SUMMARY OF DISCUSSION

Cancer Drug Development Forum (CDDF)

Multi-Stakeholder Workshop

Involving Patients in Oncology Drug Development

18–19 June 2019

Amsterdam, Netherlands

Prepared by Excerpta Medica

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Day 2

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INTRODUCTION

Patient involvement in research and development, regulatory decisions, and drug appraisals by health technology assessment (HTA) is a new paradigm that requires a collaborative, multi-stakeholder approach. There are many encouraging initiatives where the patient is central to decision making; however, as with any change in mindset, challenges remain.

This meeting aimed to discuss the opportunities and challenges of incorporating patient-relevant evidence into oncology drug development and the drug approval and appraisal process from the viewpoint of patients, regulatory authorities, health technology assessors, the pharmaceutical industry, and academia.

INVOLVING PATIENTS IN ONCOLOGY DRUG DEVELOPMENT: OVERALL VIEWS AND EXPECTATIONS

EMA Perspective

Pierre Demolis, Oncology Working Party, EMA, NL

The science of patient input

The science of patient input is a new field bringing with it specific challenges of how to integrate evidence that can be very *subjective* in nature into objective regulatory decision making. Patient-reported outcomes (PROs) (i.e. pain, feelings, burden, fears) vary patient by patient and are influenced by many factors, i.e. the changes in disease and prognosis over time (cure, remission, relapse), treatments and adverse events (AEs), and emotional, social, and financial consequences.

Over the years, the European Medicines Agency (EMA) Management Board has adopted specific frameworks to support and structure the agency's interaction with patients and consumers. Any patient perspective matters, and this includes the viewpoint of individual

patients (regardless of whether they are expert patients or not), caregivers (e.g. parents), and their relatives, and patient associations and organizations.

Case study

A good case study in this context is the approval of lenalidomide for multiple myeloma (MM), a drug that has shown significant clinical benefits but can be harmful to the unborn child. Consultation with victims of thalidomide as well as patients with MM on what is important to them resulted in patient access to the drug in conjunction with the development and adoption of the REVLIMID risk evaluation and mitigation strategy (REMS). This is a restricted distribution programme of birth control precautions designed to prevent embryo/foetal exposure to the teratogenic influence of Revlimid.

FDA Perspective

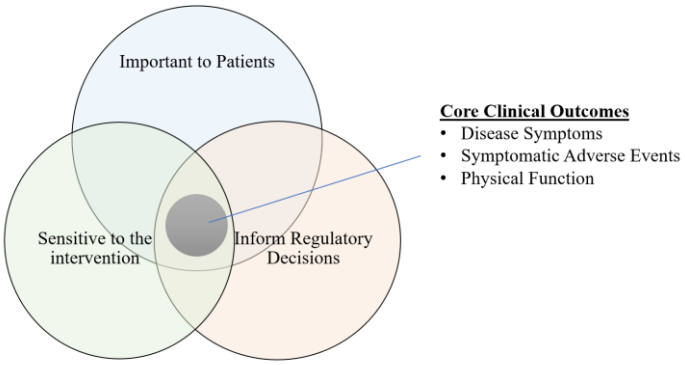
Paul Kluetz, FDA, Oncology Centre of Excellence, USA

Standardizing a core set of clinical outcome data in cancer trials

Robust data about *what patients are likely to experience on treatment* can provide a valuable addition to efficacy and safety assessments to better inform benefit:risk decision making. Moreover, it can be included in the product label to describe safety and tolerability. Since 2009, the FDA has incorporated PROs in multiple labels to inform safety as well as efficacy and in 1 case, patient preference. Crizotinib prescribing information (PI) is an example of how descriptive PRO data can complement clinical safety findings.

Most of the information on how patients feel and function while undergoing therapy come from PROs. Traditional health-related quality of life (HRQoL) measures are generic multi-scale instruments with several domains that were developed to assess the effects of chemotherapy. However, given the heterogeneity of novel cancer therapies and their associated AE profiles, a flexible PRO strategy adapted to the context of the individual trial may be a better approach. Dr Kluetz and his team have identified a set of core concepts that can form a consistent minimal expectation for patient outcomes in trials. This core set focuses on individual measurements of 3 key concepts selected from the HRQoL spectrum:

Disease Symptoms, Symptomatic Adverse Events, and Physical Function.



Kluetz, P.G., et al., *Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials: Symptomatic Adverse Events, Physical Function, and Disease-Related Symptoms.* Clin Cancer Res, 2016. **22**(7): p. 1553-8.

