EORTC
European Organisation for Research and Treatment of Cancer
The future of cancer therapy

EMA
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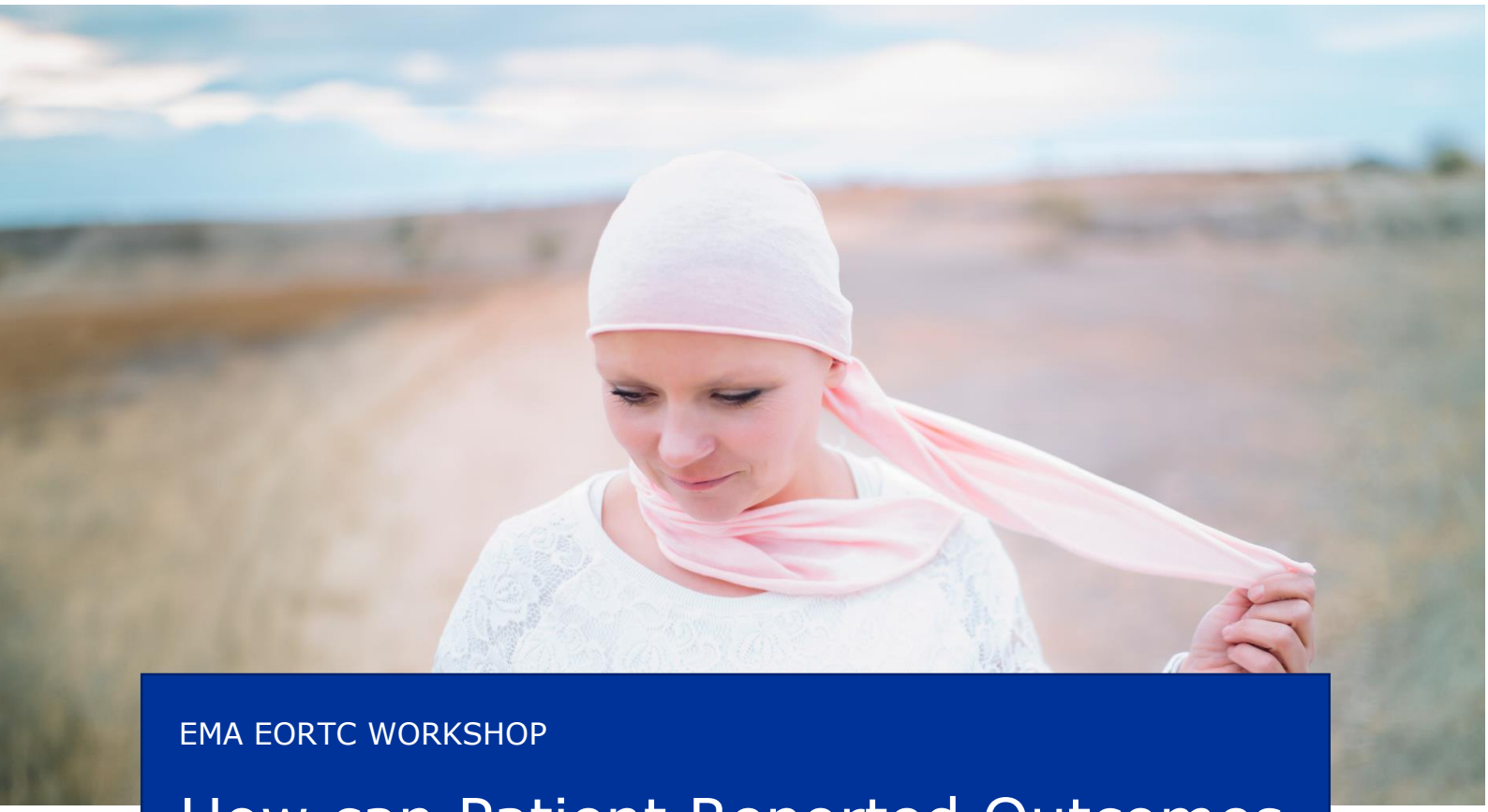

EMA EORTC WORKSHOP

How can Patient Reported Outcomes (PROs) and Health Related Quality of Life (HRQoL) data inform regulatory decisions for cancer treatments?

29 February 2024
Hybrid meeting - EMA (meeting room 1C), Amsterdam and virtual

Meeting Report: How can Patient Reported Outcomes (PROs) and Health Related Quality of Life (HRQoL) data inform regulatory decisions for cancer treatments?

1. Introduction

Patient-reported outcomes (PRO) and health-related quality of life (HRQoL) assessments are an integral part of cancer clinical research and cancer drug development. The relevance of incorporating the patients' voice through HRQoL and other PROs is currently reflected in the EMA guidance on health-related quality of life (2006), with a more specific application to oncology in the Appendix 2 in the EMA guideline on the evaluation of anticancer medicinal products in man (2016).

The Oncology Working Party (ONCWP) work plan (2024) highlights consideration for emerging HRQoL and PRO tools to fit the evolving clinical trial environment. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) reflection document on *patient focused drug development* (2021) reinforces the need to consider how to appropriately incorporate the use of PROs and HRQoL in drug development and regulatory decision-making.

In recent years, the science of PROs and HRQoL research within cancer clinical trials has advanced considerably, with global multi-stakeholder efforts on how to use PROs and HRQoL results in decision-making. Tools to measure PROs and HRQoL have evolved, with validated measures to assess core HRQoL outcomes, and item libraries to allow measurement of trial-specific/treatment-specific related issues.

2. Purpose of the Workshop

Overall aims of the workshop:

1. Understand the current global landscape on the use of PROs and HRQoL for evaluation of anti-cancer treatments across different stakeholders' groups.
2. Understand the use of validated PRO questionnaires to measure core HRQoL outcomes and disease-related symptoms; and PRO item libraries in the development of trial-specific/treatment-specific item lists.
3. Facilitate interactions among relevant stakeholders aiming at international collaboration.

