CDDF
Cancer Drug Development Forum

MEETING REPORT

CDDF Multi-Stakeholder Workshop

Endpoints in Cancer Drug Development

26-28 April 2021

Online Workshop

Prepared by the CDDF

PROGRAMME COMMITTEE

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Introduction

Dear all,

Cancer Drug Development is all about endpoints – they define the value (not just financial) of clinical trials and of new therapeutic options. Therefore, a critical and collaborative review is important and the CDDF has brought stakeholders from all relevant areas – regulatory agencies, patient advocacy, academic research, pharmaceutical industry, and health technology assessment – together in a three-day online workshop. This meeting report summarizes the presentations. CDDF members and partners can find the presentation slides, videos, and this report on our website, www.cddf.org.

Some say that the discussion about endpoints should not be that complicated as **overall survival** and health-related quality of life are seen as sufficient for this purpose and other endpoints would be unreliable. This approach, however, would lead to a halt in cancer drug development in many indications where the disease is rare, survival is long, or many subsequent therapies are available. Regulatory agencies have therefore accepted endpoints like progression-free survival for approval. However, it is key to understand that a single endpoint cannot determine an approval of a therapeutic and the totality of evidence must support this decision. In some indications new endpoints, like measurable residual disease, have been developed and the discussion should address the validation necessary to accept such endpoints.

Cancer drug development is determined by considerable urgency to improve patients' life. **Expedited approval pathways** have been developed by FDA and EMA to allow patients with no other therapeutic options access to therapeutics that are likely to demonstrate clinical benefit. The FDAs 'Accelerated Approval' pathway was intensively debated lately[1] . Usually, it is based mostly on single-arm trials with endpoints like overall response rate and response duration while the obligatory confirmatory trials analyze time-to-event endpoints like progression-free survival and overall survival. If these trials fail to confirm the expected effect the approval can be revoked – as recent examples have demonstrated. Charged with establishing comparative effectiveness health technology assessment is difficult with single-arm trials. It is therefore recommended to seek advice from the respective agencies early enough to align clinical development plans with the assessment needs to the degree possible (considering the still rather heterogeneous landscape in this area).

While all stakeholders put the patient in the middle of their efforts more work should be done to include patient input into the clinical development. One area is the definition, collection, and analysis of **patient-reported outcomes**. Much is still to be done to reach the full potential of these endpoints and guidelines would be very helpful. Best practices include an early (phase I or even pre-clinical) development of hypothesis for such outcomes with input from experts and patients, the selection of the most appropriate tools (with a good regard to standardization), a sensible application in the clinical trials (from phase II at least) and analyses and publications that serve the needs of all relevant stakeholders.

In summary, the workshop has demonstrated a strong collaborated effort to understand and improve the science and practical use of endpoints further. The CDDF welcomes all interested parties to use this report to get an update on the discussions mentioned above.

[1] See Endpoint News, FDA's oncology head Rick Pazdur defends the accelerated approval pathway, claiming it is 'under attack. July 29, 2021. https://endpts.com/wp-content/uploads/pdfs/829a235702b37cebf5f4dcbfb16ad844.pdf

We would like to thank the very diligent program committee, the excellent speakers and session chairs as well as the many who participated in the discussions for creating this workshop! We hope that that it may serve to improve our joint objectives.

Kind regards,

Axel Glasmacher

CDDF Board, Workshop Program Committee

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Day 1: When Overall Survival Cannot Be The Primary Endpoint

Reflection on the challenges

Axel Glasmacher, Prof. Dr Med.
Treasurer, Cancer Drug Development Forum; Department of Internal Medicine III, Univ. of Bonn, Germany

This presentation gives an overview of the discussions regarding alternative endpoints to overall survival in cancer drug development.

Key points of the presentation

Cancer drug development needs to balance the urgency of finding therapeutic approaches to the many severe unmet medical needs in this indication with the need to avoid exposing patients with inefficient or unsafe therapeutics. **Overall survival** is one of the most important outcomes and therapeutic objectives for those affected by cancer. It demonstrates a direct clinical benefit. Its assessment is unambiguous. However, it has become difficult to use in several indications, not the least due to the success of previous cancer treatments.

Alternative endpoints have been proposed to address this problem. However, critical assessments have pointed to the risk that they may not correlate with survival at all or may measure endpoints, like change in tumour size, that may not be relevant for survival, or are subject to bias concerning the method or timing of assessment. On the other side, alternative endpoints like progression-free survival (PFS) offer specific advantages as, when survival is relatively long, it is difficult to capture it in clinical trials. Post-progression survival is often highly influenced by the available subsequent therapies since unintended treatment switching may occur and distort the influence of the intervention therapy on overall survival. Therefore, PFS has been used in many indications as the primary – but not the only – endpoint in the assessment of regulatory approval.

In some indications, like **multiple myeloma** where 14 new therapeutics have been approved since 1998 based on PFS/TTP, overall survival massively increased over this period.[2] This demonstrates that – at least for multiple myeloma – the use of PFS has been successful.

In solid tumours, however, there is still debate whether the use of such endpoints is acceptable. To address these arguments several approaches have been developed to offer additional understanding and analysis:

- **Post-Progression Survival (PPS)**: Overall survival can be structured into the PFS period and the post-progression survival period. Depending on the length of the post-progression survival the assessment of OS as an endpoint becomes difficult. "OS is a reasonable primary endpoint when median [PPS] is short but it is too high a bar when median PPS is long, such as longer than 12 months."[3]
- **Progression-Free Survival 2 (PFS2)**: One additional (secondary) endpoint is PFS2, defined as the time from randomization to the second objective disease progression. PFS2 is of importance if an effect of earlier treatment on the efficacy of later treatments might be a concern and it has been used in haematological malignancies

[2] Anderson KC, Clin Cancer Res 2016; 22: 5419. Fonseca et al. Leukemia (2017) 31, 1915–1921
[3] Broglio KR et al., JNCI 2009; 101: 1642.

and solid tumours. One challenge is to maintain a similar assessment schedule in both arms in the post-progression period. It is regarded as an optional safety endpoint and not used by the FDA.

- **Other significant aspects** of overall survival, esp. if PPS is longer, are unintended treatment switches, if the interventional agent is available outside of the trial, and the interference of, at times, multiple subsequent therapy that may confuse the endpoint.

In some diseases it is necessary to develop new endpoints as overall survival or progression-free survival are now practical to use. It seems necessary to **validate new alternative endpoints** by demonstrating meaningful correlation with overall survival on a patient- as well as on a trial-level. Two important examples are **follicular lymphoma** were 'CR at 30 months' (see Figure 1) has been validated in an analysis of 3.837 patients from 13 randomized multicentric trials.[4] Similarly, in multiple myeloma **'measurable residual disease' (MRD)** has been validated in large meta-analyses.[5] Both, FDA and EMA, have issued guidelines on the use of MRD in pivotal clinical trials[6] and several CDDF workshops have addressed these questions (see www.cddf.org). These examples demonstrate that it is possible to define reliable new endpoints in indications, such as these, where overall survival is too long to allow reasonable drug development.