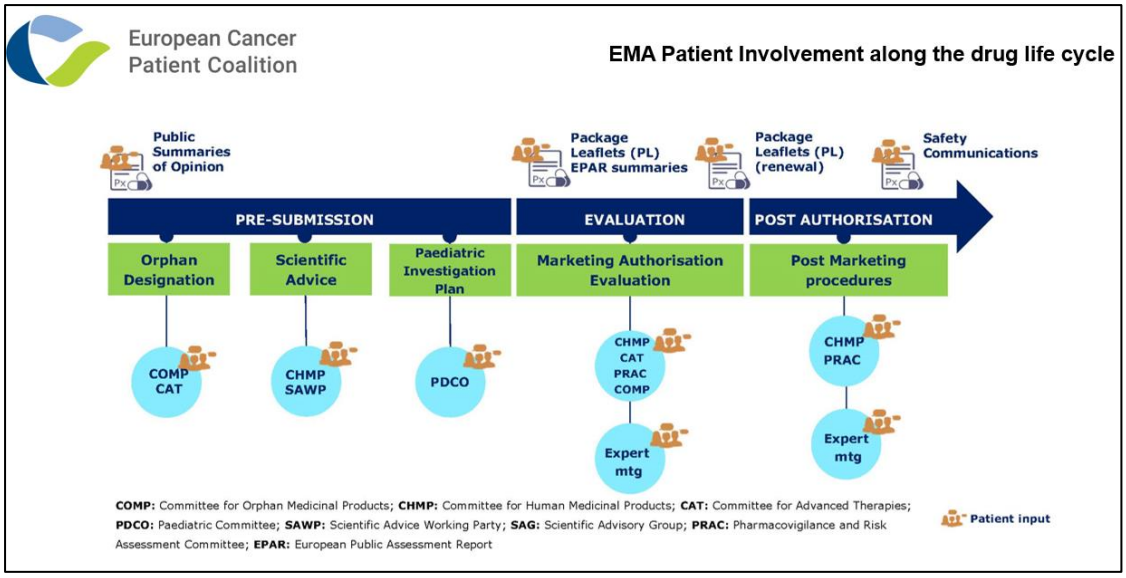
Of importance, key PRO concepts can be identified by using well-defined scales and item libraries to select only relevant symptoms. For instance, the Myelofibrosis Symptom Assessment Form evaluates the impact of treatment on 7 key symptoms. This modular approach is also expected to minimize burden on the patients and optimize the quality of the collected PRO information.

Moving forward and as a longer-term vision, the FDA OCE is planning to further engage patients throughout the drug development process; to improve eligibility, decrease disparities, and bring trials to patients; to use technology to improve symptom and function measurement; and to standardize analysis and communication of symptoms and function.

Patient Advocate Perspective

Francesco De Lorenzo, European Cancer Patient Coalition, IT

Professor De Lorenzo spoke on behalf of the European Cancer Patient Coalition (ECPC), which, with more than 400 organisations across 46 EU and non-EU countries, is the largest European cancer patients' umbrella organisation. ECPC believes that cancer patients are the most important partners to policy makers, researchers, doctors, and industry in the fight against cancer. ECPC is involved in several collaborations aiming to improve patient access to care in Europe, including with the EMA. From ECPC perspective, the EMA is a good example of involving patients in drug development across the drug cycle (EMA Figure).



PREFER

ECPC leads the patient advisory group within Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle (PREFER). PREFER is a 5-year project funded by the European Commission's Innovative Medicines Initiative (IMI) 2 programme to evaluate different ways of assessing clinical patient preferences. The project will establish recommendations to support the development of best-practice approaches and guidelines for industry, regulatory authorities, and HTA bodies on how and when to include patient perspectives on benefits and risks of medicinal products.

ECPC position statement on HTA and access to innovation

ECPC has published a position statement in response to the European Commission's proposal for a regulation on HTAs. In brief, ECPC lobbies for HTA harmonization at EU level that will allow for joint clinical appraisal of new medicines. The goal is to speed up the HTA process and provide faster patient access to promising medicines.

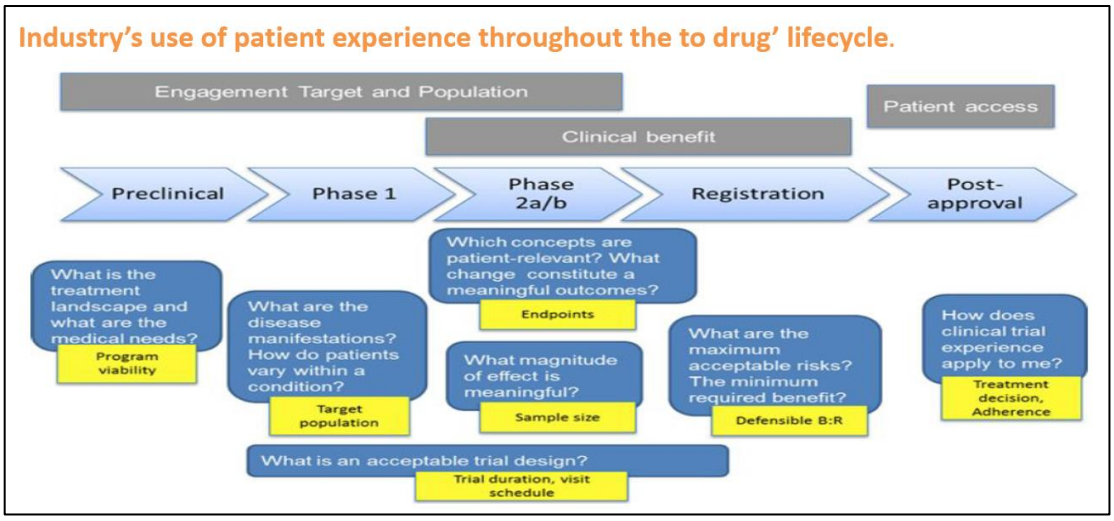
Industry Perspective

Elisabeth Piault-Louis (Genentech, USA)

The paradigm of patient involvement is transforming the industry with patients seen as true strategic partners. From industry perspective, there are numerous pathways to engage patients throughout the drug development cycle (Figure), including listening to patients,

feedback solicitation, as well as generating patient preference data. Increased partnering with academic researchers, regulators, and patient communities ensure better informed protocol development and inclusion of patient-relevant endpoints that measure the impact of treatment, e.g. tolerability, HRQoL, and convenience to complement clinical benefit:risk data in clinical trials.