3. Workshop Report

The workshop was organised in the following sessions:

1. **Welcome**
   Scientific Advisor for Oncology, EMA
   Head of Quality of Life Department, EORTC

2. **Introduction and meeting objectives**
   Appointed EMA and EORTC Joint Chairs of the Workshop

3. **Session 1: How can PROs and HRQoLs data inform regulatory decision as well as to cover HTA needs?**
   Invited speakers (see session report below)

4. **Panel discussion**
   All speakers with additional panellists and open forum for questions

5. **Session 2: Novel Approaches to the measurement of HRQOL and other PROs**
   Invited speakers (see session report below)

6. **Panel discussion**
   All speakers with additional panellists and open forum for questions

7. **Wrap up and conclusions**
   Appointed EMA and EORTC Joint Chairs of the Workshop

Guidance to the reader: *This report summarises the key aspects which were discussed during each session of the workshop. Abstracts and panel discussions are summarised under each session. This report should not be understood as the official views of The EMA or its scientific committees.*

3.1. Welcome

Francesco Pignatti (EMA) and Madeline Pe (EORTC)

F. Pignatti welcomed everybody to the joint EMA and EORTC workshop on how can Patient Reported Outcomes (PROs) and Health Related Quality of Life (HRQoL) data inform regulatory decisions for cancer treatments.

From this inception, this workshop has evolved with ambitious goals. When assessing treatments as regulators we often grapple with choosing between precisely quantifiable pharmacological effects and the broader but more challenging to measure impact on health and well-being.

Today is a great opportunity to look at strategies to bring these gaps and to explore ways to optimise regulatory decisions.

M. Pe provided a background of the development of the EMA/EORTC workshop on the use of PROs in regulatory decision-making. This workshop was initially planned in 2020 but has been postponed because of COVID-19 pandemic. The original agenda had to be changed for the current workshop because a lot of movement has happened in the PRO field since then. It was important that the current workshop reflects the advancements in the field over the last four years. Some key initiatives were highlighted: the standardisation efforts such as SPIRIT-PRO and CONSORT-PRO, SISAQOL, PROTEUS; the EMA oncology working party strategy plan and the activities EMA is doing on patient experience data; the FDA's series of guidelines on patient focused drug development and the use of PROs specifically in oncology drug development; the release of the EUnetHTA endpoints guideline (which is now HTAr), and the plan of ICH to develop guidelines on patient focused drug development.

To move the discussions forward, it was important to highlight key presentations that would resonate across various international stakeholders and provide more time for a panel discussion with the goal of developing concrete action points by the end of this meeting. This platform is an opportunity for an international multi stakeholder discussion to concretely identify how patient reported outcomes and HRQOL can inform benefit-risk assessment of cancer treatments. All chairs, speakers and panelists were thanked because of their contribution to this workshop.

3.2. Introduction and meeting objectives to the EMA and EORTC multi-stakeholder workshop on PROs and HRQOLs data to inform regulatory decisions for cancer treatments

Chairs: Jan Bogaerts (EORTC) and Caroline Voltz (EMA)

Patient's involvement, what does that mean? Variability between diseases and patients

Pierre Demolis, Chair of the Oncology WP and Vice Chair of the SAWP, ANSM, EMA

P. Demolis emphasised the importance of patients' perspectives in oncology which is unique due to the variability of cancer and its treatments. When a patient is diagnosed with cancer, he/she will be diagnosed with cancer and will usually receive a neo or adjuvant treatment. The patient might or might not be cured and might progress with metastases. It is important to highlight that every patient and every cancer is different. Therefore, it is interesting to ask patients to ask them what matters to them (quantifying side effects vs efficacy). PRO might vary a lot throughout the course of the disease. For example, when asked before taking a medicine, the expectations might be very different to when a patient is taking its treatment, after treatment or if they have progressed. The same questions are also relevant when assessing Progressions Free Survival (PFS).

It is therefore important to understand which time point we are interested in getting the data. Patients are given treatment usually at maximum tolerated dose to maximise efficacy, therefore it is expected that adverse events will take place. Assessing QoL is multicomponent (depending on the treatment, the disease and the time). There is a clear need for PROs in providing additional information on the benefit/risk assessment of a new treatment (eg Is a 3-month increase in PFS <treatment-free period> worth it? is a maintenance delaying the next painful chemotherapy by 3 months' worth it? Is an adjuvant therapy increasing the cure hope from 80% to 90% worth it? Do you expect a last painful chemotherapy that may bring a few more weeks to your life expectancy?). It is important to highlight the relevance of the estimand specifically what is it that we would like to know. As this could inform regulatory decision and should be an endpoint. Robustness, relevance and utility are key criteria to consider PROs for regulatory decisions.

Evaluating cancer treatments based on overall survival and quality of life: Why improving patients'HRQOL is part of EORTC's core mission?

Winette van der Graaf, President, EORTC

W. van der Graaf introduced EORTC's mission which is to increase patients' survival and improve their quality of life through a) generating robust medical evidence through designing, coordinating and conducting multidisciplinary clinical and translational trials that would lead to new standard of treatment in care; and b) setting standards by being a reference for methodological research and an authority in establishing the standards of treatment in care. But how does one study patients' best interest? In cancer research we often evaluate the activity of a treatment, and the balance of safety vs toxicity. However, the impact of treatment on patients' HRQOL depends on much more than the treatment alone. The patients' voice is very much needed in the evaluation of treatments because clinicians may not know very well what the impact of cancer and its treatment is on patient's daily life and HRQOL.

Evaluation of clinical trials traditionally focus on objective outcomes such as disease free, progression free survival, overall survival, response rate, adverse events. However to get a holistic view of the impact of treatment, it is important to include patients' perspectives which can provide important additional information to evaluate benefit/risk assessment of interventions in trials. We should collect data in clinical trials and make objective relevant assessments of patients' HRQoL next to imaging and survival endpoints to serve our patients and regulators.

EORTC has long recognised the relevance of the voice of patients and patient reported outcomes. In 1986, the EORTC QLG was formed to develop HRQOL instruments for use in international cancer clinical trials, and in 1993 the QLQ-C30 was published. Disease-specific modules were also in development. Recently there is also a movement from Common Sense Oncology that advocates the assessment of outcomes that matter to patients, and improving patients' lives is one of its core visions.