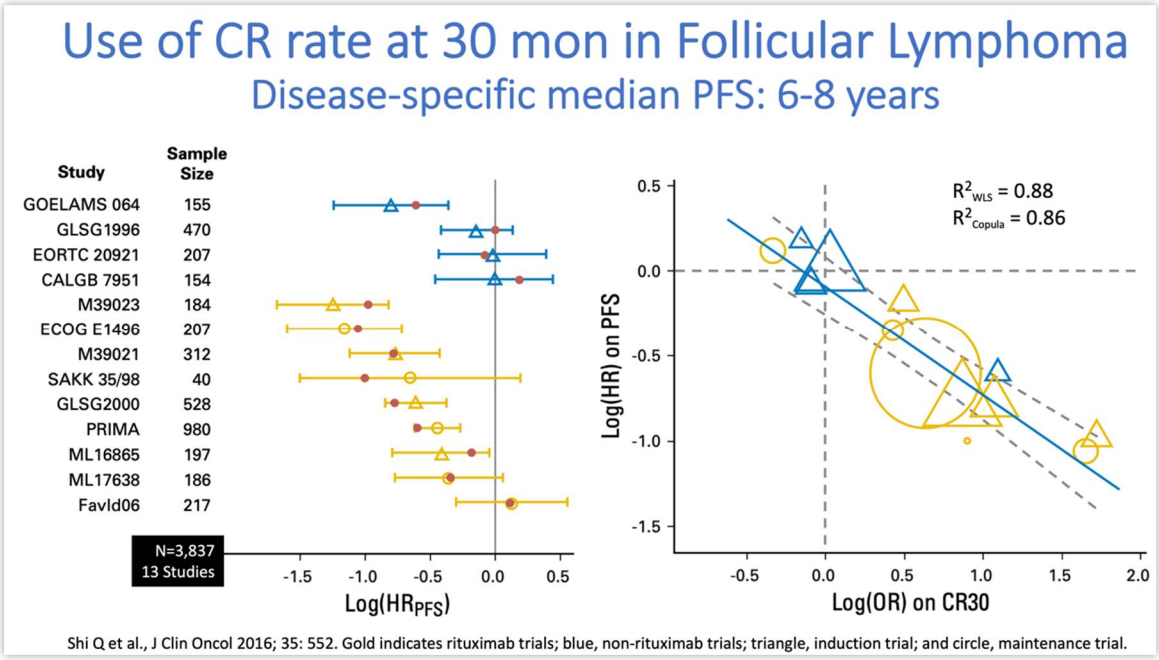

Figure 1: Validation of a novel endpoint for follicular lymphoma demonstrating both patient- and trial-level validation for the endpoint.

Summary

Overall survival cannot serve as primary endpoint in all indications as past successes achieving long OS times and larger choice of treatment alternatives lead to significant

[4] Shi Q et al., J Clin Oncol 2016; 35: 552.
[5] Munshi et al., JAMA Oncol. 2017; 3: 28. Avet-Loiseau H et al., Clin Lymphoma Myeloma Leuk. 2020; 20: e30.
[6] www.fda.gov/media/134605/download. www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-use-minimal-residual-disease-clinical-endpoint-multiple-myeloma-studies_en.pdf

difficulties for new clinical trials. Therefore, alternative endpoints, like PFS, must be used to enable further drug development in oncology. For some indications, novel alternative endpoints need to be developed and validated.

In any case, the primary endpoint cannot be assessed in isolation of other endpoints or the disease context (e.g. PFS plus a trend in OS and/or PFS2 in addition to toxicity).

New alternate endpoints must be carefully validated with evidence across different trials for the specific population and treatment modality. Specific biases, like measurement errors, assessment and attrition bias or informative censoring must be controlled.

Monitoring long-term trends in population-based registries is a valuable tool for the overall regulatory strategy.

Pathway towards solution: Metastasis-Free Survival - A novel endpoint in non-metastatic castration-resistant prostate cancer

Chitkala Kalidas, PhD
Vice President & Head Oncology and in vitro Diagnostics, Global Regulatory Affairs, Bayer US

Metastatis Free Survival (MFS) as a novel endpoint in prostate cancer led to the approval of three new therapies for the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC) in 2018 and 2019.

Key points of the presentation

nmCRPC is a disease state defined by rising levels of prostate-specific antigen (PSA) despite castrate levels of testosterone and the absence of radiographic evidence of distant metastatic disease. **Metastasis Free Survival (MFS)** endpoint definitions have been designed to include distant metastatic events but exclude local progression, which is not considered as likely to cause morbidity or death contrary to distant metastatic disease. Therefore, treatment recommendation for metastatic and non-metastatic CRPC are different and new treatments need to be developed for nmCRPC.

This novel endpoint was confirmed to be meaningful by three prospective, randomized trials (SPARTAN, PROSPER, and ARAMIS) and three new drugs have been approved based on MFS as the primary endpoint and OS as either co-primary or secondary endpoint[7]

- apalutamide, enzalutamide, and darolutamide.

All three drugs demonstrated substantial improvement in MFS and following approval, demonstrated an improvement in overall survival as well.

The use of MFS as the primary or co-primary endpoint in the above mentioned trials was novel instead of OS which had served for the approval of treatments like docetaxel, cabazitaxel and abiraterone. Relatively long overall survival periods in nmCRPC patients along with the availability of multiple subsequent therapies that can confound results rendered overall survival an impractical endpoint.

Development of MFS as an accepted endpoint

In recognition of the increased interest in developing therapies for the nmCRPC population, the FDA convened a non-product specific ODAC in September 2011 to discuss clinical trial

[7] Brave M, et al. An FDA Review of Drug Development in Nonmetastatic Castration-resistant Prostate Cancer Clin Cancer Res 2020; 26: 4717-4722

endpoints and trial designs that might be used to support drug approval. This ODAC emphasized that MFS is a reasonable endpoint if clinical benefit of a drug is ensured by

- A substantial magnitude of improvement and
- A favourable benefit–risk evaluation.

Similar conditions were formulated by the SAG Oncology of the EMA.

In 2012, another FDA ODAC examined the results of denosumab in a randomized, placebo-controlled trial[8] involving men with nmCRPC and BMFS as primary endpoint. Although the study was positive, given benefit-risk considerations, ODAC members recommended that longer metastasis-free survival would be required to justify approval.

Following these meetings, multiple companies designed trials examining systemic therapies in nmCRPC using metastasis-free survival as the primary end point with overall survival as a co-primary or secondary end point which led to the FDA and EMA approval of apalutamide, enzalutamide, and darolutamide in the years 2018 and 2019.

Key common elements of the pivotal trials for all three drugs were

- Stratification of patients at randomization by PSA doubling time
- Blinded independent central review of imaging studies
- Scheduling of an interim analysis of OS at the time of final MFS analysis.
- In the US each trial was agreed under FDA's Special Protocol Assessment mechanism
- In the EU CHMP Scientific Advice was obtained.

Regulatory Guidance Documents

The FDA published a draft guidance document in 2018[9] and concluded that MFS can be an acceptable endpoint for approval:

- Large magnitude of treatment effect on MFS with an acceptable safety profile should be used to demonstrate clinical benefit and support product approval
- The sponsor should conduct a formal interim analysis of OS (at the time of final MFS analysis) - to support a favourable benefit-risk assessment, this analysis should demonstrate a favourable trend and provide assurance that OS is not adversely affected by the treatment. In addition, FDA expects continued follow-up for final OS.
- The acceptable magnitude of improvement in MFS required to support drug approval will depend primarily on the trial design (e.g., add-on design, active control versus placebo control), toxicity profile, enrolled population, and overall benefit-risk evaluation
- The sponsor should establish the definition of MFS before initiation of the trial, need to clearly describe methodology for assessing, measuring, and analysing MFS (local progression events should be excluded).

While not specific for nmCRPC the EMA Anticancer Guideline discusses similar topics relevant to such studies (Appendix 4[10]).

[8] https://clinicaltrials.gov/ct2/show/NCT00286091

[9] FDA Draft Guidance for Industry: "Nonmetastatic, Castration- Resistant Prostate Cancer: Considerations for Metastasis-Free Survival Endpoint in Clinical Trials", https://www.fda.gov/media/117792/download

[10] www.ema.europa.eu/en/documents/scientific-guideline/appendix-4-guideline-evaluation-anticancer-medicinal-products-man-condition-specific-guidance_en.pdf

Summary

Factors that supported development of the new regulatory endpoint

- **Unmet medical need**: ongoing discussions among oncology experts / academia / regulators / industry sponsors to address development of new therapies for patients in the pre-metastatic stage
- **Condition:** Long natural history of disease, transition from nmCRPC to detectable metastatic disease was recognized as a clinically relevant event (ODAC 2011) that can be associated with morbidity and the need for additional medical interventions
- **Choice of endpoint**: OS was considered not feasible in this setting (long survival periods, multiple subsequent therapies could confound OS results), need for a clinically meaningful endpoint especially in view of asymptomatic patients, time to metastases alone was considered less relevant as primary endpoint since MFS would also cover a survival benefit and take into account toxicities
- **Measurable**: Prolonged delay of metastatic disease is an objective and clinically relevant measure
- **Benefit-Risk:** A substantial effect of MFS is expected**,** absence of detrimental toxicity, and positive trend for OS

Future considerations

- Heterogeneity of disease, novel imaging methods (PSMA-PET) might change definition of disease and assessment of MFS
- Due to long term use of approved drugs based on MFS, need to better understand impact on overall long-term safety and QoL

Considerations for tumour types

- Need to understand target patient population and natural history of disease, knowledge will evolve over time based on emerging biomarker (e.g., CTC, ctDNA) or new diagnostic tools
- When looking at opportunities to move into earlier lines of disease or even disease interception this would result in trials with very extended times, so novel endpoints will be important
- Alternate endpoints can bring higher uncertainty, and require best available evidence (biological plausibility), relevant magnitude of effect, understanding of association with OS or impact on QoL
- Important to integrate the patients' perspective and outcome measures in trial design especially when moving into earlier line or a largely asymptomatic disease stage
- Overall, developing and validating a novel endpoint this will be a collaborative and multi-stakeholder effort in the anticancer drug development community

Pathway towards solution: Alternate Endpoints – Case Study Avelumab in Merkel Cell Carcinoma

Dr. Elmar Schmitt
Executive Director, Global Regulatory Oncology, Merck Healthcare KGaA, Germany

This case study describes the avelumab approval in the indication metastatic Merkel Cell Carcinoma (MCC) in 2017.

