 2 moderators to ensure that each stakeholders' type would be represented and would contribute to the three topics as follow:

- **Group 1** on data elements;
- **Group 2** on quality assurance;
- **Group 3** on governance.

Throughout the working group discussions, the moderators made notes of the participants' observations (also taking into account the responses to the pre-work package received before the workshop) to be reported back to the plenary, and to provide content for the final workshop report.

### **Afternoon plenary**

A representative from each group presented the outcome of the breakout sessions' discussions to the plenary for further considerations.

Following the meeting, the EMA drafted the summary of the day including the observations made by each of the three groups and circulated the report to the participants for comments, before the final report was published.

## **4. Workshop observations**

### **4.1. Data elements**

#### **General considerations**

Prior to the workshop, participants suggested potential data elements for collection in registries to support regulatory assessments of cancer therapies related to genetic and molecular features. During the workshop, Group 1 evaluated these elements, commented on their relevance and the feasibility of their collection, and highlighted some general reflections pertaining to certain topic areas of data elements. A compilation of data elements suggested by participants prior to the workshop can be found in Appendix 3.

The need for collection of specific data elements depends on their anticipated use to support regulatory assessment. While many data elements were considered core in the context of cancer treatment (malignant tumours based on molecular and genetic features in particular), the objective was to streamline the selection of certain additional elements considered essential to be captured in some scenarios, whilst they may not be ultimately necessary in others. Potential use scenarios considered were:

- to support questions on prevalence and prognosis of conditions,
- to build comparator cohorts for single arm trials,
- to generate evidence on post-authorisation efficacy and/or effectiveness,
- to generate evidence on post authorisation safety.



Each of these scenarios could lead to different yet overlapping sets of data elements that would be required to support regulatory assessment and thus could also have impact on defining necessary quality standards for data collection and data sharing.

Overall, the number of data elements evoked by the respondents was very high, implying the need to focus on essential data elements. The burden of data collection would need to be considered in order to avoid missing data entries. It was noted that this would in particular be the case for scenarios involving primary data collection. The burden may be lessened if linkage possibilities to health claims data are used and access is gained to more data elements through secondary data analysis.

The reflections of Group 1 on the data elements for cancer registries are summarised below.

### **Patient information**

The group considered the following data elements as important for regulatory purposes:

- Patient identifier(s), date of birth, age, gender, height, weight, centre, country, paediatric assessment and development as applicable, last date of follow up, reason for loss of follow-up, clinical trial participation (some elements may need to be recorded repeatedly)

The following data elements were considered less or not relevant for regulatory purposes:

- Insurance status, address, education, physical activity

The group made general comments and observations regarding data elements on patient information:

- The possibility of merging data from different data sources is an important aspect. This could be facilitated using pseudonymisation algorithms allowing the merging of data elements from patients across different data sources including different registries. Some registries and initiatives have already implemented pseudonymous identifiers and authorised data sharing / access concepts.
- As the field of tumours defined by molecular and genetic features is quickly emerging, it was highlighted that preferences towards specific data elements might change over time. Enhanced collaboration between clinical registries, register-like initiatives and epidemiological registries was flagged to be important to be able to adapt to these changes.

### **Current malignancy – diagnosis**

*Diagnosis*: The group discussed challenges regarding the concept of “diagnosis” for molecularly or biologically defined cancers or pre-malignant conditions; such a diagnosis may not conform to the World Health Organisation, International Classification of Diseases (ICD) or ICD-O but could be based on one marker or a combination of markers (e.g. as a signature). The approach to the documentation of diagnosis was considered essential. It was flagged that documenting the availability of samples is important for future testing in case of evolving clinical research questions. Documentation of diagnoses with respect to molecular and genetic methods used was seen as complex, and it was recommended to use classification systems in particular Human Genome Variation Society (HGVS). The importance of appropriately detailed documentation of patients diagnosed with a cancer for which no molecularly and genetically based diagnosis could (yet) be assigned was also stressed during the discussions.

The group noted that possibilities for further refinement of diagnosis should be considered in view of later access to relevant data and/or samples. As the landscape of genetic testing is evolving, the need to access the raw test results was raised. It was considered important to document histological, genomic and molecular data as available, and to characterise the data sources that contributed to the diagnosis. Documentation of the origin of samples and specimens was also emphasized including provenance (blood, tissue) and whether the origin is from the primary tumour site or from metastases.

If such details on molecular or biological testing are not recorded in a registry, they could become accessible through data linkage with a repository or the testing laboratory, for example.

The group observed that the discussion on data elements for biomarkers (see below) is partially overlapping with the discussion on the concepts of diagnosis in the setting of molecular and genetically defined cancers.

Future uses of samples or data from genetic testing: The need for appropriate informed consent from patients for future use of information for scientific purposes was highlighted. Some of the participating registry holders have implemented such procedures and have had positive experience. For example, informed consent forms can include several options of data usage to which patients can selectively consent or not. It was perceived that there is in general a high willingness of patients to consent to future uses of their data.

Performance status: This element was considered as important information to be recorded at each follow-up of the patient, but documentation in the clinical setting and subsequently in registries may be incomplete. Such information could however be derived based on medical records in case clear documentation or data entry is lacking within the patient registry files. The need to understand how this data has been derived or generated was highlighted, as this would influence the interpretation of the data (e.g. direct documentation by physician versus indirect derivation from files).

Performance status within registries constitutes also relevant information for the understanding of quality of life in the context of regulatory use. However, it was noted that the collection of data on performance status may follow different methodological approaches (including tools and scales) depending on the setting, e.g. clinical trials versus observational settings.

## **Biomarkers**

The group highlighted that information on mutations and details such as fusion and copy number aberrations would be important data elements for the documentation of genomic testing.

Testing methods: The following testing methods were mentioned by participants to be considered as part of data elements: methods such as IHC, FISH, PCR, NGS, using targets such as DNA (whole exome and / or whole genome and / or gene panel) or RNA, DNA Methylation; type of assay, biomarker targets, with meta-information such as on gene panel coverage, tumour cell content. Where possible, germline data should also be captured (e.g., cancer predisposition syndromes).

It was highlighted that testing would be offered in line with existing medical practice and that depending on healthcare systems, genetic and molecular testing may not be offered to all eligible patients. Therefore, where testing is not systematically and freely offered and performed, derived rates for the natural history of diseases from registries may underestimate the true prevalence and incidence of associated conditions and importantly registered patient sets are biased.