Important future opportunities for PFDD include standardization of collection, analyses, and interpretation of this PRO data to achieve more robust and credible evidence. Moreover, the use of digital health applications is expected to increase trial access by allowing for decentralized trials as well as decrease completion burden as patients will be completing feedback sessions in their homes. Most of these opportunities are at international level, however, there are regional differences in legislation, payer pathways, clinical practices, and patient input. Ongoing multi-stakeholder dialogue can drive towards consensus on the evidence of patient experience required for decision making both at national as well as at individual patient level.



Health Technology Assessment Perspective

Margarida Oliveira (INFARMED, PT)

Dr Olivera spoke on behalf of INFARMED, the Portuguese authority that is responsible for medicines in Portugal across the life cycle, i.e. the evaluation, authorization, pharmacovigilance, and HTA. HTA is a critical step as it can lead to reimbursement of the product. In general, HTAs are very interested in PROs and patient experiences. Of note, reimbursement decisions are national-level decisions, taking national practices into account.

Academic Perspective

Rosanne Janssens (KU Leuven, BE)

Drug development begins and ends with patients

Patients offer unique insights because they have experiential knowledge of the disease and the treatment. As they are directly affected by treatment decisions, they are the end consumers of healthcare, and their priorities and preferences may differ from those of other stakeholders. Furthermore, better alignment between drug development decisions and patient values and unmet needs can lead to higher-quality drug development decisions. However, continued efforts by all stakeholders are required to reach consensus on the definitions and methodology, timing and application of patient preferences and involvement throughout the drug life cycle. Based on her research, Rosanne Janssens recommended 3 critical opportunities to involve patients: (i) characterizing the unmet need to inform early development decisions, (ii) clinical trial endpoint selection, and (iii) clinical trial protocol design, e.g. acceptability of benefit:risk trade-offs.

Discussion

- **The patient voice is not uniform,** and it reflects a multitude of subjective experiences. These are determined by the patient's health literacy and socio-economic status as well as by the individual patient journey. Therefore, it is important to solicit patient feedback broadly and consult both naïve and professionalized patients.
- Professionalized patients are often consulted by various bodies and the industry. These patients are well-informed and know what to expect from an intervention. They can provide valuable information on trial design and acceptability of trials. However, they are usually better informed than the average patients, and in that sense are not truly representative. Including naïve patients in consultation can provide additional perspectives and creates **transparency**.
- One should be aware of **conflict of interest (COI)** as patients engaged with the industry may not be involved with regulatory bodies. Patient organizations are advised to have 2 separate pools of patients in order to meet this requirement.
- Healthcare providers should recognize the importance of collecting patient experience information. This is particularly relevant for the priority medicines EMA

(PRIME) scheme and early market access medicines, where long-term follow-up data is important.

- It is recommended to **simplify PRO questionnaires** to decrease the burden on the individual patient and increase compliance.

SESSION 2: INVOLVING PATIENTS IN ONCOLOGY DRUG DEVELOPMENT: WHEN AND HOW?

FDA Secondary Analyses of Submitted PRO Assessment Strategies and Data

Belinda King-Kallimanis, (FDA, USA)

At the beginning of her talk, Dr King-Kallimanis discussed the FDA OCE PFDD research activities. The aim of these activities is to enhance the understanding of how to incorporate PROs in the drug reviews and identify rigorous methodology to assess the patient experience. Conceptually, activities fall into 4 main categories:

- Translational *(What matters most to patients and how can it be measured?)*
- Clinical studies *(What patient outcomes should we measure? How can trials be more patient-friendly?)*
- Pre-market review *(How can patient data be best integrated into FDA benefit:risk determination?)*
- Post-market review *(How is clinical outcome assessment (COA) data best communicated? How can COA data be generated in the post-market setting?)*

PRO assessments and key learnings

Assessment across various drug submissions shows use of variable PRO tools and a lack of standardization. Furthermore, there is:

- Mismatch between what is asked and what is experienced by the patients as tools are not tailored to assess AEs of therapies with novel mechanisms of action (MoAs). For example, an FDA study assessed PRO coverage of key symptomatic AEs across 21 immunotherapy trials of PD-1/PD-L1. PRO tools were variable and did not consistently assess important symptomatic AEs. No trial assessed all key symptomatic AEs selected based on reported PD-1/PD-L1 therapy AE profiles. Furthermore, no instrument used included an item to capture rash and itch, 2 frequently seen immune-related AEs.

- Inconsistency in completion rates. Lower completion rates tend to be reported more often for open-label trials and may include a larger portion of incomplete assessments

in the control arm than in the investigational arm. Thirty percent of studies do not report completion rates in their clinical study reports.

- Variability in patient follow-up and completion rates for PRO assessment post-study discontinuation. Out of 29 breast cancer therapy studies reviewed, only 38% collected PROs after treatment discontinuation. For breast and prostate cancer, only approximately 50% of trials reported completion rates for follow-up assessments; for liver and pancreatic cancer, no completion rates were reported.