Key points of the presentation

Merkel Cell Carcinoma (MCC) is an aggressive skin cancer associated with poor survival outcomes and sparse treatment options.[11] The incidence of MCC is estimated[12] to be

- 0.3 per 100,000 in Sweden in 2012,
- 0.6 per 100,000 in US in 2009, and
- 1.6 per 100,000 in Australia, 2006–2010.

Treatment options at the start of development of avelumab were limited to surgery, radiation, adjuvant chemotherapy in stage I-III and to cytotoxic chemotherapy in stage IV with no standard treatment in second line.

The submission strategy containing of the single-arm trial design for the pivotal and the confirmatory study using the alternative endpoints overall response rate (ORR) and duration of response (DoR) in a pivotal and a confirmatory study (Figure 1 and 2).

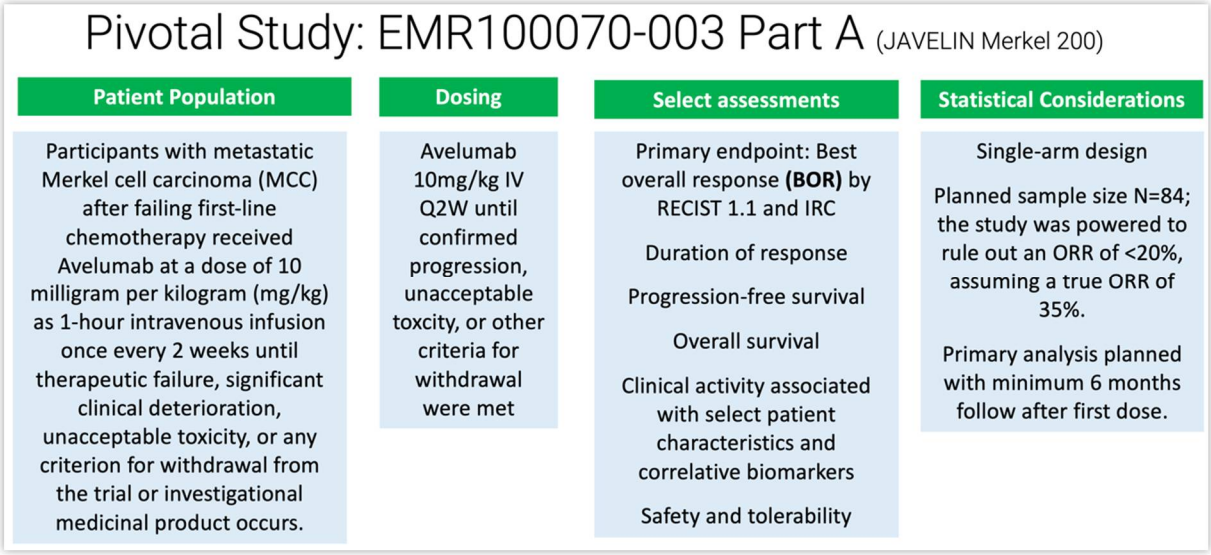

Figure 1: Details of the pivotal study for avelumab in MCC[13]

The **regulatory pathway** was guided by several FDA and EMA/CHMP agency interactions with starting early prior the pivotal trial initiation. Initial agency feedback focused on the preference of a randomized controlled trial and that ORR alone would not be sufficient to support approval. Further discussions led to an agreement that a single-arm trial with ORR as endpoint, at least 6 months follow-up and a sufficient clinical benefit demonstrated by improvements of PFS and OS could be acceptable. With this feedback the pivotal study (Figure 1) and a comparative quality-controlled retrospective observational study[14] with two cohorts (US, EU) were started. The results from these studies led to FDA Accelerated Approval and EMA Conditional Marketing Authorisation in 2017.

The required **confirmatory trial** was discussed with both agencies in 2015 and 2016. The initially agreed plan of a randomized controlled trial was not feasible anymore due to

[11] Harms KL et al. Ann. Surg Oncol 2016; 23: 3564-3571
[12] Becker JC et al. Nature Rev 2017; 3: 1-17
[13] https://clinicaltrials.gov/ct2/show/results/NCT02155647

[14] Cowey CL, et al. Future Oncol. 2017; 13: 1699-1710.

significant changes[15] in the treatment options. The change to a single-arm trial design was accepted as the only option for a confirmatory study with duration of response as the primary endpoint (Figure 2).

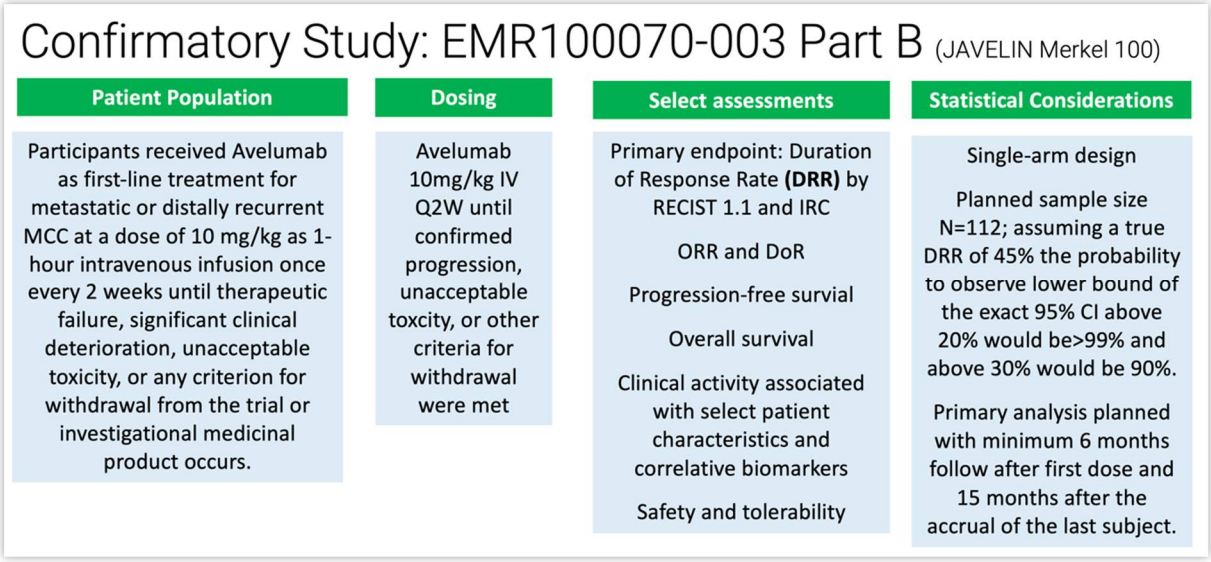

Figure 2: Details of the confirmatory study of avelumab in MCC.[16]

Importantly, the totality of data, such as overall survival, duration of response, and long-term PFS data showing the 'tail' of the curve were key aspects to demonstrate the clinical benefit as the results of the primary endpoints ORR and DoR alone would not have been sufficient.