Participants acknowledged that while using a single test might be the optimal situation, different testing methods are currently used as part of clinical practice. In that case, comparison and discussion of available methods might be important as well comparing and discussing the choice for local testing versus central methods.

Testing validation: Regarding documentation of the status of validation of finding(s) on genomic testing, participants mentioned that validation would be in general performed with a second method.

The group discussed that current documentation would be driven by the clinical relevance of findings, but that these concepts may evolve in the future and that access to raw data (e.g. details on sequencing results and possibility to access further biological samples) may be needed to manage the

evolution of science in this field. The current concept of diagnosis in the field of molecularly defined cancers or pre-malignant conditions is driven by treatment choices and availability of treatment.

Registry holders mentioned that data on molecular and genetic testing results is currently recorded in specific projects, but not current standard of practice. If such details on molecular or biological testing are not recorded in a registry, they could become accessible through data linkage with a repository or the testing laboratory, for example.

### **Current malignancy – treatment**

The group noted the importance of documentation of treatment history, including reasons for treatment choices and reasons for discontinuation while acknowledging that documentation of such information is resource intensive.

Lines of therapies: The concept of lines of therapies can be subject to variable interpretations and consequently variable documentation. It was suggested that documentation of actual and prior therapies may be less amenable to diverse interpretations and should therefore be preferred to documentation of line of therapy (which may still be relevant and clear in some cancers, although its definition could readily be more harmonised). It was mentioned that the recording of information on the first patient's contacts with an oncologist and the respective dates could be considered. The need for appropriate and detailed description of the generation of records on treatment history within registries was noted to facilitate understanding and interpretation of those data elements within registries.

Disease progression: The level of detail on documentation of progression is very heterogeneous, if documented at all. Some registries tend to use the start and stop dates of treatments to define timing of progression of diseases. Participants noted that understanding how data on progression of disease is generated in different registries and completeness of documentation of tumour assessments is important for use in the regulatory setting, as it has implications on the validity of these data (e.g. actual documentation by treating physician, including regular documentation of e.g. radiology reports versus an approach of assignment of dates through secondary data analysis of other documented information) and on possible comparability with clinical trial data (see also participants' comments on documentation of data on performance status under section 4.1 *Current malignancy – diagnosis*).

### **Current - other treatment**

Participants commented that relevant supportive therapy would need to be considered, e.g. treatment with haematological growth factors or treatments for preventing infection.

### **Medical history – conditions**

The group took note of the large number of data elements suggested for documentation.

Potential use of registry data in the context of clinical trials: An alignment across registries of the data captured on medical history that would have contributed to the exclusion from or inclusion into relevant clinical trials (e.g. factors leading to exclusion from a clinical trial should be documented as part of medical history like renal or hepatic impairment) should be considered. This would allow ascertaining which of the patients from a specific registry would in principle have been eligible for clinical trials and which not. This could also help the grouping of patients in registries into groups comparable or non-comparable to clinical trial populations, which could facilitate understanding and interpreting data generated for the different groups of patients in the various settings. However further data elements might be used as potential in- and exclusion criteria in this regard.

## **Medical history – treatment**

While several proposals arose from the pre-work package responses, it was noted that the data elements would be similar to those collected on the treatments of malignancies and other treatments.

The group agreed that documentation of treatment history is important to understand the concept of lines of therapies and evolution of the treatment history of patients. Reference was made to the prior discussion on the complexities of the lines of therapies concept and challenges in documentation (please see section 4.1 *Data elements - Current malignancy – treatment*).

It was mentioned that the time for inclusion of a patient can differ between registries: some include patients from the first date of diagnosis while others at later stages of treatment and disease. In the latter case, a system should be put in place to address the handling and recording of information on prior treatments and history of disease.

## **Outcomes - safety data**

Scope: A variety of concepts for documentation of safety data were mentioned including documentation of adverse events, adverse events of special interest, serious adverse events and adverse drug reactions. The group noted that pharmaceutical companies in general document and record adverse event data as part of their studies.

Capture of late effects of tumour therapies was mentioned as an additional element and it was acknowledged that one registry holder is currently collecting such data.

Participants mentioned that HTA bodies may give priority towards safety information for costly treatments or on adverse events with resource intensive implications.

The possibility to ascertain information on adverse events from patient reported outcomes was also mentioned as a possibility in case that dedicated data collection on safety events is not in place.

Challenges of data collection: Registry holders mentioned the burden to collect general data on adverse events. Many registries are currently collecting restricted safety information such as serious adverse events or adverse events of special interests. It was highlighted that registry holders may have the ability to adapt collection of safety data to specific safety questions and to introduce data collection on new data elements. However, such amendments would depend on resources and funding, and not only on the feasibility of data collection.

The group discussed that in circumstances where collection of safety information is focussed on a set of specific preselected events, challenges may arise from new emerging spectra of adverse events over time. Possibilities to adapt data collection at a later stage to meet new issues would need to be considered upfront.

Workshop participants noted that the data collection for safety events within registries would in general not be as complete and comparable to the collection of safety data in clinical trials.

Registries stressed that they could collect data on specific safety aspects and could adapt data collection over time, while complete coverage on all adverse events like in the setting of clinical trials could be very challenging.

## **Outcomes - patient data**

It was noted that the priority for data collection on patient reported outcomes (PRO) may be higher for HTA agencies than for regulatory agencies, due to the influence knowledge of treatment assignment by the patient can have on scoring a PRO.

During the discussions, the group noted the need to consider recording the evolution of patient functioning and the impact on social and professional life (e.g. work ability).

The availability of a large variety of different tools to assess PRO leads to complexity of data collection. It was highlighted that PRO are an evolving field with the need to consider ongoing activities and evolving recommendations to harmonise tools used for collecting PRO in oncology.

### **Outcomes - efficacy data**

The group considered the recording of efficacy data as highly interesting and relevant field and highlighted that information on disease progression is important.

*Progression of events:* It was highlighted that identification and description of the underlying concepts to determine progression of events (e.g. clinical findings, radiological findings, assessment by RECIST, RANO or other, usual assessment interval) are important, noting however that not all concepts are routinely use outside clinical trial settings. Approaches to data collection can differ depending on variability of visits, assessment approaches and different schedules for data collection. Capture of outcome information requires the need for regular follow-ups. Recording of outcome summaries at the end of treatment was mentioned as another possible concept for data collection.