Scientific advice from the regulatory agencies should be solicited as early as the trial design stage to ensure inclusion of a PRO strategy that can allow for complete, unbiased understanding of the patient experience. The use of symptoms libraries to design PRO measures to assess expected toxicities is recommended. Maximizing completion rates is important because it provides the data quality necessary to inform regulatory decisions and supports potential inclusion of PRO results in product labels. The FDA recommends that studies collect and report PRO completion rates per arm per visit and document the reasons for missing data.

The expectation is that future trials will be more patient-focused as the 21st century legislation will be applied prospectively. Of note, under the 21st Century Cures Act, the US FDA regulators are required to "make public a brief statement regarding the patient experience data and related information, if any, submitted and reviewed as part of the application".

Case Study: Pancreatic cancer

Natalija Frank (Medical University of Vienna, AT)

The case of 61-year-old patient with metastatic pancreatic cancer was discussed. The patient achieved partial response with a novel systematic therapy, e.g. navelbine, irinotecan, and 5-fluorouracil (nal-IRI) and was able to undergo surgery for the primary tumour and the liver metastasis. This case highlights the importance of bringing life-extending novel therapies to patients quickly.

Case Study: Patients feedback into oncology drug development through patient advisory board meetings

Claudia Hey, PhD on behalf of Tanja Keiper, (Merck Healthcare KGaA, DE)

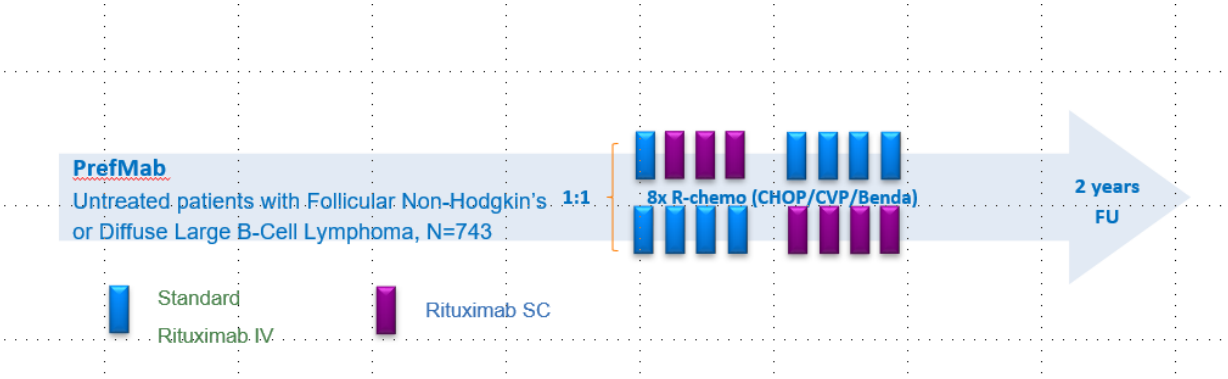
Patient advisory boards (PABs) are a mechanism to solicit input or feedback from and engage with patients and caregivers to ensure design and conduct of patient-centric clinical trial programmes. A patient-centric clinical trial refers to any improvements, including use of new technologies or any other additional service that directly or indirectly positively impacts the experience of the patient participating in the trial. PAB meetings (10–12 people invited by the patient organizations) are conducted as a focus group discussion, in a neutral venue, and are moderated by a third party. Programme-specific feedback includes clinical trial logistics and impact on patients' daily life such as visits to the hospital, travel arrangements, reimbursement, etc.; understanding and readability of informed consent form (ICF) and clinical trial information; use of medical apps; management of AEs and how these are captured; access to the drug, e.g. toolkit, etc. PAB meetings can also be held when there is a high rate of trial discontinuations to provide context and help identify solutions.

These meetings should be run on a global scale to ascertain that cultural and regional differences are reflected.

Case Study: Rituxan Hycela™ - Preference for mode of administration

Elisabeth Piault-Louis (Genentech, USA)

The PrefMab study was a large open-label randomized controlled trial that tested whether previously untreated patients with non-Hodgkin lymphoma preferred subcutaneous (SC) rituximab (Rituxan Hycela™) administration over intravenous (IV). The primary endpoint was Patient preference as assessed by a Patient Preference Questionnaire.



Trial design allowed patients to experience both treatments (Figure). Results demonstrated that 81% of patients preferred SC administration of rituximab. The most common reason for preferring SC was that it required less visits to the clinic. However, 11% preferred IV administration as it made them feel they were being monitored for longer.

The Rituximab Administration Satisfaction Questionnaire was developed for the trial based on the FDA guidance on PROs for label claims. The analysis revealed that convenience was the main driver of preference. Based on these data, a "Patient experience" section was added to the Rituxan Hycela™ US label (section 14.4) based on the results of the trial.

This case study illustrates that rigorous and reliable assessment of the direct patient experience of treatment is doable. Most importantly, information on patient experience should be included in patient-facing materials to facilitate patient discussion with their physicians on choice and tolerance of treatment.