The EMA described the rationale for approval in the EPAR: "*Although ORR is not very impressive, the duration of response is considered clinically relevant advantage over chemotherapy. The duration of response with avelumab therapy in 2L+ is favourable when placed in context with chemotherapy.*"[17] A similar assessment was published by the FDA: "*Durable objective response rate of sufficient magnitude is a surrogate endpoint that is reasonably likely to predict clinical benefit (i.e., improved survival) in patients with metastatic MCC. … The durability of responses provides an advance over that observed with off-label use of chemotherapy which produces nondurable response rates (reported and observed median durations of response less than 3 months).*"

Summary

The alternative endpoints best overall response and duration of response were acceptable in this rare disease metastatic MCC, because the single-arm design was the only feasible ethical study set-up to keep the equipoise for patients.

[15] At that time, the situation in the US had changed dramatically due to MCC data released for pembrolizumab at ESMO late 2015. By March 2016, there was widespread uptake of pembrolizumab in 1L mMCC in the US with academic advisors now refusing the chemotherapy controlled study. See Nghiem P, et al. ESMO 2015; abstract: 22LBA and Nghiem P, et al. N Engl J Med. 2016; 374: 2542–2552.

[16] https://clinicaltrials.gov/ct2/show/results/NCT02155647

[17] *https://www.ema.europa.eu/en/documents/product-information/bavencio-epar-product-information_en.pdf

- Based on evolving knowledge in the clinical evidence of this rare disease from various immune-checkpoint inhibitor study results, a RCT with standard time-to-event endpoints was agreed with agencies not anymore seen feasible.
- Continuous interaction with the agencies to present and agree on the study design was crucial to find most pragmatic way.
- With company initiated historical control data and available literature, the single-arm design and alternative endpoints, ORR and DoR, could be placed in clinical context, to generate an adequate benefit/risk balance.
- Finally, both agencies accepted the data for a 'conditional' and 'accelerated' approval. In the EU the conditional could be converted into a full approval in 2020.
- Importantly, the totality of the data (including overall survival data, duration of response, and long-term PFS data showing the "tail" of the curve) were key aspects to demonstrate the clinical benefit as the results of the primary endpoints ORR and DoR would have been alone not sufficient.

Non-survival Endpoints: an EU Regulatory Perspective

Filip Josephson, M.D., Ph.D.
Alternate Member, Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency (EMA); Clinical Assessor, Läkemedelsverket (Medical Products Agency, MPA), Sweden

This presentation summarizes the EMA regulatory guidance on non-survival endpoints.[18]

Key points of the presentation

EU regulatory guidance[19] on anticancer drug development states that "*confirmatory trials should demonstrate that the investigational product provides clinical benefit*." Non-survival endpoints considered to capture this include **Progression Free Survival (PFS),** Event Free Survival (EFS), and Disease Free Survival (DFS). "*An effect on prolonging PFS of sufficient magnitude … is in itself a clinically relevant effect because documented progression of the disease is generally assumed to be associated with subsequent onset or worsening of symptoms, worsening of quality of life, and the need for subsequent treatments generally associated with lower efficacy and worse toxicity*.".

PFS is the most common registrational endpoint for anticancer therapies. Importantly, in scientific advice for sponsors, EU regulators generally encourage the use of OS, rather than PFS, as primary endpoint in situations where post progression survival is short. The shorter post-progression survival, the more correlated PFS and OS are anticipated to be. HTA's have frequently questioned whether a PFS gain is itself a clinically relevant effect. Notwithstanding this, PFS will remain an important endpoint to capture clinical benefit in randomized controlled cancer trials.

No demonstration of a correlation of PFS and OS, or of PFS and documented symptomatic benefit, is required in the specific case. There is no assumption of the surrogacy of PFS for OS. If PFS is the efficacy endpoint, OS is considered a safety endpoint and no signs of a detrimental effect on OS should be present.

[18] The views expressed are those of the author and may or may not coincide with EMA, CHMP or MPA policy.
[19] Guideline on the clinical evaluation of anticancer medicinal products (EMA/CHMP/205/95 Rev.6; "CHMP Anticancer Guideline"). All quotations from the guidance are in italics.

Similarly, **PFS2** is considered a safety endpoint. "*In order to capture possible negative effects on next-line therapy and to outbalance tolerability and toxicity concerns related to therapy, it is expected that time from randomisation to PFS2 in the experimental arm show no detrimental effect compared to the control arm*". The measurement of PFS2 is generally not necessary, and is most often not captured directly. Determination requires continued systematic monitoring for progression in trials, following a PFS event, which otherwise concludes systematic monitoring for progressive disease.

Overall Response Rate (ORR) is used as registrational endpoint in late line settings, or rare cancers, since, as opposed to time-dependent endpoints, it isolates drug effects in single arm trials. "*Resorting to non-randomized trials should be duly justified – for instance (…) a large treatment effect on endpoints such as ORR and DoR, likely to translate in true clinical benefit*". As opposed to a gain in PFS, objective responses are not themselves considered clinical benefit and it remains controversial among EU regulators how this measure captures benefit. However, "*ORR, despite all its shortcomings related to patient-selection, etc., is a rather convincing measure of anti-tumour activity as for most tumours, spontaneous regression fulfilling criteria for at least partial response is a rare phenomenon.*".

Patient-reported outcomes (PROs): "*Selected PROs, such as symptom control, could also constitute clinically relevant and valid primary endpoints, provided high data quality is ensured*". However, in applications, there are frequently no satisfactory considerations on how to handle intercurrent events in the analysis (e.g., death, change of therapy). Further there is often considerable amounts of missing data. It remains unclear if we can rely on PROs in open-label studies. Furthermore, equivalence claims based on PRO's are controversial given uncertainties about assay sensitivity to show differences.

Beyond ORR: There are EU regulatory guidelines on Pathological Complete Response (pCR) as well as on Minimal[20] Residual Disease (MRD) in several haematological conditions. Such endpoints are not considered clinical benefit per se. Therefore, trial-level surrogacy for PFS/DFS or OS ought to be established.

Patient level surrogacy does not isolate the causal effect of the drug on the time dependent endpoint, through its effect on the surrogate marker. Rather, it compares outcomes in patients with good and with poor prognosis. To establish a trial-level surrogate, one needs to show that the between-arm differences in the surrogate endpoint accurately capture or predict the between-arm differences in the relevant, time-dependent endpoint.[21]

Summary

The anticancer drug development- as well as treatment paradigm, is based on the notion of impacting tumor growth. Thus, clinical benefit is anticipated to be mediated through drug effects on tumor kinetics. Drug impact on tumour burden is, in many settings, a parameter that can be reproducibly quantified. Consequently, it is reasonable to base conclusions on clinical benefit on a measure of drug impact of tumour growth, when data on the impact of treatment on OS are absent or inconclusive.

The magnitude of drug impact on tumour growth that is considered to represent clinical benefit, may be a matter of communal agreement based on clinical practice and summary understanding, rather than on conclusive scientific inference.

[20] Also named Measurable Residual Disease

[21] See e.g. Cortazar P et al., Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014; 384: 164-72.

Day 2: Endpoints in expedited regulatory approval pathways

Patients‘ perspective

Hans Scheurer
President, Myeloma Patients Europe

This presentation discusses different objectives and modes of the involvement of patients in the drug development process and the patient perspective on intermediate endpoints, like MRD, in expedited approval pathways. Importantly, the last step of drug development, ensuring access for patients, should be kept in mind and included in the acceleration.

Key points of the presentation

Patients' involvement: Looking at practices of integrating the patient voice in the field, we need to make a distinction:

1. An **individual patient** is asked to give input, from his or her own experience. The input is of a single patient is what we call anecdotal input, experiences and insights of an individual. The value of this is that seeing a patient that 'lives' the treatment and the disease puts the audience in the mud of the daily living of a cancer patient. It can make a strong impression, more than any table with data can provide. The weak part is that it is anecdotal information, so as 'evidence' it is not very useful.
2. The second practice of involving the patients aims at a more **representative and scientific process**: The company or research group asks the patient organisation to be partner in the drug development process. It is the task of the patient organisation to give input based on the preferences and experiences of a whole group of patients, and this input can be used as evidence when collected in a professional way, with a scientific accepted approach. This is what we call evidence-based patient advocacy, and this is the field that is young but developing fast towards professionalisation and will be of increasing importance in the field.

Accelerated pathways: Another focus of the patient group – because it oversees the whole group of patients – is that new drugs and innovations that are really valuable, needs to reach patients and not only the congresses and scientific journals.