Registry holders mentioned different concepts to derive information of timing of progression, such as indirect calculation through availability of date of scans. Some registry holders indicated that time to progression can be defined as the stop date of treatment and highlighted the need to record reasons for stopping treatments and corresponding dates accurately in this setting. The possibility to define progression of disease based on available imaging data was also cited.

Information on markers of resistance at time of progression represents key information for the setting of cancers defined by molecular and genetic features, but it was highlighted that such information is not always recorded in patient files. This type of information can be overlapping with testing discussed in sections above (e.g. "*Diagnosis*" and "*Biomarkers*"). For the purpose of documentation of resistance, the necessity to document the kind of treatment received and specific response to the treatment received was highlighted.

Participants mentioned that the collection of efficacy data may also depend on legal frameworks determining which and how detailed follow-up information can be recorded as part of observational data collection. The possibility that a high granularity of information on efficacy being recorded could impact on the distinction between observational data collection versus data collection differing from usual clinical practice was cited. Some registry holders shared experiences of being denied detailed data collection on efficacy measures as part of non-interventional studies.

### **Supplementary data**

The group noted that not all the elements cited have a high priority for data collection in the setting of regulatory uses. However, information on pregnancy status and outcomes was noted as being important information. It was also considered that data collection on fertility would be valuable information.

### **Other general proposals and observations from the group**

The group noted that taxonomies of biological aberrations need to be further developed. It was also noted that application of next generation sequencing is desirable.

Participants highlighted that registry holders should consider the possibility to apply inclusion and exclusion criteria from clinical trials to identify patients in registries that are comparable to clinical trial populations.

The group noted that a [minimum core data set](#) has been developed for rare diseases in the context of the RD policy that was designed at EU level by the [Expert Group on Rare Diseases](#), and implemented under the umbrella of the "EU RD Platform" as a cooperation between DG JRC and DG SANTE of the EC. The ERNs, established in March 2017, should implement this minimum core data set in their registry(ies), and may define additional elements specific to their area of expertise. It was also noted that other core data models have been developed that could be used as reference for further discussions and developments, e.g. Conley RB et al. ([Core Clinical Data Elements for Cancer Genomic Repositories: A Multi-stakeholder Consensus](#). Cell. 2017; 171: 982-986. doi: 10.1016/j.cell.2017.10.032.).

## **4.2. Quality assurance**

The group discussed the measures necessary to ensure registry data are of suitable quality to support regulatory assessments, to conduct data analyses and permit registries interoperability. The quality aspect of a registry is important because it allows regulators to have confidence in the data provided to support regulatory assessments of medicines (pre and post authorisations). Whilst most quality measures are relevant to implement in all registries, the group highlighted some specific considerations that should be given to registries collecting data on therapies based on tumour genetic and molecular features, especially tumour histology independent products.

### **Registries workflow**

The group highlighted that it is important to understand the process flow of registries, as the quality of the data does not only apply to the registries but also to the data providers (e.g. hospitals, private care providers, death certificates from responsible national institutes, claims institutes) involved in the data feeds. These transfer cancer patient data electronically into the (national) registries. The frequency of upload varies across countries/registries, e.g. monthly in England.

Most registries have implemented system validation checks, e.g. automatic (built-in checks in the database like drop down lists, lookup tables, alerts, mandatory fields, automatic checks on consistency and completeness of the values, warnings etc.), and manual (primary source verifications to confirm data or find missing information). Some registries have the possibility to set up ad-hoc links to collect additional data as appropriate.

All participants agreed that quality measures should be implemented by all data providers/coordinating centres, and at all levels of data collection/transfers/uploads/analysis.

### **Definition of the term "quality" and main issues**

The participants were asked to indicate what they think would define the quality of a registry to allow its use for regulatory purposes. The following characteristics were cited as important to consider when evaluating the quality of a registry and its data: completeness, missingness, representativeness, consistency, and accuracy.

The main issues raised by the participants were:

- Completeness of the data collected in registries, especially the completeness of patients' follow-up, which becomes key when considering the use of registry to monitor the long-term safety and effectiveness of medicinal products;
- Representativeness/coverage: in the context of a study, need to consider whether it is better to include all identifiable registries, or rather to focus on a few with a better quality;

- Misclassification of information recorded: e.g. cancer diagnosis, which would instore bias in registries data.

All participants agreed that the required “quality” for a registry would depend on the purpose for which the registry has been developed and is being used, and in case of a registry-based study, this would depend on the study question. Therefore , specific measures and thresholds could be set only when a clear question has been defined in order to assess which registries would be suitable to participate in the study.

### **Ideas for quality improvement**

A few ideas were raised to improve the issue of completeness:

- Better integrate data collection through registries into the healthcare system, clearly explain the needs and purpose of patients’ data collection to health care professionals;
- Involve patients in the review of their own documentation through facilitated electronic interactions, involve patients’ associations to increase follow-up;
- Mandate data collection in registries governance, at national level;
- Finance a dedicated nurse responsible for the data entry and checks;
- Give feedback to the centres;
- Accreditations of centres;
- Establish semantic interoperability with electronic health records, which could only be possible using a unique identification number for each patient;
- Focus in a first stage on centres of excellence from each country to create templates that could then be rolled out to other centres.

Reference was also made to the Registry Evaluation and Quality Standards Tool ([REQueST®](#)) used by health technology assessment (HTA) bodies.

### **Additional input extracted from the pre-work package responses**

Other aspects to assure the quality of registries data were highlighted in the responses to the pre-work package but were not discussed in detail during the breakout sessions. These include:

- The need for a clear definition of each data fields and the use of standard terminologies to improve consistency and allow for the mapping of data sources and interoperability: e.g. MedDRA for as Adverse events (AEs) and/or Adverse Drug Reactions (ADRs), ICD-O for cancer histology subtypes level, ICD 10, e.g. for comorbidities, TNM for staging (UICC, AJCC, ENETS), SNOMED, ICPC, READ, ULMS coding system, OPCS, NICIP and HGVS mutation nomenclature, methylation profiling.
- The need for a clear differentiation of terminologies used in the context of a post-authorisation non-interventional registry-based study compared to clinical trials (CT), e.g.: homogenous methodological approach is expected to ensure that “progression-free” in CT means systematic tumour assessments at least at all known areas of tumour manifestation in appropriately defined intervals showed no evidence of progression. Such detailed procedure to reach high quality of information on tumour progression may not be possible in the context of secondary use of information from other data sources like medical charts or registries.
- Documentation of performance status within registries constitutes an important quality indicator in the regulatory context.