It was concluded that we should collect patient reported outcome data in clinical trials and make objective relevant assessments of patients' HRQoL next to imaging and survival endpoints to serve our patients and regulators.

The tale of two trials: Improving the use of PROs and HRQoLin cancer clinical research

J. Reijneveld introduced the issue of conflicting HRQOL findings from two similar trials in newly diagnosed glioblastoma that were both published in the same journal in the same year. These two trials had a similar patient population, similar treatment and sample size, similar overall survival and PFS findings, but had conflicting HRQOL findings: one trial provided evidence for an improvement in HRQOL whereas the other showed a deterioration in HRQOL. Going through these trials showed that although it seemed that the two trials were providing conclusions on HRQOL, because of the differences in their analysis decisions, their conclusions were not based on the same analysis population, HRQOL domains and time points, and HRQOL endpoint. These two trials showed that there is a gap in how HRQOL data are being designed, analysed and interpreted in cancer clinical trials. There is a need for harmonisation on how PRO/HRQOL measures are developed (e.g., COSMIN guidelines; EORTC QLG measures), how PRO data are reported in protocols (e.g., SPIRIT-PRO), how PRO/HRQOL data are analysed and interpreted (e.g., SISAQOL-IMI), and how they are reported in trial publications (e.g., CONSORT-PRO). There is a long history and on-going academic work on the development of various PRO and HRQOL tools within oncology. The role of academia, including EORTC, is to not only build these tools, but also demonstrate how to use them. The next challenge will be to assess how PRO and HRQOL data inform regulatory decisions.

EMA current and future activities on patient experience data (PED) including PROs and HRQOL in medicines' development and evaluation

Juan Garcia Burgos, Head of Public and Stakeholder Engagement Department, EMA

J. Burgos provided an overview of EMA's journey of patient involvement. EMA has a long history of patient involvement starting in 1996 where dialogue with patients were initiated, followed by patients becoming part of committees and recently EMA is also looking into the systematic patient input along medicine's life cycle. Patients are involved in several EMA regulatory activities from pre-submission, to evaluation and post-authorisation. He also gave an example on how patient engagement has been useful in the pre-submission phase, specifically during scientific advice.

EMA recognises the relevance of patient participation in EMA regulatory activities. PROs is a type of patient experience data (along with patient preferences and patient engagement). Need for systematic inclusion of PED in medicines development and regulation.

EU Network Strategy's delivery plan and CHMP's 2023 workplan incorporate two key deliverables: Reflection paper on the best EU approach to generate, collect and analyse PED (framework for discussion or clarification particularly in areas where scientific knowledge is fast evolving or regulatory experience is limited); and explore how to improve transparency in the Assessment Report.

3.3. Session 1: How can PROs and HRQoLs data inform regulatory decision as well as to cover HTA needs?

Chairs: Jaap Reijneveld (EORTC) and Pierre Demolis (EMA)

Learnings from PROs used for regulatory approval of oncology medicines in the European Union

Carla Torre, CHMP co-opted member, INFARMED

C. Torre presented a literature review work on how PROs are used for regulatory approval of oncology medicines in the European Union (Teixeira *et al,* 2022). She started the presentation indicating the relevance of capturing patient's perspective during clinical trials in the oncology setting. This is viewed as an opportunity to collect unique information on the patient's experience of the disease, its treatment, including the impact on their quality of life (QoL > longevity). Cancer diseases and their respective

treatment regimens are associated with significant negative symptoms side effects and functional limitations. Collection of patient reported outcomes in clinical trials gained special interest and is recommended by regulatory authorities since PROs may provide evidence to support medicines approval, labelling and marketing claims.

The review that was being presented made an assumption that PRO label claim was intended. The aim was to identify potential causes for PRO claims not being granted. Such insights would provide an important perspective on the future challenges of using PROs in oncology clinical trials field.

Results of the review showed that out of 128 approved oncology indications between 2017-2020; 100 (78.1%) included PROs in their confirmatory trials. In these indications which included PROs, 22 (17.2%) indications included label claims in the SmPC (the majority corresponding to solid tumors). Trial designs used for the 22 indications: 11 were supported by randomised open label studies, 10 (45.5%) by double blind RCT and 1 (4.5%) was by an open label single arm trial study. 76 of the 100 indications had EMA reviewers' comments provided on PRO included in the EPAR. EMA reviewers comments provided possible reasons for not including PRO data in the SmPC for 34 (44/7%) of the indications. Reasons not included in SmPC include clinical relevance is unclear, missing data, using open label designs.

It was concluded that despite growing recognition of the value of PRO data for the development of improved cancer therapies, PRO implementation remains challenging. Between 2017-2020, EMA granted PRO labelling to 22 (17.2%) out of 128 oncology indications. 78.1% included PRO data in confirmatory trials. Similarly, Gnanasakthy et al (Value in Health 2019) showed that between 2012-2016, EMA granted PRO labelling to 21 (32.8%) out of 64 oncology indications approved. 70% included PRO data in confirmatory trials.

Several key concerns were identified regarding PRO implementation including the rationale, study conduct (data collection, training, management and analysis), influence of study design, missing data and PROM selection.

While PRO implementation remains challenging there is added value benefits in their use namely for both research and clinical practice contributing to share decision making processes supporting HTA decisions, and ultimately enhancing healthcare systems. But methodological robustness, consistency of outcome reporting and early dialogue with regulatory agencies are paramount.

FDA views, practices and challenges in assessment of PROs - what does FDA need?

Vishal Bhatnagar, Associate Director for Patient Outcomes, Oncology Center of Excellence, FDA

V. Bhatnagar introduced FDA's perspective on including PROs during oncology product drug development. Measurement of core PRO symptoms and functioning provides valuable complementary safety and efficacy information in different phases of trials (dose finding, dose expansion, late phase registrational, post-marketing).

Patients are uniquely positioned to inform understanding of the therapeutic context for drug development and evaluation. Patient-Focused Drug Development (PFDD) is part of FDA commitments under PDUFA V and VI*. Additionally, 21st Century Cures includes important language about PFDD.

From the FDA's perspective, the core patient generated data that they are interested in are: disease symptoms, symptomatic adverse events, overall side effect burden, physical functioning, and role functioning. They also presented their views on the assessment frequency for the various PROs. These patients generated data provides additional information from clinician reported and biomarker data.