The topic of this session in this regard, is about accelerating this, by looking at endpoints of clinical trials. Is it possible to use earlier flags for approval of new treatments? For myeloma we discuss the use of MRD (minimal/measurable residual disease): An early point of enthusiasm or even an endpoint that we can use for market authorisation?

The **EMA** has three pathways of expedited approval: Accelerated assessment, Conditional marketing authorisation and PRIME, which stands for priority medicines scheme. The **FDA** has four pathways: Fast track, Accelerated approval, Priority review and Breakthrough therapy. The overall aims to accelerate the procedure can be achieved by alignment in an earlier stage and during the development of the product, by shortening the review process by a few months or by accepting surrogate/intermediate endpoints that could predict the value of the drug earlier.

How do we look to these options to accelerate from a **patient group perspective**?

The **opportunities** seem clear: Faster access to novel treatments is what we want, especially as patient groups with multiple myeloma, where the continuation of life depends on having new therapeutic options when refractory to former used treatments. The other opportunity is

for diseases that are rare, where the patient group is that small that collecting data to get to robust outcomes that can be presented to regulators is a long process. Or where the group has such a short life expectancy that recruiting for research is difficult.

The regulators have specific pathways for this kind of approvals, the COMP committee at the EMA prepares approvals specific for rare diseases. The patent period can be longer so there is a longer period for Return on Investment for the company. These are all welcome pathways that give hope for patients, and sometimes really lifesaving options.

Expedited regulatory pathways is not the same as faster access for patients:

Looking at the **challenges:** Approval of drugs on the level of the FDA and the EMA often is picked up by the media and provides hope for patients. But they often do not realise that approval is not access. Looking within the European region, which is my field, there is a gap between the approval of the EMA, and the consideration of the national HTA bodies. The EMA looks mainly into the efficacy of the new drug itself, the HTA bodies look also to the context where the drug adds its value in the treatment pathway. Mostly they only look at the comparators, but there is a tendency to also look at the impact of a new drug on the whole treatment pathway. All because the clinical value as to be balanced with the economical limitations, the budget of the society. The gap is even bigger when the drug followed an expedited approval pathway, where evaluation against comparators was not required.

What both bodies, the EMA and FDA, and the national HTA bodies, have in common is that they want to define the value of the drug. From a patient group perspective, we are – like a lot of our stakeholders in the field – inspired by the concept of Michael Porter, the "Value Based Healthcare" idea – but we added *Access* to it and call our concept *Value Based Access*: the higher the value, the more patients need to get access to it. **When a drug proved value for patients, it needs to reach patients.**

Expedited approval pathways lead to faster recommendation, but that does not guarantee faster access. In that sense it would be good to not only look at earlier endpoints but also evaluate the whole pathway to access for patients. That is in the end that patient experience as improvement, not the impressive scientific publications of new approaches.

Early endpoints: Looking at early endpoints – I mentioned that in my disease area the use of MRD as an early predictor of efficacy of a new drug is intensively discussed. If it could be used as an early endpoint it would accelerate the approval process.

From the patient group perspective: MRD is in fact fine-tuning the stage of complete remission, and that is a good thing, while we know that reaching complete remission in myeloma does not mean that the disease is gone, there is a rest of the disease that will relapse at some time. With the MRD techniques you can detect the depth of response with much more precision. The idea is that the deeper the response is, the longer the patient will be in remission. So, measuring MRD can be seen as an early endpoint that predicts efficacy of the drug.

So far, MRD measuring is mostly bound to clinical trials and rarely used in the routine-care clinical setting. Currently, MRD measuring is only reliable with a bone marrow puncture, and that is not popular among patients. From our perspective as patients, it is a mayor improvement to see that also the MRD measuring can be done with a blood sample in the nearby future. The developments in that direction are very welcome because it is not only about collecting data, it is about patients, and they also experience the way data is collected. All efforts that are needed to make this common practice should be supported.

Another aspect, or more a worry we have from the perspective of the group of patients, is that when MRD is accepted as an endpoint for accelerate approval pathways, that treatment designers and companies will anticipate on that route and tend to create treatments that show

more MRD negative outcomes in an early stage of the trial, which could result in much more intensive treatment and combination therapy with more adverse reactions. It must be considered – from our perspective as patient group – what the longer-term effects are of more intensive treatments in earlier lines. If, for example, this leads to a larger proportion of patients suffering from polyneuropathy, it has a negative effect on the quality of life in the end.

Summary

- For patient involvement, you need to look for what is needed: If you want your employees hear the experience of living with the disease and the treatments, then a patient story is a good method. But when you want to understand in a broader sense what the patients as a group experience, what the value and the impact is on the life of the patients, a single patient is not the right source, you should contact a patient advocacy group to get a more complete picture.
- The use of earlier endpoints to predict efficacy of a drug is an opportunity to get earlier approval, but that is not the same as getting earlier access. This last aspect matters for patients.
- The use of MRD as an early endpoint should be seen in the context of the impact the novel drug in a specific combination therapy has on the whole treatment pathway and the health condition of the patients on the long run.

Regulatory perspective

Vishal Bhatnagar, M.D.
Associate Director for Patient Outcomes, Oncology Center of Excellence (OCE), FDA

This presentation summarizes a FDA regulatory perspective on non-survival endpoints.

Key points of the presentation

In the United States, drugs are approved based on adequate and well-controlled clinical trials demonstrating substantial evidence of clinical benefit based on prolongation of life, a better life, or an established surrogate for either of the two.

Accelerated Approval (AA) was created in 1992, allowing for an alternative pathway to expedite delivery of promising drug products for serious or life-threatening illnesses. It requires a meaningful therapeutic benefit to patients over existing treatments. Approval is based on an effect on a surrogate endpoint reasonably likely to predict clinical benefit or on a clinical endpoint other than mortality or irreversible morbidity . AA also requires meaningful therapeutic benefit to patients over existing treatments, and confirmatory postmarking trials may be required to verify anticipated clinical benefit.

Overall Survival (OS) is a direct measure of benefit and less prone to bias than other endpoints. No interpretation of the event is needed, and the event timing (date of death) typically known to the day. It includes information regarding safety, as deaths due to drug toxicity are part of the endpoint. However, as death is the last event in a disease's natural history, measuring it requires longer and larger trials that have to be randomized and controlled. Comparisons with historical control are of limited value due to differing populations, differing standards of care, etc. Also, overall survival may be confounded by cross-over (depending on magnitude of effect) and subsequent therapies if given unequally between arms. Still, meaningful clinical benefit of a survival advantage is still based on toxicity of drug and magnitude of OS result.

Earlier endpoints can be used for either regular or accelerated approval, depending on the magnitude of effect, safety, and the disease context. They may be necessary in the current context of drug development, e.g. small molecularly defined subgroups. In oncology, most accelerated approvals are based on trials with objective response rate (ORR) as the primary endpoint.

AA has largely been used to expedite the availability of oncologic therapeutics, as 82 of 98 of FDA's accelerated approvals between 2010 and 2019 were for oncology indications[22].

An example of how AA has led to earlier access to effective therapeutics is in **multiple myeloma**. Since 2003, eight out of 13 approved therapies for relapsed refractory multiple myeloma (MM) were initially approved using accelerated approval (seven using ORR). Overall survival for patients with MM has improved dramatically over the same time span, largely driven by therapeutic advancements (combination therapies with novel agents). For example, the four-year survival for newly diagnosed MM patients at Mayo clinic[23] increased from 50% for those diagnosed 2004-2007 to 75% for those diagnosed 2013-2017.