Discussion

- **Health literacy and social setting** should be taken into consideration when having discussions with patients.
- To ensure **various perspectives are reflected**, PABs should include "naïve" patients. Healthcare provider (HCP)'s point of view is also relevant as most patients on these currently boards are well-informed and thus not representative.
- A concern was expressed that CTs are delayed due to contractual challenges and **ICFs are too complex**, taking too much time and energy from patients and physicians. Complex ICFs can also be a reason for slow recruitment.
- **PRO assessments are highly valuable as supplemental evidence** at both regulatory and HTA meetings. Therefore, the **quality of these assessments** is paramount. HCPs should be educated to collect PRO data consistently and for the full duration of the study (e.g. including during follow-up post study).
- Involving the patient at various stages of drug development is a complex multi-stakeholder arena. **There are huge educational needs and opportunities**. For example, there is lack of information of how HTAs work and how patients can contribute. Although there are various programmes and trainings that prepare patients to communicate to bodies (i.e. training by the FDA, patient organizations, EUPATI on the drug research and development process), there are still perceived gaps in education.
- **Patient advocacy groups struggle with limited resources**, such as short-term engagement of the individual patients (e.g. the patient gets healthy and does not want to hear anything about the cancer any more, or they die). This requires a new cycle of

training, that in turn exacerbates the already limited financial resources of these organizations.

- **Advocacy at national level** can be essential to ensure access to new medicines, however, there are few training opportunities at national level.
- **EMA and HTA joint scientific advisory committee discussions** are particularly valuable in gaining understanding of the evidence required for drug approval and appraisal in cancers where hard endpoints such as overall survival (OS) benefits are difficult to obtain within a reasonable time frame.

SESSION 3: INVOLVING PATIENTS IN ONCOLOGY DRUG DEVELOPMENT: IMPACT ON DECISION MAKING

How FDA is Using Patient Experience Data in the Determination of Risk and Benefit

Belinda King-Kallimanis (FDA, US)

FDA standard information request for PRO data

To standardize submitted PRO information, the FDA has introduced a standard template document that captures consistently patient disposition; PRO completion rate; mean subscale scores over time; change from baseline on subscales; and descriptive bar charts for single-item AEs. The FDA review strategy is aiming to assess the overall strength of the results to generate conclusions. This is based on the PRO instruments used; PRO endpoints inclusion in the statistical hierarchy; presence of confounders that could limit the generalizability of the results; missing data; and whether timing of the assessment is reasonable given the drug(s) being tested. The implications of any updates to the product label for patients, caregivers, and HCPs are also considered.

Case study – pertuzumab for breast cancer

The FDA reviewed pertuzumab for adjuvant treatment of HER2-positive early breast cancer patients. In this trial, the PRO data were carefully reviewed and included in the benefit:risk assessment. Three PRO instruments were included: the European Organization for Research and Treatment of Cancer core quality-of-life questionnaire (EORTC-QLQ-C30), EORTC breast-cancer-specific quality-of-life questionnaire (EORTC-QLQ-BR23), and the EuroQol 5-dimension instrument (EQ-5D). Patients' overall physical function when looking at mean change from

baseline was largely similar between the intervention and control arm, however, differences were seen with single-item symptoms (e.g. diarrhoea). FDA stressed that a lack of superiority is not the same as "no difference", and the trial was not powered for non-inferiority or equivalency in physical function. Because of these considerations on the consistency of effects and overall strength of the data, the claim of "no meaningful difference" for physical function was rejected and PRO data was not included in the label. Therefore, creating a clear endpoint and analysis plan upfront is critical, if the goal is an efficacy claim and a product label update.

Patient Involvement in benefit:risk Discussions at EMA

Nathalie Bere (EMA, NL)

The EMA promotes multi-stakeholder (e.g. academia, HCPs, industry, patients/consumers) engagement in all its activities to drive strong exchange of information and foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public health in the European Union. Patient engagement has been a progressive journey for more than 20 years, since the EMA was established in 1995:

- 1996 – Initial dialogue with patients
- 2000 – Patients become committee members
- 2005 – Framework of interaction with patient and consumer organizations
- 2006 – Patient and Consumer Working Party
- 2014 – Public Engagement Department
- Ongoing – Systematic inclusion of patient input along the medicine life cycle

Patient involvement has increased over the years with > 900 patients involved across different EMA activities in 2017. This is a transparent process and the EMA publishes an annual report of stakeholder engagement activities.

Patients provide input on various aspects of development plans, e.g. endpoints, population of interest, quality of life (QoL), standard of care, comparator choice, and study feasibility. Patient organizations representing EU patients or consumers as well as individual patients/carers may express an interest to work with the EMA (eligibility criteria and application forms can be found on the EMA website). EMA offers regulatory process trainings as well as personalized support to participating patients.

Patients are invited systematically to expert group meetings discussing a medicine. Committees/Working Parties also conduct direct consultations, including face-to-face

discussions and surveys. Patients are invited to workshops and public consultations on development/updates of regulatory guidance. They also review all intended literature for patients for appropriate language, including package leaflets, educational materials, communication campaigns, and safety communications.