What is the PRO trial objective that needs to be considered? Questions to consider: Is it to describe patient experience on treatment? Inform safety/tolerability? Inform efficacy?

What is the US regulatory goal for PRO data? Questions to consider: supportive data for overall benefit:risk? Descriptive patient experience data in product label? Make a claim of treatment benefit in product label (then substantial evidence of efficacy or improved safety is needed)?

Their view on the use of PROs for safety/tolerability was also elaborated on. It was emphasized that the PRO-CTCAE is not the same as the CTCAE, where the PRO-CTCAE is used to report symptomatic adverse events from the patients' perspective, whereas the CTCAE is from the clinician's perspective. They provide information that are complementary to each other. However, in addition to assessment of individual toxicities, it is also relevant to have an assessment of overall side effect burden measure. drugs cause may symptomatic side effects and how individuals "weigh" one symptom over the other can differ. The question is: could an overall side effect measure be a useful summary metric? Commonly used item to assess overall side effect burden is the FACT GP5 Question "I am bothered by the side effects of treatment" or the EORTC Q168 "To what extent have you been troubled with side effects of your treatment". The OCE Core PRO in Cancer clinical trials guidance and the white paper from friends of cancer research on "supporting a patient-centric approach to dose optimisation in oncology: the essential role of PROs" are available as a reference.

It was concluded that: Patient-reported outcomes and healthcare utilization can complement standard efficacy and safety measures. PRO concepts should be well understood; instruments should be fit-for-purpose and well-defined. Tolerability can be assessed in all oncology trials, including dose escalation and expansion. Item libraries can be used to parsimoniously meet the respective needs of regulators, payors, and all stakeholders. Well-collected and meaningful PRO information should be communicated to patients, caregivers, and providers.

Application and importance of HRQoL/PRO assessment from HTA perspective

Beate Wieseler, Head of Department Drug Assessment, IQWIG

B. Wieseler presented the importance of HRQOL/PRO assessment from an HTA perspective. PROs (including HRQoL) provide important information for HTA, they have the same relevance as other endpoints. Decision and goals from HTA is different from regulatory decisions. HTA asks two core questions: a) Enable choice of best treatment and b) enable pricing (for sustainable health care systems). Data needed should address comparative effectiveness and safety vs standard of care. Decision is based on clinical added benefit (including less harms) and cost effectiveness. These HTA decisions will then lead to both treatment decision and reimbursement and pricing decision (what is reimbursed is what patients see in the clinic).

What is the relevance of PROs in HTA? HTA endpoints focuses on how a patient feels, functions or survives. This is reflected as mortality, morbidity and HRQOL dimensions. PROs respond to morbidity questions through assessment of disease symptoms, disease complications and impact on functioning; and health-related quality of life, specifically the impact of disease and its treatment on physical, emotional and social well-being. PRO is part of evaluation of clinical added benefit and cost-effectiveness. PROs should be part of the treatment decision, answering patients' and clinician's questions.

The current issue faced by HTAs is that PROs are less robust than other endpoints (trial design, data collection, analysis and reporting). Of critical importance is the robust methodology because PROs are important for HTA. SISAQOL initiative has been helpful in developing specific recommendations for analysis of PRO endpoints**.**

It was also highlighted the relevance of collecting post-progression data. Limited PRO data collection (eg until progression) does not answer HTA questions. Often as a result of data collection until progression only, differences in observation period between arms pose additional problems. The issue of using item lists was also presented. Although item lists may be a possibility to optimise data collection for a specific disease or treatment, robust methods for item list development is required to avoid selective compilation of items which will not cover the complete construct/symptoms of interest. Caveat: HTA is interested in

(fair) comparative effects, therefore, item lists need to capture the characteristics of both the test intervention and the comparator(s). HTA may use indirect comparisons across studies, therefore, instruments need to be standardised between studies and over time. A set of studies with different isolated item lists would be less relevant.

It was concluded that PROs (including HRQOL) provide important information for HTA, they have the same relevance as other endpoints. Collection of high quality PRO data remains important and is an important step of patient involvement because these data represent the patients' voice. However the relevance of this data requires robust methodology for study planning, data collection, analysis and reporting and interpretation.

A Patient-Reported-Outcome-based Multi-State-Modelling approach to Benefit-Risk Assessment

Douwe Postmus, University of Groningen, NL and Seconded National Expert, EMA

D. Postmus started his presentation explaining the typical trade-offs in the benefit/risk assessment in oncology. Typically, benefit/risk assessments weigh (progression-free) survival improvements against detriments in toxicity (e.g., is 11 months of PFS with 40% toxicity preferred to 9 months PFS with 10% toxicity). Although these trade-offs are important in the Benefit/Risk assessments, they don't capture the patient reported experience and burden over time. So the question is: would evaluation of time spent in a certain state help overcome these limitations (e.g., is 9 months of PFS with toxicity followed by 2 months with no toxicity preferred to 9 months PFS with no toxicity?)

A hypothetical case study was presented to assess whether such methodology would provide a better understanding of the benefit/risk of a treatment. A multi-state modelling was used to assess states that differentiated time spent progression free without significant toxicity, time spent progression free with significant toxicity, time spent in the progressed disease state; time spent in the death state. And with this methodology, it allows the presentation of how long patients in the control arm (vs experimental arm) spent progression free but with toxicity compared to progression free without toxicity.

One issue that was highlighted was that currently QoL data is not collected in the progressed disease state so it will not be able to distinguish between time in progressed state with significant toxicity vs no significant toxicity. Having such data can provide a more comprehensive view of Benefit/Risk profile.

The presentation concluded with avenues to explore new approaches to complement traditional benefit/risk assessments. Multi-state modelling allows integrating diverse data types to define health states (like HRQOL or toxicity. This can also be combined with health-state utilities to perform quality-adjusted survival calculations. Next steps are to explore the usefulness of this approach in informing benefit/risk assessments.