Accelerated Approval – Key Conditions

- Serious and life-threatening disease
- Substantial evidence of Efficacy and Safety
- Endpoint reasonable likely to predict clinical benefit
- Meaningful therapeutic benefit over available therapy
- May require confirmation of benefit

Reconsideration of AA: This may be reconsidered in settings where confirmatory trial has not verified benefit, or clinical benefit has not been confirmed in other settings, or treatment landscape has evolved over time. In the words of Dr. Richard Pazdur: **"***The program allows the FDA to approve a drug or biologic product intended to treat a serious or life-threatening condition based on an outcome that can be measured earlier than survival that demonstrates a meaningful advantage over available therapies. However, when confirmatory trials do not confirm clinical benefit, a reevaluation must be performed to determine if the approval should be withdrawn***."**[24]

In addition to the AA pathway, other ways of expediting drug development are

- **Breakthrough Therapy Designation (BTD)** which enables more frequent meetings, eligibility for priority review, rolling review, and intensive guidance on an efficient drug development program. Each year, over 40% of all BTDs are in oncology.
- **Priority Review (PR)** which reduces the timeline for supplemental drug applications to six months and the timeline for NME marketing applications to eight months.
- **OCE Real Time Oncology Review (RTOR) pilot**: For 20 RTOR applications submitted between 2018-2020, median time from application submission to approval was 3.3 months (range of 0.4–5.9 months).[25]

[22] Singh H, Pazdur R. Contribution of Early Clinical Benefit End Points to Decreased Lung Cancer Mortality Rates. JAMA Oncol. 2021; 7: 829-830.

[23] Nandakumar B et al., Continued improvement in survival in multiple myeloma (MM) including high-risk patients (ASCO 2019). Journal of Clinical Oncology 2019 37:15 (suppl): 8039-

[24] https://www.fda.gov/news-events/fda-brief/fda-brief-fda-oncologic-drugs-advisory-committee-review-status-six-indications-granted-accelerated. March 11, 2021.

[25] de Claro RA, Gao JJ, Kim T, Kluetz PG, Theoret MR, Beaver JA, Pazdur R. U.S. Food and Drug Administration: Initial Experience with the Real-Time Oncology Review Program. Clin Cancer Res. 2021; 27: 11-14.

Summary

Smaller trials with molecularly defined populations and use of early clinical endpoints such as overall response rate are a reality of oncology drug development. However, where clinical benefit is not confirmed, AAs may be re-evaluated. FDA is committed to streamlining drug development, which also includes use of other expedited programs such as breakthrough therapy designation, priority review, and other Oncology Center of Excellence pilot programs.

An HTA perspective

Professor Carole Longson
Independent Senior Adviser, Life Science Policy, HTA and Market Access
Life Science Adviser, National Institute for Health and Care Excellence

This presentation summarizes the Health Technology Assessment (HTA) perspective on expedited regulatory approval pathway and on options how to bridge the evidence gap between the data available at accelerated approval and what is needed for the HTA assessment.

Key points of the presentation

HTA seeks to establish the relative/comparative effectiveness of technologies:

- **Efficacy**: Incremental benefit of using a technology for a specific indication in ideal conditions of use, for example, in a strict protocol of a randomized controlled trial.
- **(Comparative) Effectiveness**: Comparative Incremental benefit of using a technology for a specific indication in general or routine conditions of use.

HTA in expedited approval processes leads to several challenges (Figure 1):

- **Problems with clinical trial design**: HTA assessors see many such trials not designed to inform clinical practice, e.g., adaptive designs difficult to interpret. Surrogate endpoints have unclear relationship with OS and HRQoL.
- **Fewer comparative randomised clinical trials**: Increasing number of single arm trials is submitted. Often, historical comparisons are not considered robust.
- **Increasing frequency of conditional/accelerate approvals**: Survival outcome measurement in such trials is usually not complete and ongoing data collection not 'tuned' to HTA requirements which leads to increased uncertainty.

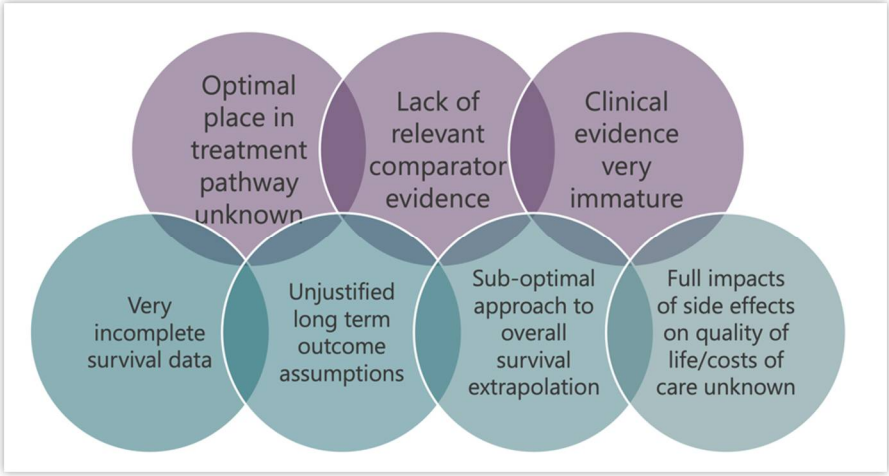

Figure 1: General issues in generation of clinical evidence for HTA

In the discussion of an example (HTA of avelumab in Merkel cell carcinoma, a rare aggressive cancer) the respective uncertainties were noted:

- **Lack of a head-to-head comparison** with a small single-arm trial. Comparisons using observational data were seen as not robust. No adjustment for prognostic factors were made and indirect comparisons were seen as highly uncertain.
- **Immaturity of data:** Small groups of patients (N=29) with short (3-6 mon) follow-up.
- **Extrapolations:** Extrapolations of OS and PFS not seen as sufficiently reliable as not based on direct available evidence and sensitive to the methodology used. Therefore, the estimates for PFS and OS were seen as highly uncertain.

How can this **evidence gap be bridged**? How can the uncertainty in overall survival, that leads to uncertainty in clinical and cost-effectiveness estimates, be overcome?

Key issues should be considered and discussed as early as possible.

- **Optimisation of pivotal clinical trial design for HTA** and identification of **robust observational data** to compare it with established practice.
- Understanding the **relationship between surrogate outcomes and mortality/health-related quality of life**.
- **Justifying proposed extrapolation modelling approaches** - based on plausibility and using data available to date - to deal with uncertainty.
- Developing **evidence generation plans** that result increase relevance of post-marketing authorisation studies including clinical effectiveness.

The NICE Decision Support Unit Technical Support Documents can provide helpful guidance.[26] In addition to quantitative processes to bridge the gap qualitative options (including dialogue, debate, interaction, and consultation) can be very helpful.

With the Cancer Drug Fund (CDF) the NHS England has created a mechanism to fund drugs that have a potential to satisfy the criteria for routine commissioning, but the remaining clinical uncertainty requires more investigation.

[26] http://nicedsu.org.uk

Summary

- HTA bodies are most interested in 'final' end points
    - It is crucial to demonstrate a predictive relationship between the 'surrogate' and 'final' end point and to anticipate what data is required to bridge from expedited regulatory processes into HTA
- Early dialogue with HTA bodies essential
    - NICE Scientific Advice and Office for Market Access as well as EUnetHTA
- Need to plan to reduce uncertainty and decision risk
    - Plans for post launch evidence generation must take account of HTA requirements
    - Pricing strategies important

Patients' perspective

Jayne Galinsky
Head of Patient Evidence, Myeloma Patients Europe

This talk focused on findings from discussing patient-reported outcome measurement and data with patients.

Key points of the presentation

Patient-reported outcome data (PRO) is data collected directly from a patient without interpretation by clinicians or others. PROs are designed to measure the signs and symptoms of disease, functioning (activity limitations), health status/health-related quality of life (HRQOL), and treatment satisfaction from a patient perspective.

For patients and families PROs can be an opportunity to have their experience of illness taken seriously and acknowledge the impact of disease on day-to-day life. Because patients value being asked about their experiences of illness and impacts of treatment - the use of inappropriate instruments and the lack of explanation for the choice of PRO measures in clinical trials / clinical practice is a concern. Poorly designed PROs mean that some patients fail to answer questionnaires they consider irrelevant.

Myeloma patient perspectives on PRO (quotes):

- *"What does a score of 20 on a questionnaire really mean, how does this translate into clinical action and what supportive care interventions can be offered to help? Equally, if a change of 5 points after these interventions is seen on the questionnaire, does this mean that I have improved?"*
- *"I completed this questionnaire at the minute and it has a seven point Likert scale on how true something is. So, it's like very seldom true, seldom true, sometimes true and it's just so complicated. It takes 10 minutes just to get your head round what's being asked in the Likert scale, never mind applying that to experience"*

Patients suggest that

- PROs that measure the impact of disease rather than a description of side effects for example, are preferred.