- Importance to keep centres motivated and focused through e.g.:
  - Pragmatism regarding the “must have” versus “nice to have” data fields to avoid “data fatigue” at sites;
  - Appropriate training programs;
  - Transparency/benchmarking: Publication of periodic reports on registries data and comparison between centres could be a way to keep interest/focus;
  - Recognition: Some sort of official certification status of care providers/hospitals for registration and documentation of cancer patient data has also been mentioned.

### **Importance of the study question**

The quality of a registry to contribute to regulatory decisions depends on the question asked to that registry and on the data sources the registry uses. Regulatory questions may focus on epidemiology e.g. to report quality indicators like incidence, prevalence of a specific disease, life span for populations with a specific disease and for specific diagnostic subpopulations; to provide natural history of diseases; or to improve quality of patients care by comparing centres performance. But it can also focus on clinical assessment of the safety and effectiveness of a medicinal product. In case of a registry-based study, the quality (including the levels of completeness and representativeness) will also be assessed in the context of the study question (e.g. PAES, PASS or definition of historical comparative group) in order to identify whether the registry is a suitable data source for this particular study taking into account quality thresholds defined in the study protocol.

Some participants highlighted the importance of a clear description of the information process flow and of the issues encountered by registries. It is difficult to change national clinical settings considering the possible resistance of HCP to add-on to their daily workload. But knowing the issues upfront can allow a better assessment of what variables are/can be collected through registries for regulatory purposes and under which conditions.

It was proposed to standardise the way to assess the quality, as well as thresholds that would be considered acceptable based on different types of study questions. These standards would then be applied across registries to assess their suitability for specific study questions and designs. Different scenarios of regulatory use would in general imply different levels of quality requirements. While for example quality requirements for the use of data as external controls in clinical trials would be very high to meet appropriate evidentiary standards supporting the interpretation of high quality clinical trial data, quality requirements for use of the data to support regulatory information on the natural history of disease may be lower.

### **Measurement of quality**

As specified above, the quality of a registry could be measured against pre-defined thresholds that would depend on the purpose of the registry and on the study question, e.g. % of the mandatory data fields not completed, % of patients with a specific disease represented in the registry. Some European countries use national requirements and Performance indicators to compare performance of the data providers against what is expected, regionally and nationally (e.g. data completeness; data on follow-up; proportion of death certificate only cases; microscopic verification rates; no specific morphology code rates; mortality to incidence ratios; treatment rates).

Performance indicators that address completeness and quality of the baseline dataset and of each follow-up dataset are necessary to define in respect to effectiveness and safety. For example, the requirement to collect pathology results, information on biomarker (incl. methods used) leading to treatment decisions with full information details (read out), treatments regimens/cycles/doses, as well



as information on suspected adverse drug reactions (SADR) in relation to a specific treatment regimen could constitute quality indicators in the context of a registry-based study.

During the breakout session, participants indicated that it was crucial to understand the missingness of the data in the context of a registry-based study and mentioned a maximum threshold of 10% of missing data based on a sample of 200 patients.

It should be possible to verify the information captured against original data sources.

In the pre-work package, participants indicated that registries should be regularly audited by independent national institutions.

### **Importance of patients' follow-up**

Long-term follow-up in all patients' care pathway is important to determine disease progression, outcomes of cancer care, treatments effectiveness but also helps identify any data bias that could have been integrated into a registry. In the pre-work package responses, some participants provided examples of figures that could be taken into account: 80 % follow-up rate should be maintained for all eligible cases; 90 % follow-up rate should be maintained for all eligible analytic cases diagnosed within the last five years or from the cancer registry reference date, whichever is shorter. In England, once a patient is registered, data collection continues through the different care providers up to death (the Office for National Statistics submits notifications on all cancer and non-cancer deaths). Follow-up by registries staff members with the data providers exist in case of inconsistent or missing vital information. However structural follow-up is currently not implemented in all registries. Moreover, access to death certificates is not legally possible in all countries.

During the follow-up phase, missing data(sets) can easily compromise the outcome results: e.g. missing data(sets) on treatment may lead to attribution of an observed response to the wrong treatment, or missing data(sets) on tumour assessments may lead to the attribution of "no progression" at a specific time point. Moreover, missing data on safety may lead to an underestimation of the true toxicity. The most likely effect is the interpretation of a clinical outcome as a "success" (in terms of no progression or no adverse effect) whilst it is not.

### **Specific quality measures for cancer therapies based on tumours' genetic and molecular features**

The group tried to identify the areas of focus for registries collecting data on cancer therapies based on tumours' genetic and molecular features. Completeness, consistency and accuracy should particularly apply to the type of genetic markers and related tests. Easy access to the raw data (e.g. readout, next generation sequencing), raw materials for validation of tests (biobanking) and contact points of the centres for source data verification would be important. Misclassification, especially of diagnosis, should be avoided. The way to follow-up patients including frequency may be country specific, but should be clearly defined in the registries processes, as well as the documentation of loss to follow-up (numbers and reasons).

## **4.3. Governance**

The objectives of the working group 3 was to discuss practical considerations for accessing/sharing data to be used for regulatory purposes, as well as clarify the roles of all involved stakeholders.

### **Data collection**

Registry holders need clear guidance on which variables related to tumours' genetic and molecular features should be collected for regulatory purposes. Depending on the data expected, the registry

model should be aligned with the scope of data collection, so arrangements should be put in place to allow for the data capture on e.g. drug treatments, genetic / metabolic features and adverse drug reactions. Collaboration between registry holders and clinicians is essential to allow more flexibility in amending or adding variables in the routine data collection. Reference was made to the multi-disciplinary “tumour groups” within the Dutch registry.