3.4. Panel Discussion

Moderators: Jaap Reijneveld (EORTC) and Peter Mol (EMA)

Panellists:

(i) Paul Kluetz, Deputy Director, Oncology Center of Excellence, FDA
(ii) Maxime Sasseville, Clinical manager, Oncology Division 2, Health Canada
(iii) Friedrich Wittenbecher, Swissmedic
(iv) Shun Tezuka, Medical officer, Office of New Drug I/IV/V, PMDA
(v) Harald Enzmann, Chair of CHMP, Bfarm, EMA
(vi) Anja Schiel, Special Advisor, Norwegian Medicines Agency
(vii) Bettina Ryll, Founder of MPNE and WECAN representative

(viii) Joseph Cappelleri, Executive Director of Biostatistics, Pfizer

(ix) Christopher Booth, Director, Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute

The panel discussion addressed the following key topic areas:

1. What is needed for more systematic use of PROs in submissions?
2. What are the differences among regions and decision-makers that require harmonisation?
3. What concrete next steps would you propose?

All panelists were asked to introduce themselves and provide their overall views on what needs to be done so that PROs can be more useful for regulatory decision making.

Overall views of panelists on the use of PROs in decision making

P. Kluetz (FDA) mentioned that PROs are used best to isolate the effect of a treatment for a specific disease and emphasized that more intentional, thoughtful use of how to use PROs in clinical trials is needed. A harmonisation that needs to happen is on the assessment of PROs post-progression and the use of large and validated item selection of libraries. **M. Sasseville (Health Canada)** shared that it would be helpful to have drug development programs where they have robust PRO data collection and statistical design. The hope is that this will allow companies to pay attention to the details on how they incorporate PRO data in their program. This results in an additional component to look at for regulators but when PROs are incorporated appropriately, it makes the regulatory work easier to evaluate PRO data. **F. Wittenbecher (SwissMedic)** shared that a clear PRO hypothesis in the statistical analysis plan would be needed to include it in the labelling. Moreover, having a more harmonised and robust methodology, more common way of visualisation of the data (e.g., KM curve for the other endpoints) would be helpful to know what regulators need to look at**. Shun Tezuka (PMDA)** shared that PMDA has one guidance on PROs. OS, PFS ORR are well established. However currently, anti-cancer drug can be approved in Japan without PRO endpoint. If PRO is submitted, PMDA evaluates it but evaluation method is not established, and it is not included in the assessment report or labels. PMDA wants to use opportunity to collaborate and move forward in this area. **Harald Enzmann (Chair of CHMP, EMA)** shared that regulators look at submitted PRO data and consider it in regulatory decisions. However, regulatory decisions cannot be and end in its own; it is only one step of the decision making. For PROs to support decision-making, this relies on its best possible use. And best possible use depends on scientific quality, and is not an all or nothing approach. Scientific quality needs to be proportionate to the objective. A clear objective from the beginning is important to influence the design. Will the PRO be used as a crucial basis for marketing authorisation, or are data collected to provide information for labelling, or is this information meant to support the patients when they make a decision for or against a treatment? The goal is to have a pre-defined objective to diminish the difference between the broad expectations we currently have vs the specific impact the data have on decision-making.

A. Schiel (NoMA, HTA) provided her views that a problem lies in the way PROs are reported in the dossiers that they have received. Is the PRO results in one dossier with one figure different from another dossier with another kind of figure? Without consistent systematic reporting, reviewers spend more time figuring out figures rather than evaluating the quality of the results. SISAQOL's work on having consistent figures will be helpful so the time spent is on assessing the quality of the PRO tools and results rather than trying to figure out what the figures mean. **B. Ryll (patient representative, MPNE and WECAN)** shared that regulatory science is a new field. Nobody knows everything and it is important to involve resources and forums to work on understanding what the issues on measurement are relevant for patients. This is important for patient engagement. **J. Cappelleri (industry representative, Pfizer)** discussed that industry needs to take all perspectives since all of them are linked. He highlighted the importance of standardisation such as the SISAQOL and SPIRIT-PRO initiatives. Work on agreeing on

standards should continue. That allows the focus to shift on what is relevant and reduces uncertainty of what the expectation is from a pharmaceutical sponsor. For next steps, having a combination of transparent format to put all that information in a cohesive way would be helpful, and to have case studies where we can be specific on more details and to refine those based on what we learn and we can do in future meetings. **C. Booth (clinician representative, Queen's cancer research institute)** shared that making information accessible to clinicians in clinical practice and providing results from published reports. For the clinical community, it is important to streamline PROs and make it more accessible to practicing clinicians. It is important to understand what the PRO results are showing and what a clinically significant difference is. The clinical community needs support in these areas so we can start a discussion on what the magnitude of benefit a treatment gives.

What is needed for more systematic use of PROs in submissions?

Everyone agrees that assessing PROs and HRQOL are important. However, how this can be included in the regulatory decision making is a question that should be discussed. A multi-stakeholder approach is needed since everyone has a different expertise and it can be a challenge to understand other people's perspectives. FDA is committed to use PRO data in regulatory review. The data quality of PRO submissions has improved. A consistent objective for PROs could be safety and tolerability since we can apply these objectives under the descriptive PRO objectives framework. Although the needs of stakeholders may be different for PROs, it is important to find an overlap and good compromise so that it can be used for the different settings. It was also shared that patients are not interested in simply filling out questionnaires, but they are interested in knowing about their QoL. There should be a feedback loop to inform patients about their QoL so that they know that filling out these questionnaires is also relevant for them.

How should we move forward? An important question to address is what questions do PROs answer? The estimand discussion is helpful in determining what questions to ask about PROs. It was also highlighted that the way we approach PROs should not be different from other clinical endpoints. We should still ask questions on how to apply PROs for which setting, which patients and for which decision-maker (regulatory, HTAs)? But it is critical that the different stakeholders describe what they need from the PRO results so that we can have open discussions on the value of PROs and seeing what can be harmonised across various stakeholders.