- Patients want to know what will happen to their PRO data after collection.
- What do PRO scores mean in reality?

Patient organisations suggest that culturally adapted PRO instruments, certificates of translation, data collection devices, and training manuals in local languages need to be in place at the start of a study. Patient organisations also understand the logistical complexities related to collecting PRO data during multiregional studies and are happy to help in supporting this.

Day 3: PRO Endpoints – Review of Strategies

Regulatory perspective

Vishal Bhatnagar, M.D.
Associate Director for Patient Outcomes, Oncology Center of Excellence (OCE), FDA

This presentation summarizes recent FDA developments regarding patient-reported outcomes (PRO). It will identify pitfalls with commonly used PRO analyses, describe the FDA reviewer perspective, and highlight the OCE's core outcome set and optimal assessment frequency. Also, novel communication tools to share useful PRO data with patients and providers will be discussed.

Key points of the presentation

Three **key challenges** are important for the assessment of PROs:

- PRO data are frequently submitted. However, heterogeneity exists in analysis and presentation of data.
- 21st Century Cures Act encourages FDA to review and communicate patient experience data submitted in product reviews
- Product label (USPI) offers limited space to communicate patient experience data adequately

Many studies claim "no statistically significant difference" in general quality-of-life measurements with wide confidence-intervals which sometimes have given raise to pseudo-non-inferiority claims. However, quality-of-life measures do not fully reflect tolerability of a drug intervention. It remains to be considered that 'absence of evidence (of an effect) is not evidence of absence'.

For a typical **FDA review of PRO,** the following questions are relevant:

- Which instruments are being used? Concepts proximal to disease?
- Are PRO descriptive (e.g. tolerability) or claims of treatment benefit?
- What confounders could limit interpretability of results?
- How much data is missing?
- Is the assessment timing reasonable given the drug(s) being tested?
- Can conclusion be made based on the strength of results?
- What are the implications for patients, caregivers and practitioners?
- What is the best way to share PRO data (results) with the public?

The FDA has defined a **core outcome set** that should be measured in every trial (Figure 1). This set is not exhaustive and should be complemented with additional relevant questions arising from the disease and treatment context (e.g. swallowing function, xerostoma in head and neck cancer). The **measurement frequency** for these variables is another very important aspect and it is recommended to be more frequent at the onset of the therapy when changes are most likely.

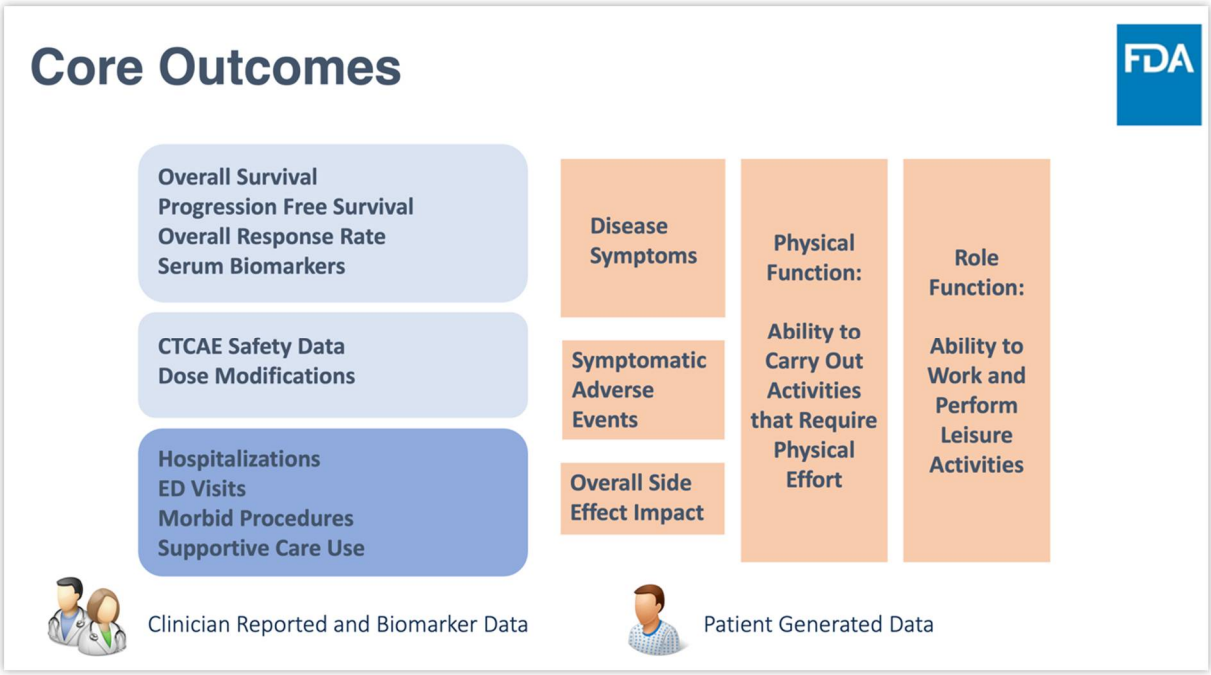

Figure 1: FDA Core Outcome Set

The **communication of patient experience data** is very important. Therefore, the FDA has initiated the "Project Patient Voice" [27]. It should be seen as complimentary source for tolerability information.

Summary

- Measurement of patient-reported disease symptoms every three months is not enough. More frequent assessment, esp. at the onset of a new therapy, is key.
- PRO objectives, research questions and endpoints should be prospectively defined in close dialogue with the FDA prior to the start of the trial.
- Focus of PRO on key areas that are directly related to the disease/treatment studied.
- PRO data should be collected and analyzed in a way that is meaningful and interpretable for patients and providers.
- Consider alternative methods to collect patient experience in addition to traditional PRO: wearables, sensors, etc.

[27] https://www.fda.gov/about-fda/oncology-center-excellence/project-patient-voice

Industry perspective on Patient-Reported-Outcomes (PRO) endpoint design and implementation in cancer drug development in the PFDD era

Paul Kamudoni, MSc., Ph.D.
Scientific Director – Patient Centered Research, Merck Healthcare KGaA

This presentation gives an industry perspective on development and implementation of PROs in cancer drug development.

Key points of the presentation

The integration of patient experience into clinical development is essential and requires considerable time and resources. Several stakeholders, esp. regulatory agencies, health technology agencies (HTA) and clinicians, have an interest in PRO data, with divergent viewpoints and intentions (see Figure 1). Progress has been made with increasing standardisation for PROs in anti-cancer drug development and in other health conditions (see FDA Oncology Core Outcomes or Patient-Focused-Drug-Development (PFDD) guidance).

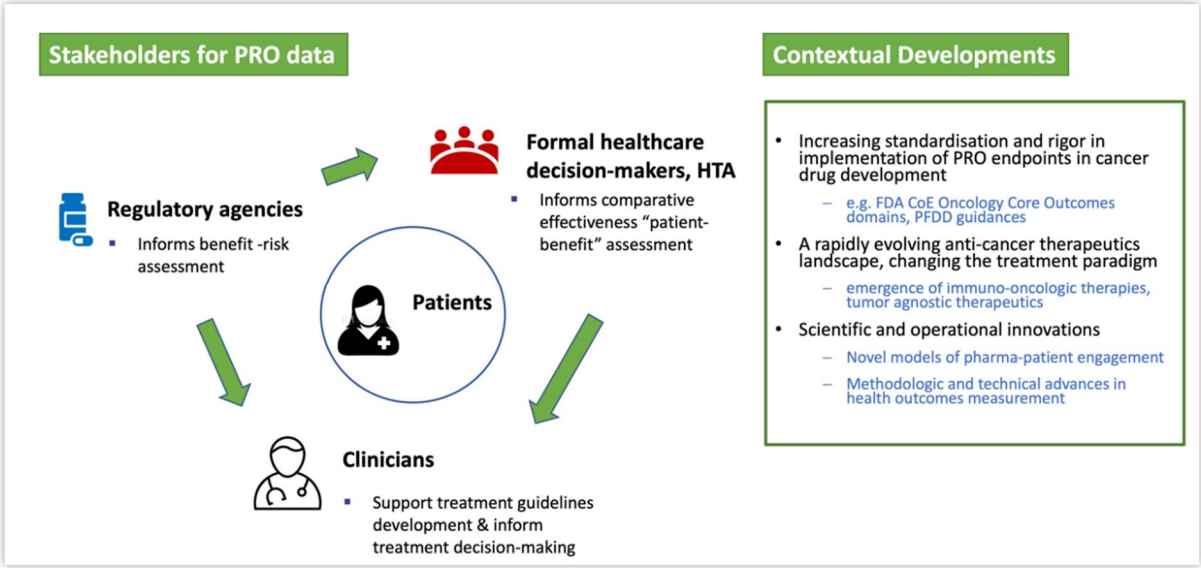

Figure 1: Stakeholder map for PROs

Figure 2 shows a schematic of the design and implementation of PRO endpoints from the perspective of a pharmaceutical company. Careful planning, strong commitment and an early start are necessary to ensure the successful development of PROs in parallel with other aspects of the clinical development. Strong alignment across multiple layers of the organization on the value of PRO endpoints for asset and the necessary resource commitments are required, incl. the support of the senior management and internal governance bodies. The resulting complexity is a challenge and an opportunity for the pharmaceutical industry.