There is added value of patient input into regulatory decision making. A study of patient involvement at the EMA indicated that patients bring real-life experiences (59% of cases), offer a different perspective (32%), or raise issues not previously considered (13%). Patient input led to further discussion (53%), and modification of the outcome (24%); patients agreed to the proposed plans (19%). However, additional data is required to ensure that this information is representative of the larger community. Currently, EMA is looking at undertaking patient preference studies working together with PREFER and encouraging sponsors to collect quality-of-life data using PROs. Considerations for the future include increased patient data generation (e.g. preference studies, QoL and patient-reported outcomes) and use of big-data technologies. The latter brings in a requirement for a strengthened regulatory system that can efficiently integrate evidence from real-world data into its assessments.

Patient Involvement in HTA in Portugal – a part of the INCLUIR project

Margarida Oliveira (INFARMED, PT)

INCLUIR (Portuguese for "include") is a framework for patient involvement in the HTA decision-making process in Portugal. Both patient associations and individual patients can be trained to participate provided they fulfil eligibility criteria, e.g. do not have any COI. Patient engagement is on a case-by-case basis upon a reimbursement request for a new medicinal product. In Portugal, a positive reimbursement decision allows access to the drug via the National Health Service.

The first step of the HTA decision-making process is assessment of the initial proposal, using the PICO methodology to collect patient feedback on the relevant Population, Intervention, Comparators, and Outcomes. Patients provide input during this step together with experts and marketing authorization holders. INCLUIR uses a dedicated form, that is pre-filled with specific product information, and sent to the patient association that represents the condition or disease for which the medicine is being assessed. The form aims to evaluate the current patient unmet needs and experience with the disease and available treatments, as well as the

expectations of, and perception about, the medicinal product under HTA. A final score is generated.

The subsequent decision-making steps of the HTA process, assessment of added benefit and HTA commission recommendation, are done by experts taking into account patient involvement with PICO.

Discussion

- It might be challenging to engage with the right patients, as regulatory bodies and industry may not engage with the same patients. There is some flexibility in the existing policy, however, the recommendation for patient organizations is **to stratify patients to manage COIs**.
- Another challenge is to **reduce the burden on the individual patient** from a time perspective.
- At times, industry and regulatory bodies may receive contradictory input from patients. The best approach to avoid such situations is to **engage the regulators early** in the process, during the trial design phase, to iron out potential differences.
- There are no standardized endpoints that are relevant to all patients; disease context and unmet need are important considerations for QoL endpoints and their appropriate place in the statistical hierarchy during the trial design.
- **PRO outcomes reflecting tolerability may play a role in dose-finding studies**. The field is changing with new strategies being deployed to come up with endpoints in the early phase trials that can be tested in later development.

SESSION 4: PATIENT PREFERENCE STUDIES

Patient Involvement in Patient Preference Studies

Rosanne Janssens (KU Leuven, BE), Nicole Wicki (Myeloma Patients Europe [MPE])

Patient preference entails a **trade-off** between the negative and positive effects of treatment. The FDA defines patient preferences broadly as:

"**Qualitative or quantitative** statements of the **relative desirability or acceptability** to patients of specified **alternatives or choices** among outcomes or other attributes that differ among alternative health interventions" (FDA, 2016).

By giving their preference in a preference survey, patient preference information can help researchers understand what outcomes of treatment (life expectancy, AEs, therapy-free intervals, etc.) are important to patients and how much patients value these outcomes, and whether disease-related factors (i.e. line of therapy, time since diagnosis, etc.) can determine differences in patient preferences.

The lack of guidance on how to design robust patient preference studies poses challenges for the use of this data to inform decision making. Involvement of patients in multi-stakeholder focus group discussions can help better understand the context of the disease and select the most feasible method available for the patient population, include the most patient-relevant treatment attributes, and ensure that the preference survey is easy to understand to reduce the cognitive burden on patients. It can also help with patient recruitment and interpretation and dissemination of the results. From a planning perspective, it is important to involve patients at regular time points of the study to avoid information overload.

Patient advocates are increasingly taking the lead in developing preference studies. In this regard, a preference study is being conducted as a collaboration between academia and MPE. MM is a relapsing and remitting disease, with complex treatment pathways and an advent of doublet and triplet combination with various **benefit:risk profiles**. As resources are becoming increasingly limited, it is important to understand how patients value the various treatments in terms of perceived benefits and tolerance for risks. The aim of the research is to quantify the value of patient-relevant attributes of MM treatment and understand how preferences may vary according to disease and patient characteristics.

From the MPE perspective, collaborations are critical to achieve scientific rigour and utility of research for regulatory and reimbursement decision making.

What is Next for Patient Preference Studies in Cancer Drug Development? An Overview, Challenges, & Opportunities

Vikas Soekhai, Samare Huls (Erasmus University Rotterdam, NL)

Vikas Soekhai presented the results of systematic literature review mapping out the various methods used for measuring patient preference. 32 unique methods were identified that fall into 2 major categories:

- Preference exploration (*qualitative* methods that can be divided in 3 main groups includes individual, group, and individual/group methods)
- Preference elicitation (*quantitative* methods that can be divided in 4 main groups, i.e. discrete-choice-based methods, ranking methods, indifference methods, rating methods)

Subsequent discussion focused on the discrete choice experiment (DCE) method. This method measures trade-offs and is supported by a wealth of evidence in the literature. The DCE generates statistics that allow objective comparison (utility scores, odds ratios, probability scores, etc). The method also accounts for heterogeneity – as perceptions can differ, patients can be stratified into different classes based on their preference. DCE is increasingly being applied in health-economic evaluations because it considers healthcare delivery and cost (waiting time, subsequent interventions, etc.) in addition to clinical outcomes. For all these reasons, DCE is a suitable method for decision making by industry, regulators and HTA bodies, and reimbursement agencies at different stages of the drug life cycle.