Although AE or SADR are considered crucial by regulators to be collected in order to allow them to monitor cancer therapies, this reporting requirement was considered not practical/feasible/practiced by the participants in the context of the concerned registries. According to registry holders, it is not their responsibility to collect such information but rather the one of physicians’ through spontaneous reporting. Many registries are not organised to collect and quickly report SADRs. However, MAA/MAH have well-defined legal obligations for collecting and reporting AEs/SADRs in studies where they are involved. These obligations depend on the methodology used to collect safety data, i.e. primary data collection or secondary use of data. The approach towards data collection also depends on the objectives of the registry-based study, e.g. “real-time” monitoring of the occurrence of some severe adverse reactions for a new product, or long-term surveillance of clinical outcomes in treated patients, including severe and non-severe adverse events. The capacity of the registry to collect and report AEs should therefore be carefully evaluated, including the current (and future) capacity to quickly and systematically report adverse events of special interests. This evaluation should be performed in collaboration between registry holders, regulators and companies as it will determine the appropriateness of the registry for specific study objectives. If data collection and required reporting is possible, appropriate arrangements should be put in place before the start of the study. The role of each stakeholder involved must be clearly written down up-front in the study protocol.

Most patients are willing to share their data but also wish to keep control of it. The group agreed that patient organisations could play a key role to facilitate data collection and represent the voice of the community in registry governance. Whilst patient-led initiatives are important, they should be kept transparent to avoid any bias in data collection.

The group also suggested that methods should be developed to capture PROMs/QoL in a standardised manner across different registries but agreed this is a challenging task.

### **Data sharing**

Transparency around data sharing between all involved stakeholders is very important. Clear roles and responsibilities of the different stakeholders regarding data collection, ownership, sharing, usage and analyses are key, and should be officially outlined in any contractual agreements. The data elements to be shared, how and to whom they should be transferred, the data format, and timeframes should be clearly agreed beforehand between the parties involved. Patient confidentiality and informed consents must be respected.

Currently, the sharing of data is mainly done nationally based on the countries’ legislations, national requirements on particular endpoints and use of similar formats. Informed consent for registration is not requested by most EU countries as long as the data are used for public health and patients’ benefit.

### **Collaborations**

The group brainstormed on ways to facilitate and support relevant data collection and data sharing.

Acknowledging that data linkage may not be possible with all databases as not all will collect the required data or at least not in a uniform way, proposals from the group included:

- Registry-based studies could follow the same approach as randomised clinical trials (RCT) whereby specific endpoints and related variables are clearly defined in their protocols which are used as source for collaborations. The protocols could require the incorporation of the patient's electronic health records upon receipt of informed consent;
- Use of analytical platforms that would allow pooling and access to selected anonymised individual or aggregated data, the raw data remaining in their source databases (investigated in some projects, like EHDEN, HARMONY). This requires the implementation of a common data format and collection as well as regulatory acceptability of some analyses based on aggregate data;
- For data sharing, emphasis was made on the importance of the use of common international standards on core elements to allow interoperability and automatic transfer of information between data sources and across countries.

Several countries (e.g. Norway, Sweden, Iceland, Belgium, Denmark, Estonia, Finland, UK, NL) were noted to be ahead in terms of development and use of registries data. Their learnings are important to consider going forward. Besides, the need for coordination at EU level to lift data beyond national level was unanimous, especially in the context of rare cancers. European initiatives like the establishment of the ERNs (e.g. cancer ERNs like EURACAN, PeadCan, GENTURIS and EuroBloodNet) are welcome and will hopefully facilitate interactions and registries data sharing in the near future through the EU Rare Disease Registration Platform and JRC "Common Data Elements".

Within the pre-work package responses, reference was also made to the EURID system to be able to track individual patients across different ERNs (e.g. numbers of patients with a particular disease, gene mutation etc.). The metadata can then be made available to ERNs researchers after approval by the governance and scientific ERN board, allowing researchers to contact individual members (hospitals) and discuss/negotiate the release of additional data within a research consortium setting.

#### **Enabler: Funding**

Registries are mainly funded by public organisations (e.g. Department of Health and Social Care, European projects, academic institutions, charities or other public bodies). The ERNs can apply for a grant from the European Commission, but additional European funding would be very useful. The group discussed possible funding scenarios to support the sustainability of registries:

- Structural public funding could be allocated to the collection of core data elements;
- Supplementary funding from companies for the data collection of additional variables for specific products, e.g. NTRK products;
- Fee-for-service for expertise (protocol, analysis...);
- Joint studies between companies through the registry: governance models already exist.

## **5. Next steps and actions following the workshop**

The following actions have been drawn-out as outcomes of the workshop:

### **5.1. Actions for Regulators**

- Regulators should seek information from registry holders regarding the challenges of collecting specific data elements that may not be part of the information routinely recorded;
- When assessing an oncology product based on tumours' genetic and molecular features and the need for data collection, regulators should have clarity about the data required for the concerned

regulatory question, and the current and future capacity of data collection and reporting in the potentially relevant registries. In the context of a study using registries or similar type of observational data, and depending on the study objective(s), they should clearly outline in their regulatory requirements the following aspects:

1. which data elements are considered crucial to support their assessment and conclusions on the study question(s) related to cancer therapies based on tumours' genetic and molecular features (e.g. data on treatments, genetic and molecular tests, follow-ups, AE/SADR, see section 4.1);
2. which levels of details and completeness (e.g. % of missing data linked to crucial variables, % of misclassification, loss to follow-up), measures (regular source data verification, description of patients' follow-up procedure/frequency) and acceptable standard terminologies would be considered acceptable to ensure the quality of the data provided;
3. how and with whom should the data be shared/made accessible and under which timeframe.

All these criteria depend on the study objective(s), and on the feasibility for a registry to provide the necessary data ("suitability of registry"). The study protocol could serve as the reference documents to detail such important information and terminologies.

- They should consider the possibility to agree on a set of quality standards that would be acceptable based on the types of study questions and that would serve as regulatory requirements for registries to take part in registry-based studies;
- They should provide guidance to registry holders and support registry efforts to optimise measures for assuring the quality of the data, e.g. through the EMA [qualification](#) procedure;
- The EMA will publish in 2020 for public consultation a guideline on registry-based studies, including considerations on what regulators consider good registry practice on methodological and operational aspects of registries to be used for regulatory purposes.