It was recognised that FDA is a bit ahead in PROs although other international regulatory agencies are also moving forward in this area. So it was queried on how FDA has approached its own journey of acceptance and familiarisation with PROs? What would FDA recommend to other fellow regulators from what FDA learned to their journey? What are the low hanging fruits that we can harmonise and progress in a similar way? FDA's advice was to move away from black or white perception of data (i.e., needing to show comparative benefit which requires pre-specified hypothesis and statistical tests). It is also possible to look at PROs as a supplementary information for safety and tolerability across the board (where there is no pre-specified statistical test). PROs will not change the regulatory decision all the time (like safety does not change our decision all the time), but safety is always incorporated in the decisions. It is possible to use PROs to show a favorable benefit/risk by demonstrating that it is more tolerable from a more descriptive framework.

For HTAs, it is important to base decisions on comparative benefit. The estimand framework can be defined for regulatory and HTA bodies. There will be an upcoming joint scientific advice between EMA and HTA, and it is important to embrace this opportunity to discuss what is needed from PROs from the dossiers that are submitted.

It was also highlighted that unobservable symptom can be best reported by PROs. But the challenge will be on the analysis considerations. SISAQOL-IMI is trying to tackle this for PROs.

Another challenge that was discussed was the use of PROs in open-label designs. It was acknowledged that the issue of open label trials is not going to go away (a single arm trial is *de facto* an open label design). When using PROs as a tolerability endpoint, we can draw parallels to safety reporting. We don't stop assessing safety data when we have open label, so a similar approach can be used for PROs. The challenge will be on assessing efficacy for open label trials. However, there are also issues on the use of blinding in trials. For example: One treatment is oral and the other requires going to the hospital every two weeks for an injection. What does it mean to the patient if you have a placebo injection? What does that mean in terms of generalisability? You may have an imperfect design or data but that design may be more appropriate for the question that is being asked.

What are the differences among regions and decision-makers that require harmonisation?

When discussing about alignment or harmonisation, what is exactly the goal? Will we end up removing the cultural specificities across various international stakeholders? Identifying what needs to be aligned is important because aligning can also be detrimental that we don't lose relevant issues on PRO data for specific groups. Regulatory and HTA have different questions and therefore it is not possible to align everything, and even HTAs in Europe have different health care systems so aligning might not be appropriate or fitting for a specific health care system.

However, what can be aligned is the standardisation of methodology, data quality or reporting. It is possible to align how the PRO questions are formulated (eg estimand framework) but the specific research questions asked about PROs may not be something that could be aligned especially in the view of appreciating the differences across countries.

What concrete next steps would you propose?

For clinicians, an important missing piece is the knowledge translation to the clinic. PROs/HRQOL has come a long way in the last decade. However, many clinicians are still confused on the concept of PROs and HRQOL. There is a need to include this topic in the residency and fellowship trainings among clinicians.

For patients, they care about their quality of life and making the findings from the questionnaires actionable would be relevant. Moreover, the possibility to add items in the item library increase the clinical value of PROs.

Moving forward, the estimand discussion becomes very important because it helps address the question on defining the PRO objective more concretely (what do we really want to achieve). It is also important to understand which decision-maker am I collecting these data for? If there are evidence gaps in the findings, it is good to identify who or what can fill those evidence gaps.

PROs are not different from any clinical outcome: there is a need to describe the scope of the study, formulate the setting and for which patients. Importantly, we need to describe or explain better how we are using PROs so we can discuss whether we agree or not with how this is being currently implemented. Through these discussions, we are then able to make more progress in the field.

The way we view PROs these days has gotten better because people are interested in using these data. In order for PRO findings to be convincing, good quality data is key. Results coming from good quality PRO data can potentially make a difference in the assessment of cancer treatments.

3.5. Session 2: Novel approaches to measurement of HRQOL and other PROs

Chairs: Chantal Quinten (EMA) and Madeline Pe (EORTC)

EORTC's strategy on the development and implementation of PRO and HRQOL measures for cancer clinical research

Mogens Groenvold, Professor in Palliative Care and PRO Assessment, University of Copenhagen and Bispebjerg/Frederiksberg Hospital

M. Groenvold raised the question on: What does fit-for-purpose instruments mean? How do we achieve it?

The standard approach for the use of HRQOL/PRO measures in oncology has been the use of validated questionnaires with a core measure and modules (e.g., EORTC and FACT measures). This approach focuses on rigorous development following a common approach across different cultures and languages. However, it was becoming clear that the traditional strategy was not enough: the standard approach is not enough to ensure content validity of new trials with new adverse events. Moreover, the classical way of summing scores from different items of the same construct can be improved and does not utilise new technology of computer adaptive testing (CAT) which allows more precision and personalised questions based on patients' previous responses. CAT individualizes assessment, improves measurement precision, power and range while reducing floor/ceiling effects. CAT provides increased score precision across continuum of respondent ability, arguably making assessments fairer for high and low ability respondents.

For EORTC, there was a need to add flexibility to traditional approaches in its measurement strategy. In an era of new treatments, the use of EORTC PROMs can be a mix of a core questionnaire, module, item list from item library (which is discussed further in the next presentations). And if there is a need for a primary or key secondary outcome with more precision, a CAT of the specific concept can be used (eg diarrhea).

Some key concepts were defined:

- Static(validated) questionnaires: E.g., EORTC QLQ-C30 + EORTC modules, FACT-G;
- Computer-adaptive testing(CAT): E.g., EORTC CAT Core, PROMIS;
- Item bank: A numberof items calibrated for CAT, e.g., EORTC CAT Core emotional functioning item bank;
- Item Library: a database of items, e.g., EORTC Item Library, PRO-CTCAE;
- Item List: A selection of items from an item library.

Measuring HRQoL core outcomes and disease specific symptoms

Johannes Giesinger, Assistant Professor of Health Outcomes Unit, Medical University of Innsbruck

J. Giesinger explained the assumptions behind the development of HRQOL/PRO questionnaires.

Key to the use of PRO measures is that it should measure what matters to the target patient population. Content generation of these questionnaires are critical and should have a strong focus on content validity. This is produced through an exhaustive list of HRQOL issues relevant to the target population based on literature reviews and interviews with patients and health care professionals. It is also critical that patients participating in the interviews are recruited in line with a pre-defined matrix to ensure inclusion of patients with various treatment types or disease stages. This will ensure generalisability of HRQOL issues for the target population. Another aspect of questionnaire development is assessing the

relevance of these issues over time. For example, the QLQ-C30 showed that the core issues of cancer patients today are still captured in the QLQ-C30.