Erasmus Choice Modelling Centre has a program of studies in oncology and actively collaborates with patients. However, further research is needed for preference studies to reach their full potential. A systematic review of the use of patient preference studies in HTA identified the research priorities to advance these studies. From an academic perspective, key priorities included methodological (e.g. choice of method, validity, generalizability), procedural (e.g. what the weight of information in the decision-making process is), and normative research questions (whose preferences are relevant).

Discussion

- **Whose preference is captured** is an important focus of ongoing research. Preferences might shift after starting therapy. For example, only after starting therapy can patients truly assess their tolerance to AEs.
- There are **multiple factors that influence patient preferences**. Patient characteristics, such as experience with earlier lines of therapy, point in the patient journey, etc., can also determine how they perceive the benefit:risk of treatment. This information as well as the time point of assessment should be captured in the study to support interpretation of the results.
- In addition, preferences are driven by aspects that might be not be directly related to the illness, such as family-life issues, socio-demographic, economic factors, and

education level. Preference studies should be able to provide insights into what factors are driving patient preferences.

- This heterogeneity in patient preferences is challenging from a regulator's perspective. Ideally, **product-specific preference studies should be representative of the clinical trial population or the intended indication**.
- **Preference studies are not linked to products but to attributes**. The preparatory work before development of a survey is important in terms of selecting the attributes that matter to patients based on the preference literature and based on direct input from patients.
- **Survey questions should be understandable** to patients while remaining accurate. One of the challenges is how to translate side effects and outcomes, and other attributes into patient-friendly language and preserve the meaning. An approach is to use confirmed sources of patient-friendly language (US government, National Comprehensive Cancer Network), then get this language validated by a patient organization representative.
- Qualitative and quantitative methods of assessing patient preference and experience should complement each other.
- To leverage the full potential of preference studies, there should be a theoretical framework that links the study outcomes to the individual patient and helps informed decision making about treatment choices.

SESSION 5: BREAKOUT SESSIONS - ROADBLOCKS AND SOLUTIONS

Co-chairs: Axel Glasmacher (CDDF/University of Bonn, DE) & Ralf Herold (EMA, NL)

BO1: Patient involvement in research and development

Breakout Session Chairs: Natalija Frank (Medical University of Vienna, AT) & Claudia Hey (Merck Healthcare KGaA, DE)

Discussion on the scope and timing of patients' involvement including experiences and challenges in, e.g. involvement in protocol and ICF development, safety review, beyond individual trials, and advisory boards.

Feedback

The discussion focused on identifying gaps and priorities. The following recommendations were shared:

1) Create **patient communities within organizations** that can serve as a platform for feedback and input into development programmes, e.g. protocols, study design, etc.

2) **Broaden the eligibility criteria for clinical trials** to include special patient populations, e.g. elderly, high-risk patients, etc.

3) Aim for **patient-friendly trial protocol and designs** by engaging with patients early on. Ensure that regional needs are reflected in global clinical trial programmes.

4) **Facilitate patient access to clinical trials**. Further discussions are needed to address questions around inclusion of cross-border patients.

5) Provide **multi-stakeholder education** on oncology trials by consolidating various activities and resources for patients and clinicians in a global approach.

Conclusions

As each of these recommendations needs discussion and has multiple perspectives, it was proposed to form a network within the CDDF as a platform for further discussion and collaboration and possibly align on action plans in a consensus statement.

BO2: Patient involvement in assessment and use of medicinal products

BO2 session chairs: Ralf Herold (EMA, NL), Belinda King-Kallimanis (FDA, USA), Giovanni Tafuri (EUnetHTA, NL) & Mariëlle Gallegos Ruiz (Roche, NL)

Discussion on what type of data is important, why, and for whom when it comes to patient involvement in regulatory/HTA decision making.

Feedback

A hypothetical trial of second-line cancer therapy versus standard of care with clear progression-free survival (PFS) gains but very different AE profiles was used to stimulate the discussions. The following takeaways and ideas were reported back to the forum:

1) **PROs are important to supplement PFS/OS data**. An effort should be made to capture robust information, highlighting the importance of using standardized tools as much as possible, and strategies to increase completion rates at required time points. Patient preference information should be captured as well, ideally before and after the trial to provide the full picture.

2) There should be careful **selection of endpoints** in the statistical hierarchy that helps differentiation, e.g. for drugs with similar MoAs but different toxicity profiles; this would mean a non-inferiority trial design for the primary endpoint, and differentiation based on toxicity profiles by including PROs among the endpoints. In certain situations, focusing on PROs as the key outcomes of the trial could be the best approach.

3) **Patient-centricity** should be applied to clinical trial design to improve understanding and decrease the burden on the individual patient. For example, it was suggested that ICFs are shortened to 1-page summary documents. There should be focus on education, facilitating communication, and building trust between trialists and patients. Videos were suggested as simple approach to providing patient and their families with the relevant information in an easy-to-digest format. Overall, managing patient expectation is expected to improve **patient compliance** and PRO completion rates, and improve the overall quality of the trial.