## **5.2. Actions for Registry holders**

- Registry holders should inform MAH/MAA and regulators about the data elements that are routinely collected, and others that may feasibly be collected and shared within consent and governance parameters, and under what timeframes;
- They should inform HCPs and patients about the rationale for data collection through registries, data sharing with relevant stakeholders and participation in registry-based studies; emphasise on the benefits it can bring to public health; integrate as much as possible the data collection process into the daily routine of care through adequate training programs;
- They should involve patients in the review of their own documentation through facilitated electronic interactions, and involve patients' associations to increase follow-up;
- They should collaborate with other registries to share experience on data collection and to increase harmonised processes for quality assurance of data;
- They should provide feedback to the centres on how they perform based on (nationally) established quality indicators, publication of periodic reports on registries data and comparison between centres for transparency and to keep centres interest/focus;

- They should provide transparent information on the data process flow, including clarification on which data are directly entered by the treating HCPs, and which information is derived through secondary evaluation of other data fields (e.g. date of progression of disease defined based on start and stop dates of treatments instead of direct data entry of the date);
- They should register their registry in the ENCePP Resources database to provide transparency on contact details, the population covered, the data collected;
- They should consider the use of common international standards on core elements to allow interoperability and automatic transfer of information between data sources and across countries; established semantic interoperability with electronic health records;
- In the context of a (registry-based) study, they should implement the collection of additional data elements (as applicable) and apply quality standards required in line with the protocol;
- In view of the evolving field of cancers defined by molecular and genetic features, they should consider the possibility to routinely collect data on treatments, genetic/molecular tests, and AE/SADR to allow the registry to be considered as a potentially suitable data source for regulatory studies and therefore support their sustainability. They should also explore possibilities for later access to raw data on testing and to samples to address new developments in the concepts of diagnosis and management of disease;
- They should consider opportunities such as the EMA [qualification](#) procedure that may provide reassurance on the suitability of the data to support regulatory decision making.

### **5.3. Actions for MAH/MAA**

- It is important for MAH/MAA to understand the regulatory data requests that are likely to arise in the event of a successful marketing authorisation application, especially for post-authorisation surveillance;
- They should engage at an early stage with registry holders to understand the feasibility of data collection (of common and additional data elements) by the registries and possibility of data sharing. Such knowledge should help better assess the registries that could be suitable for studies and that could adapt data collection to support information needs;
- They should consider using the [Scientific Advice](#) procedures to discuss the design and analytical plan of registry-based studies at an early stage of development and regulatory procedures;
- They could provide funding in the frame of registry-based studies.

### **5.4. Actions for patient groups**

- Patients may get further involved in the collection of their own data by consenting on their use for regulatory purposes;
- They could get involved in the quality of their data by peer-reviewing the information recorded in the databases (as applicable);
- There is a need to promote the data collection through registries and data sharing with relevant stakeholders → importance of patients' initiatives, patients' associations.

## 6. Post-workshop considerations

The below considerations were not discussed during the meeting but arose from post-workshop discussions as concrete ways to follow-up on the regulators' actions mentioned above.

### 6.1. *Categorisation of data elements*

Requesting registry holders to routinely collect a very long list of variables that may not be aligned with the original purpose(s) of the registries and national requirements leads to the risk that HCP and patients may not be willing to contribute / maintain these cancer registries. A possible way to bypass this situation could be to identify what data elements would be relevant for each registry's purpose(s). Regulators should first consider the possible usages of registries in a regulatory context, e.g. description of the prevalence and prognosis of biomarker-selected populations, definition of comparator cohorts for single arm trials, use as data source in post-authorisation efficacy studies (to inform on outcomes achieved overall or in subgroups or special populations), and use as data source in post-authorisation safety studies (to address drug-specific safety issues, or safety in special populations). For each of these main usages, models of research questions could be drafted and matched with the list of data elements discussed during the workshop (plus any others as applicable) to see which variables would be necessary to answer each type of study question respectively, and which ones would not. Whatever is common to all questions and main uses could be defined as "core data elements", and the others would be considered as tailored to each study. This way forward could help prioritise the information believed to be essential in the context of regulatory assessment of cancer therapies based on tumours' genetic and molecular features and could facilitate the selection of registries most suitable to answer the study questions.

### 6.2. *Post-authorisation requirements on safety data*

Most patient registries do not systematically collect adverse event information as most of them are established for epidemiological or academic research purposes, and therefore may not have processes in place to allow use and sharing of the data for other purposes. This may conflict with the legal obligation for reporting safety data applicable to MAH in the context of a post-authorisation study using a patient registry. It is therefore crucial to consider as early as possible in the evaluation of a marketing authorisation whether registries would constitute relevant data sources to generate safety data to fulfil post-authorisation requirements, or if alternative data sources should be considered to perform a PASS. Further PRAC involvement in the Registries Task Force activities established in the context of the EMA patients' registries initiative will be key to ensure focus on safety and exploration of the usefulness, opportunities and limitations of registries in identifying and processing safety data.

In addition, the EMA is considering developing a survey that would be sent to all disease registries registered in ENCePP to seek information on their current practice and their capacity to collect various types of safety data. The survey results will be useful to consider in the context of the guideline on the use of patient disease registries and registry-based studies for regulatory purposes currently being developed, but also for future discussions on the use of specific registries for safety reporting.

## 7. Conclusions

There is clear recognition by stakeholders of the opportunities and challenges of using existing registries to support benefit-risk evaluations and long-term post-authorisation follow up of new cancer therapies based on tumours' genetic and molecular features.

A first priority would be to identify what type of data is required to provide relevant evidence in the context of the different regulatory procedures on oncology products in terms of the essential elements, but also quality expectations (e.g. acceptable thresholds of missing data, measures for regular source data verification, standard terminologies). Once this is clear, considerations on the potentially most appropriate data sources including disease registries could apply. This can be facilitated by a close dialogue between regulators, registry holders and MAA/MAH at early stages of development in order to understand the feasibility of data collection (of common and additional data elements) by registries and possibility of data sharing. Such knowledge should help better assess the registries that could be suitable for studies (depending on the questions to be answered) and that could adapt data collection to support information needs. The ultimate objective would be that relevant data from patient registries will be incorporated in benefit-risk evaluations throughout medical product lifecycles.

Going forward into the evolution of cancer diagnosis, therapies and management, registry holders may consider the possibility to routinely collect data on treatments, genetic/molecular tests, and AE/SADR as a way to strongly contribute to the benefit-risk evaluation of oncology medicinal products through long term data collection on patients, and as a way to support their sustainability.