Interpretation of scores from questionnaires remain a key aspect for the inclusion of PROs in clinical trials. Guidance from instrument developers are needed to interpret PRO scores based on the setting that they will be used. For EORTC, we provide various aids to guide interpretation of EORTC measures:

- thresholds for clinically meaningful changes and differences (eg what can be used for responder definition and what can be used for interpretation of differences between trial arms);
- thresholds for clinical importance of absolute scores (eg for clinical practice used in symptom screening);
- normative data from general population; and reference data from various groups of cancer patients (eg can be used to compare PRO scores in trials or population level studies)

Measuring treatment-specific side effects from the patient perspective: trial-specific item lists from PRO item libraries

Alexandra Gilbert, Associate Professor in Clinical Oncology, University of Leeds and Claire Piccinin, item Library researcher, EORTC

C. Piccinin began the presentation by defining some concepts related to item lists and item libraries:

- Item library: collection of single items or multi-item scales that measure various PRO/HRQoL domains. The item library allows for selection of specific items;

- Item list: customised questionnaire created using select items from library. They can be derived from existing validated questionnaires (EORTC, FACIT, MDASI) or designed and developed with aim to create flexible item library (PRO CTCAE is designed as companion to CTCAE).

The current use of the EORTC item library demonstrate that industry and academic users emphasize different stakeholder needs and relevance of flexible approaches within observational studies and routine clinical care. For the EORTC item library, industry uses this tool for clinical trials or non-interventional studies; while academic users use the item library for non-interventional study, clinical trial and monitoring.

In which settings are item lists used? When there is a need to assess novel treatments to capture issues and symptomatic AEs not included in static questionnaires, rare disease groups for whom static questionnaires may not be available, early phase trials when less is known about possible symptomatic AEs and more flexibility is required. The use of item libraries is relevant because of the need to be more pragmatic in the approach of using PRO measures.

Core outcomes of cancer patients are integrated within standard instruments (e.g., QLQ-C30 for core cancer outcomes; and the disease-specific modules for core outcomes of a specific cancer population, (eg measuring disease symptoms for lung cancer patients). For the assessment of patient-reported tolerability (which can be specific for an investigational treatment), there is a need to think about how to identify issues to include in an item list (e.g., investigational brochure, literature, clinician, patient public involvement). Some special considerations to think about for incorporating PROs in trials: symptom burden item, elderly module, decision regret.

A. Gilbert provided the clinical perspective on the use of the EORTC measurement strategy, including the item libraries to assess tolerability. She presented a case study of a platform trial on how the EORTC measurement strategy was incorporated into that trial, demonstrating a balance and flexible approaches for the needs of the different phases of the trial. She further described the need to have patient-reported

adverse events, and showed a study in an early phase setting where differences were found in the tolerability reporting between clinicians and patents.

When thinking about developing Item library guidelines, recommendations should be tailored based on context of use. It is also important to measure unexpected issues from the patient perspective which an open-ended question to ask patients about issues that have not been mentioned in the pre-defined item list. Both PRO-CTCAE and EORTC item libraries have such questions available in their item libraries.

The use of the item library is an opportunity to establish the measurement of tolerability. Validated questionnaires (core and disease specific modules) cover core outcomes related to the disease, which includes the possibility to measure efficacy. It is also relevant to measure comparable toxicity (eg through an overall side effect burden item), which allow comparison across multiple modalities of treatments. When thinking of a PRO measurement strategy, it is important to measure what matters to patients, and that it covers the patient experience of the impact of the disease and/or treatment.

Application of the use of static and flexible PRO measures in global cancer trials: Challenges and opportunities

James W. Shaw, Executive Director and Head of PRO Assessment, Bristol Myers Squibb

J. Shaw provided the industry views on the use of item libraries such as PRO-CTCAE in BMS. PRO-

CTCAE provides flexibility in two ways: a) only items for relevant symptoms are selected for a particular use; and b) the majority of symptoms have more than one item but conditional branching allows for only the relevant items to be asked to a particular patient. For example: A symptom may have a frequency and a severity item, but the severity item doesn't get asked if the patient reports in the frequency item that they never have the symptom.

What was the learnings from BMS experience? In terms of strategy, clinical teams are often receptive to using the PRO-CTCAE, especially in Phase 2 trials, but costs and patient burden are a concern, especially because the measure should be done frequently to capture symptomatic toxicities and requires electronic clinical outcome assessment (eCOA). While the FDA has recommended their use for dose selection, there is currently no regulatory incentive to do so nor is there a clear model on how to incorporate them in decision-making. The appropriate/unbiased selection of PRO-CTCAE items is an ongoing concern.

In terms of analysis, analyzing PRO CTCAE data can be a challenge due to varying outcomes, response metrics, and branching logic. There is a need to educate statistics personnel on analysis and other stakeholders on interpretation of results.

In terms of operational issues, the early implementations of PRO-CTCAE involved paper use, which can cause problems with patients answering questions that aren't relevant to them. eCOA implementation is now standard but makes the ability to capture other symptoms (beyond the items chosen) - difficult as free text keyboards can be cumbersome or unavailable on eCOA devices in some languages. Finally, eCOA vendors have differing levels of familiarity with the measure and enacting conditional branching correctly is a challenge for some.

J. Shaw further discussed the comparative benefits of static vs flexible approaches but concluded with thoughts on flexible approaches as a novel way of assessing PROs. With flexible assessment, item content can be tailored to trial specifics or respondent ability. However, there are numerous barriers to using flexible measures that need to be weighed against potential benefits. The application of flexible measures requires the support of appropriate sponsor roles, processes, and platforms as well as supplier technology. Insufficient regulatory guidance and precedents as well as HTA concerns need to be addressed.