- There are multiple resources available to help improve patient-centricity in clinical trials. The book *Communicating with cancer patients* by John F Smyth (CRC Press; 2013) was recommended as a tool to improve patient-physician communication and trust building.

4) **Adaptable trial design** may be an appropriate approach for oncology trials that take years to complete. Trials do not have to be exhaustive, but rather answer straightforward questions in a robust way. The use of (wearable) technology was highlighted as an effective mechanism for real-time monitoring and a channel for direct feedback from patients to their physicians. Real-time PRO information can feed into risk management and risk mitigation strategies.

5) **There is a need to standardize PRO instruments, robust data collection, and assessment**. It is important to have early discussions with the regulators, payers, and patient advocates to understand relevant PRO outcomes and better describe them.

Conclusions

- The existing European clinical trial research environment is evolved and can be leveraged for better documenting PROs.
- It is important that there is communication back to patients, especially on PROs.
- There is a need to increase awareness among general practitioners as well as the public of the benefits clinical trials bring to patients to encourage participation.
- There are multiple platforms that can tap into patient experiences from different settings. In the USA, there is a cancer conference for patients where 15,000 patients

gather to exchange information. At major international congresses, there are patient-orientated tracks.

- Regulators and HTAs do not collaborate, and regulators are not necessarily aware of HTA requirements that determine reimbursement decisions, and ultimately patient access to medicines. There is a need to synchronize methodologies, if the goal is patient-centricity. Inclusion of PRO/QoL information in PI provides for transparency and can help inform payers on the value of a product.

SESSION 6: NEXT STEPS

The panel debated how to bring patient involvement to its full potential. It was suggested to:

- Establish a network within CDDF to periodically share information and perspectives to drive progress.
- Form a collaboration/coalition between the patient organizations attending the meeting.
- From a patient advocacy perspective, political will for change is important to establish the right framework for PFDD at EU level. However, patient involvement in national HTAs does not require political permission; patients are the driving force of the change.
- There is often pressure from the industry to move fast. This time pressure may not always allow for patient involvement in a meaningful way.
- It was suggested that the CDDF lead a consensus document on priorities for further advancement of the patient-focused paradigm with the caveat that regulators are challenged to be involved in position statements because of legal framework implications.
- The level of patient involvement in HTAs across the various European countries is heterogeneous. EUnetHTA has placed open calls for patient participation; patient input is particularly important for scoping meetings (PICO).
- Standardized outcome assessments can improve informed decision making and the quality of care. The ambitions of the International Consortium for Health Outcomes Measurement (https://www.ichom.org/) are to define global standard sets of outcome measures that matter most to patients and drive the adoption and reporting of these measures worldwide to create better value for all stakeholders. This value-

based approach has been positively assessed by the Dutch government among others (*post-meeting note*).

- From the regulator perspective, significant progress has been made. Current priorities are advancement and standardization of PRO and patient experience data collection, analysis, and communication. More data are needed to inform future policy and guidelines on PRO inclusion in product labelling. A framework of early advice on PRO and patient engagement is required.
- Regulators should propose a model for best-practice sharing. The FDA is aiming to publish papers on all patient experience assessments that have gone well.
- The use of PRO-collected data by wearable technology is currently being researched. Standardization based on standard data requirements is critical from a regulatory perspective. Furthermore, an infrastructure to support data collection and ensure its quality should be developed. Steps in this direction are eagerly awaited.
- Multi-stakeholder discussions drive change.

CONSENSUS

- The mindset change required to drive patient involvement has already happened.
- Further research is necessary to define the best methodologies for patient preference studies. It is recommended to start with a hypothesis of what will drive the preference, e.g. toxicity event profile, and incorporate the relevant attributes in a preference study.
- From an industry perspective, it is important to seek early joint scientific advice from regulators and payers on PRO strategies, especially in areas of uncertainty.
- Stakeholders are encouraged to develop policies on patient involvement.
- There is a need to raise awareness of the benefits of clinical trials and facilitate patient access to clinical trials. There are huge educational gaps.
- This forum can serve as a platform for future discussion and information sharing.

ABBREVIATIONS

AE, adverse event

CDDF, Cancer Drug Development Forum

CHMP, Committee for Medicinal Products for Human Use

COA, clinical outcome assessment

COI, conflict of interest

DCE, discrete choice experiment

ECPC, European Cancer Patient Coalition

EMA, European Medicines Agency

EUPATI, European Patients Academy on Therapeutic Innovation

FDA, Food and Drug Administration

HCP, healthcare provider

HTA, health technology assessment

IMI, Innovative Medicines Initiative

HRQoL, health-related quality of life

MM, multiple myeloma

MoA, mechanism of action

OCE, Oncology Center of Excellence

OS, overall survival

PAB, patient advisory board

PFDD, patient-focused drug development

PFS, progression-free survival

PI, prescribing information

PICO, Population, Intervention, Comparators, and Outcomes

PREFER, Patient Preferences in Benefit-Risk Assessments during the Drug Life Cycle

PRO, patient-reported outcome

QoL, quality of life

If you have any inquiry about the CDDF multi-stakeholder workshops or publications, please contact the CDDF office via email (info@cddf.org) or by phone (+32 2 880 62 70). Thank you for your interest in CDDF activities and continued support.