## 8. Glossary

- AE: Adverse events
- ADR: Adverse drug reactions
- CHMP: [Committee for medicinal products for human use](#)
- CT: Clinical trials
- DG SANTE: Directorate General SANTE
- DNA: Deoxyribonucleic acid
- EC: [European Commission](#)
- EC JRC: [European Commission Joint Research Centre](#)
- EHDPEN project: [European health data & evidence network](#)
- EMA: [European Medicines Agency](#)
- ENCePP: [European network of centres for pharmacoepidemiology and pharmacovigilance](#)
- ERN: [European Reference Network](#)
- EU: European Union
- EUnetHTA: [European Network for Health Technology Assessment](#)
- EURACAN: European Reference Network on adult cancers (solid tumours)
- FISH: Fluorescence In Situ Hybridization
- GDPR: [Generalised data protection regulation](#)
- GENTURIS: European Reference Network on genetic tumour risk syndromes
- HARMONY: [Healthcare alliance for resourceful medicines offensive against neoplasms in hematology](#)
- HCP: Health care professionals or providers as applicable

- HGVS: Human Genome Variation Society
- HTA: Health technology assessment
- ICD: International Classification of Diseases
- ICPC: International Classification of Primary Care
- IHC method: Immunohistochemistry
- Informed consent: The process by which a patient learns about and understands the purpose, benefits, and potential risks of a medical or surgical intervention, including clinical trials, and then agrees to receive the treatment or participate in the trial (medicinenet.com)
- MAA: Marketing authorisation applicant
- MAH: Marketing authorisation holder
- NCRAS: National Cancer Registration and Analysis Service
- NGS method: Next-Generation Sequencing
- NTRK: Neurotrophic tyrosine receptor kinase PAES: Post authorisation efficacy study
- PAS: Post authorisation study
- PASS: Post authorisation safety study
- Patient Registry: An [organised system](#) that uses observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, and that is followed over time
- PCR method: Polymerase chain reaction
- PRAC: [Pharmacovigilance risk assessment committee](#)
- PRO(M): Patient reported outcome (measure)
- QoL: Quality of life
- RANO: Response assessment in neuro-oncology criteria
- RCT: Randomised clinical trial
- RD: Rare diseases
- RECIST: Response evaluation criteria in solid tumours
- RNA: Ribonucleic acid
- SADR: Suspected adverse drug reactions
- SAWP: [Scientific advice working party](#)
- SNOMED: Systematized Nomenclature of Medicine
- TNM: Classification of Malignant Tumors
- TRK: Tropomyosin receptor kinase



## 9. Appendices

**Appendix 1:** Agenda

**Appendix 2:** List of participants

**Appendix 3:** Compilation of data elements suggested prior to the workshop by participants to support regulatory assessments of cancer therapies related to genetic and molecular features.

## Appendix 1: Agenda

Item	Topic	Speaker	Time
1.	Welcome, introduction, expected outcomes of the workshop	P. Mol <sup>1</sup>	09:00
2.	Regulators view on the role of registries for generating data on cancer therapies	F. Josephson <sup>2</sup>	09:10
3.	Current situation for the monitoring of new cancer therapies through existing registries: <ul style="list-style-type: none"> <li>○ European Network of Cancer Registries (ENCR)</li> <li>○ Registries for European Reference Networks (ERNs)</li> </ul>	O. Visser <sup>3</sup> ; H. Le Borgne <sup>4</sup>	09:30
4.	Experience from a registry holder: Public Health England	A. Turnbull <sup>5</sup>	09:55
5.	Introduction of the working groups breakout sessions	K. Plueschke <sup>6</sup>	10:20
<b>Break - Coffee / Tea – 10:25 to 10:50</b>			
<b>Working groups breakout sessions</b> (Rooms 0-C, 0-D, 0-E)			
6.	<p><b>Group 1 (Room 0-C):</b> Discussion on core data elements to be collected by cancer registries to support regulatory assessment, feasibility of data collection;</p> <p><b>Group 2 (Room 0-D):</b> Measures necessary to ensure registry data is of suitable quality to support regulatory assessments and to permit registries interoperability;</p> <p><b>Group 3 (Room 0-E):</b> Governance - practical considerations for accessing/sharing data to be used for regulatory purposes, roles of all involved stakeholders.</p>		10:50 to 13:00
<b>Lunch – 13:00 to 13:45</b>			
7.	Discussion on recommendations: each group agrees on & prepares a summary (slides / poster) of its recommendations for discussion with all the workshop participants	Discussion within each group	13:45
8.	Presentations of the groups' recommendations to all the participants, and discussion towards consensus	1 presenter from each group (20 minutes each)	15:30
9.	Conclusions and next steps	P. Mol <sup>1</sup>	16:30
<b>End of the workshop – 17:00</b>			

<sup>1</sup> College ter Beoordeling van Geneesmiddelen (Medicines Evaluation Board), The Netherlands

<sup>2</sup> Läkemedelsverket (Medical Products Agency), Sweden

<sup>3</sup> Integraal Kankercentrum Nederland (IKNL- Netherlands Cancer Registry), The Netherlands