3.6. Panel Discussion

Moderators: Chantal Quinten (EMA) and Madeline Pe (EORTC)

Panellists:

(i) Mogens Groenvold, University of Copenhagen and Bispebjerg/Frederiksberg Hospital
(ii) Chantal Quinten, EMA
(iii) Hans Schuerer, Vice-Chair, WECAN
(iv) Jill Bell, Head of Measurement Science Center of Excellence, Oncology R&D, AstraZeneca
(v) Michael Schlichting, Director Biostatistics, Merck Healthcare KGaA
(vi) Corneel Coens, Lead Statistician, EORTC
(vii) Ashley Wilder Smith, Chief Outcomes Research Branch, US NCI

The panel discussion addressed the following key topic areas:

1. What are the important research questions to be addressed from a methodological perspective?
2. What are the recommended practices in incorporating static questionnaires and item lists in cancer clinical trials?
3. What concrete next steps would you propose?

Considerations in incorporating PRO measures in cancer clinical trials

H. Schuerer shared that an important consideration is to read the items included in the questionnaires and item lists. It is important to make the step to ensure that patients understand the item and they can be answered the way it should be. It's also good to think about the number of items to be included for PROs (e.g., not 100 items) because how can people expect patients to fill out these questionnaires completely if there are so many items to fill out.

M. Groenvold emphasised that the use of PRO measures in trials is like a pendulum. Historically, everyone was asked to write a questionnaire and use it the next day, and this was considered not appropriate or standardised. The field spent many years to standardise the approach to development of questionnaires and persuade everyone to use standardise tools (static questionnaires). Then now, we want to add a component of flexibility because we need measures to be targeted and efficient. Understanding this movement towards balancing static and flexible approach is a valid concern. Having this collective learning experience of how to appropriately incorporate PROs in trials is important.

A. Smith focused on the cultural readiness on the use of flexible approaches to PROs. Flexibility is about having a tool to fit the needs of stakeholders. The importance of stakeholder needs is emphasized because this will contribute to ensuring that the collection of PRO data is fit-for-purpose. There is also a cultural readiness in the use of flexible measures which is important for its adaptation in its incorporation in trials.

J. Bell shared that when incorporating PROs, we should do something like what has been done historically. What is relevant to patients? What should we be measuring in our trials? What is relevant for specific context of use? We have to accept that we cannot measure everything in a clinical trial. There is an opportunity with item lists because we can tailor something for patients and their treatment. But how do we maintain the scientific rigour when using item lists? An example would be transparency on how we select those items and documenting how we selected those items. It is also important to always keep the end solution in mind: what are we delivering to patients at the end of the day? Do the results we provide from these trials address the patients' needs?

Considerations when analysing PRO data in cancer trials

A question raised by **M. Schlichting** was whether we were overengineering PROs, which also makes it difficult to assess the robustness of the results coming from these PROMs. It seems that the need for standards within PROs are much more than for tumour assessments. There's also differing standards: when regulatory would say that PROs should be captured until end of treatment, but HTA needs assessment after treatment. Industry is ready to invest in PROs but it is also important to provide clarity and an incentive to its use. Industry is ready to invest in PROs but would appreciate further guidance to routinely integrate patient experience data in the product label, in particular if tolerability is concerned as complementary information on safety.

C. Coens shared similar concerns and questioned why PRO data should be treated differently from other clinical endpoints. When asked about robustness, we should follow the standards for the other clinical data that are used. The guiding principle is the objective needed for a clinical trial. How these data are used should be the focus and not just where the data originates from. From an analysis perspective, PRO data should be treated similarly and with the same rigour as any other endpoints.

Advice on how to choose which measure to use for cancer clinical trials

The first question is not about which measure to use but the choice of outcomes that need to be assessed for specific trials. This is an area where there is still a gap and remains unaddressed. There should be a transparency on which PROs need to be measured and what questions to ask about PROs. This is an area where we can learn from previous trials and to have a transparent way of determining which PROs or adverse events are measured or were impacted. This way we have a better view on which outcomes we should be measuring for an investigational treatment.

The choice also needs to be a balance of precision breadth, feasibility and value, and may not be seen similarly by all stakeholders. When thinking of specific tools, the benefits and limitations of instruments need to be considered (e.g., information provided; how easy it is to complete; and whether patient sees value in the questions).

Choosing the right items during the design of the trial is important. It's not just the adverse events but the context of the situation is needed and how this would impact patients. An example was given about clinicians indicating that ocular issues were manageable, but from a patient perspective these ocular issues have an impact on whether they can drive or not. So this context piece on how an adverse event can impact patients' lives that can be provided by PROs is important.

Finally, the core set of minimum requirements among different stakeholders (FDA/EMA/HTA) should be considered. We need to consider the different perspectives when designing a trial.

4. Wrap up and conclusions

Peter Mol, CHMP and SAWP member, MEB, EMA

P. Mol provided the summary of the workshop and thanked C. Voltz and M. Pe for their overall contribution to the workshop. PROs has been there for a long time. Pain is a PRO, but we are in an era where we want to have a more holistic view and we want to capture what patients feel and how they function.

There is an interest in having these tools. But it is important to demonstrate to regulators that an investigational drug can do something for this specific outcome. The earlier presentation was relevant as it presented how two trials with a similar population can have different results based on the outcomes chosen or timing of the assessments because the estimands were not properly defined. The estimand

should be defined in a way that it takes into consideration what the treatment will do for the patients. There is a need to look at patient's course of the disease and how that can be translated into a trial setting and end up in regulatory/HTA decision-making.

What are the expectations of regulators/HTA? The statisticians emphasized the importance of defining beforehand what you want to know. The tools that the EORTC provides sets up way on how to incorporate PROs in trials, but there should be a plan for how to use it for different contexts. It is also important to try not to capture everything and differentiate between what can be collected and what results can be shown in a trial. It is also important to consider that HTA may need different things, and planning and thinking through what is needed should be described.

It is also good to think about PFS with or without toxicity using PROs. We should also think about what can we gain from real world data? Important what is done there and what is feasible to combine with clinical trial data. What is a clinically meaningful change? Even in areas such as blood pressure, there remains a debate on what is a responder. It is also important to ask patients about their preferences using a patient preference study to understand what their perspective is of what they want to see in their PRO data.

For next steps: We need to move forward and perhaps build a smaller dedicated group. It is important to allow the ideas to mature and identify problems and tangible solutions. EORTC/EMA will collaboratively approach this. But it is important that there is a discussion between regulators and academics, and not just industry and regulators.