<sup>4</sup> European Commission, Belgium

<sup>5</sup> Public Health England, United Kingdom

<sup>6</sup> European Medicines Agency, The Netherlands

## Appendix 2: List of participants

	Name	Affiliation
1.	Adrian Cassidy	Novartis
2.	Alice Turnbull	Public Health England (PHE)
3.	Ana Sofia Afonso	Eli Lilly
4.	Andreas Charalambous	European Oncology Nursing Society (EONS)
5.	Andreas Pettersson	Karolinska University Hospital, Sweden
6.	Anja Schiel	Norwegian Medicines Agency (NOMA)
7.	Anna Stromgren	Dental and Pharmaceutical Benefits Agency, Sweden (TLV)
8.	Annalisa Trama	European Reference Networks – Rare Adult Solid Cancers (ERN EURACAN)
9.	Carla Jonker	Medicines Evaluation Board, The Netherlands (CBG-MEB)
10.	Carmen Martos	European Commission (EC), DG JRC
11.	Claudia Baldazzi	TesaroBio
12.	Cornelis van Tilburg	INFORM Registry, Hopp Children’s Cancer Center, Germany
13.	Daniel Nogueras Zondag	European Medicines Agency (EMA)
14.	Daniela Melchiorri	Italian Medicines Agency (AIFA)
15.	Elias Pean	European Medicines Agency (EMA)
16.	Esther Choi	Bristol-Myers Squib (BMS)
17.	Filip Josephson	Medical Products Agency, Sweden (Läkemedelsverket)
18.	Giovanni Tafuri	European Network for Health Technology Assessment (ZINL)
19.	Hans Gelderblom	Leiden University Medical Center (LUMC)
20.	Heide Stimadel Farrant	GlaxoSmithKline (GSK)
21.	Hélène Le Borgne	European Commission (EC), DG SANTE
22.	Ines Brecht	European Reference Network for Paediatric Oncology (ERN PaedCan)
23.	Julianna Fogd	European Medicines Agency (EMA)
24.	Kandeepan Ganeshalingam	Merck & Co.
25.	Kelly Plueschke	European Medicines Agency (EMA)
26.	Koenraad Norga	Federal Agency for Medicines and Health Products (FAMHP)
27.	Laura Dima	Bayer
28.	Lauren Becnel	Pfizer
29.	Lonneke Timmers	National Health Care Institute, The Netherlands (ZIN.NL)
30.	Marie-Claire Beurier	Roche
31.	Marin Banovac	European Medicines Agency (EMA)
32.	Matteo della Porta	ERN EuroBloodNet
33.	Maurille Feudjo	Amgen
34.	Michel Van Speybroeck	HARMONY project
35.	Miriam Koopman	University Medical Center Utrecht (UMC Utrecht)

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37.	Myriam Chapelin	European Medicines Agency (EMA)
38.	Otto Visser	Netherlands Cancer Registry (IKNL)
39.	Paula Boudewina van Hennik	Medicines Evaluation Board, The Netherlands (CBG-MEB)
40.	Pauline Evers	European Genetic Alliance Network (EGAN); Dutch Federation of Cancer Patient Organisations (NFK)
41.	Peter Mol	Medicines Evaluation Board, The Netherlands (CBG-MEB)
42.	Pierre Demolis	National Agency for the Safety of Medicine and Health Products, France (ANSM)
43.	Rafael Almeida	European Commission (EC), DG SANTE
44.	Rafal Swierzewski	European Cancer Patient Coalition (ECPC)
45.	Ralf Herold	European Medicines Agency (EMA)
46.	Rosa Giuliani	European Society for Medical Oncology (ESMO)
47.	Sabine Brosch	European Medicines Agency (EMA)
48.	Saskia Litiere	European Organisation for Research and Treatment of Cancer (EORTC)
49.	Sinan Bardakci Sarac	Danish Medicines Agency (DKMA)
50.	Thomas Strong	The National Institute for Health and Care Excellence, United Kingdom (NICE)
51.	Ulrike Hermes	Federal Institute for Drugs and Medical Devices, Germany (BfArM)
52.	Valerie Strassmann	European Medicines Agency (EMA)
53.	Violeta Stoyanova-Beninska	Medicines Evaluation Board, The Netherlands (CBG-MEB)
54.	Virginie Hivert	European Organisation for Rare Diseases (EURORDIS)
55.	Xavier Kurz	European Medicines Agency (EMA)

## Appendix 3: Compilation of data elements

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### Patient information

- Patient identifier, date of birth, age, gender, height, weight, centre, country and address, paediatric assessment and development as applicable, vital status, last date of follow up, reason for loss of follow-up, prior clinical trial participation, insurance status, education, physical activity

### Current malignancy – diagnosis

- Primary diagnosis, tumour staging (grade, size, localisation and metastases), performance status, date of diagnosis, diagnosis laterality, clinical prognostic markers/index, imaging data, method of diagnosis, other diagnostic tests, centre making diagnosis, pathology data from biopsies, testing laboratory, histology and reference, cytology, genetic markers, molecular markers, assay platform, methylation classifier, number relapses and progression, outcomes of multidisciplinary discussions, information on tumour sample availability

### Biomarkers

- Genomic testing, molecular testing, germline testing, testing method, validation standard, reference margins, testing laboratory, date of test result, date of sample/specimen collection, sample/specimen type and location in relation to primary or metastatic site, sequence of biomarker testing

### Current malignancy – treatment

- Reasons for choice of cancer treatment (or no treatment), reason for treatment discontinuation, type of treatment (chemotherapy, immunotherapy, hormone treatments, radiation therapy, surgery including date and outcome), drug name (INN, product), drug dose and schedule (intensity), start and stop date, route of administration, administration date, dose adjustments and reasons for it, number of treatment cycles, combination therapy as well as batch number, reconstitution procedure, self-administration at home

### Current - other treatment

- Type of drug / treatment, drug name (INN, product), reason for other treatment, drug dose and schedule, start and stop date, route of administration, administration date, dose adjustments and reasons for it, conditioning regimen as applicable

### Medical history – conditions

- Allergies, tobacco smoking status, alcohol use, diabetes, menopausal status, hormone treatment, family history of cancer, autoimmune diseases, genetic diseases, renal impairment, hepatic impairment, cardiovascular disease, hypertension, psychiatric events, depression, dementia, working place hazards, co-morbidity score/scale, hospital episodes, platelet counts, HIV, HCV, HPV, organ toxicities from prior treatment

### Outcomes - safety data

- Data elements highlighted by respondents included: start and stop time of event, intervention due to event, dose modification due to event, recovery and sequelae of event, laboratory and additional diagnostics performed, new medication prescribed due to the event, classifier for causal relationship. For paediatrics: weight, height, pubertal development, cognitive development.

- Respondents mentioned classification systems like MedDRA and CTCAE criteria to record information on adverse events

#### Outcomes - patient data

- Patient Reported Outcomes (PRO), Quality of Life (QoL) Questionnaires and/or disease specific assessments (e.g. EQ5D-5L; EORTC QLQ-C30; EPIC 26) as well as information on functional efficacy and/or safety endpoints such as neurological assessments

#### Outcomes - efficacy data

- Response information, duration, depth, date(s) [cancer directed, incl. radiological];
- Information on event or freedom from event relapse-free, event-free, alive; date and type of assessment;
- Functional efficacy and/or safety endpoints (e.g., neurological assessments);
- Survival status-alive status, date of death, cause of death, new malignancy, new morbidities, disease progression, date of progression and site of progression, transplant.

#### Supplementary data

- Pregnancy status and outcome, ICU stays, Office visits, Pharmacoeconomic data