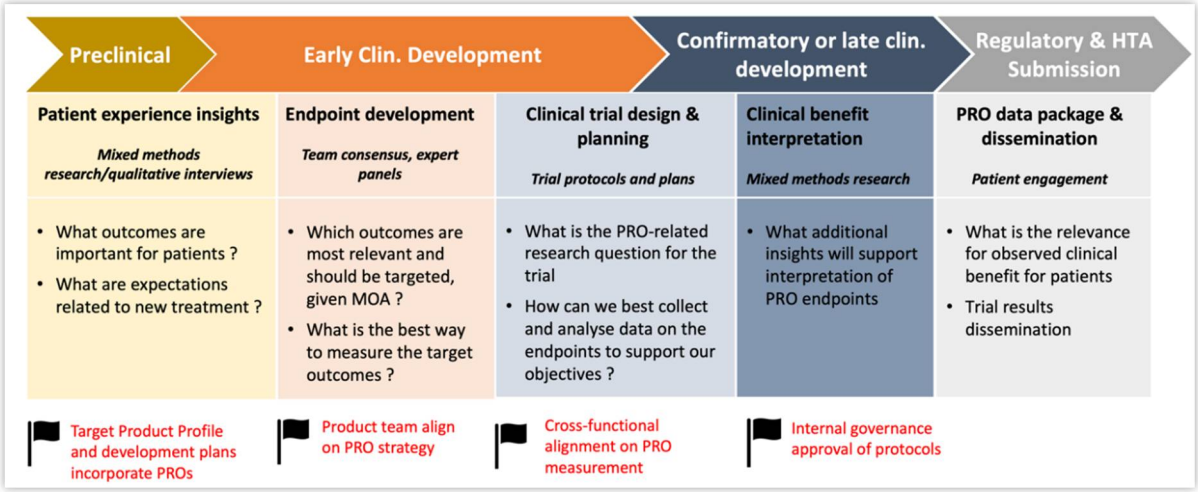

Figure 2: PRO Roadmap for pharmaceutical industry

The presentation discusses **two examples** that demonstrate the challenges of PRO endpoint development when no established instrument is available. In one example, in a **Merkel Cell Carcinoma** (MCC) development program, an instrument from Melanoma, an analogous condition to MCC, the FACT-Melanoma was validated using data from the clinical trial, including *in trial* patient interviews. The interview data were used to build a disease conceptual model and were included in the submission to the regulatory agencies, alongside the PRO data. Specifically challenging was MCC's small population size made outside trial research challenging, careful planning and substantial effort required for within trial validation of FACT-Melanoma.

The other example highlights the development of a new PRO in **hepatocellular carcinoma** that allowed the assessment of core disease symptoms and tolerability in a development across pharmaceutical companies. The project started in the pre-clinical phase and data was collected throughout the complete development process (phase I-III). Key challenges were that long lead time added to development risks and that substantive effort and resources investment were required already upfront.

Both examples emphasize the need for an early start of planning and data collection.

Summary

Challenges and opportunities

- **Transferability of evidence and generalizability of validity across settings:** Various constraints particularly in the Oncology context necessitate appropriating evidence from other disease stages or analogous cancers to support endpoints e.g., lack of natural history data, small populations
- **Special consideration for mechanism of action:** Treatment goals may differ based on the assets MOA. Emergence of tumor agnostic therapies requires special considerations.
- **Practical issues in collecting supportive evidence for PRO endpoints**: *de novo* PROs associated with long lead time and substantial upfront investments – often perceived as risky during early development.

Health Technology Assessment (HTA) Perspective on Patient-Reported-Outcomes (PRO)

Dr. Leeza Osipenko
Senior Lecturer in Practice, Department of Health Policy, The London School of Economics and Political Science;
CEO, Consilium Scientific, London, UK

This presentation gives an HTA perspective on development and implementation of PROs in cancer drug development.

Key points of the presentation

The field of endpoints is highly complex and the questions "What outcomes are relevant to patients?" and "Who actually determines this relevance?" are key to successful cancer drug development. Generally, the key endpoints relevant for Health Technology Assessment (HTA) are those that concern duration of life (survival, such as overall survival, progression-free survival, and disease-free survival) and health-related quality of life (HRQoL; patient reported outcomes such as level of pain, level of mobility, ability to self-care, anxiety-depression, daily activities). It is crucial that these data are collected in clinical trials of the investigational agents.

Currently, the collection of HRQoL data in registered clinical trials remains low (albeit it has been increasing over the last decade). In an overview of trials performed with patients with multiple myeloma, 3,179 completed or ongoing registered clinical trials were identified, of which only 12% (n=382) collected PRO data. Of these, the majority was in phase II (33%) and III (32%) (Figure 1).

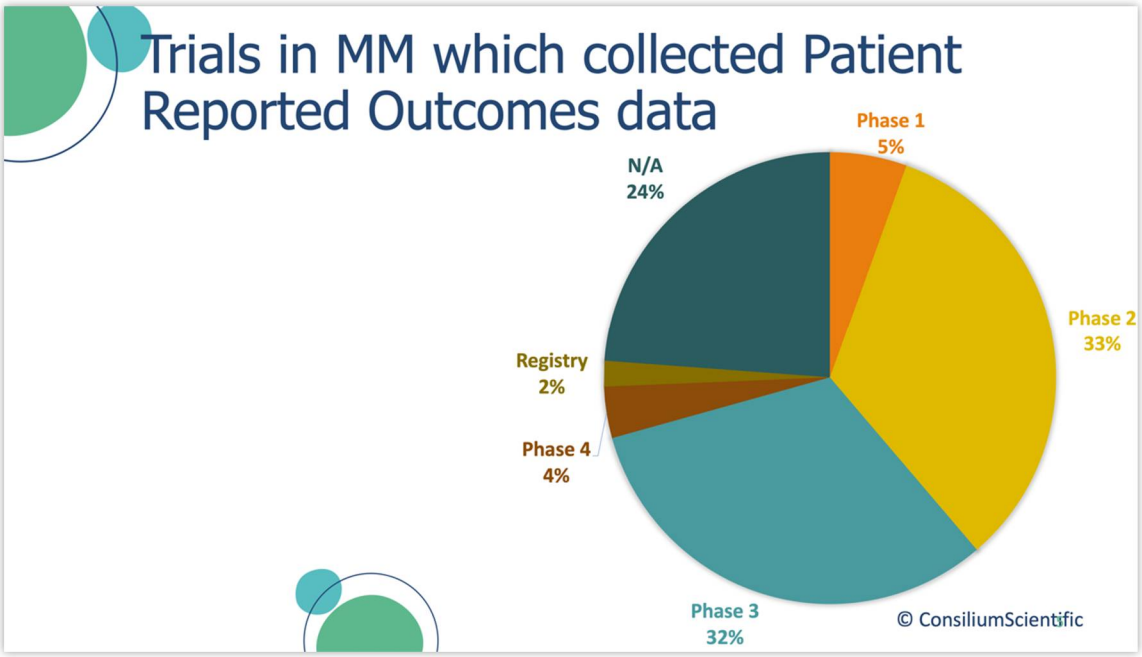

Figure 1: 382 trials in multiple myeloma (MM) which collected PROs.

Twenty-five percent of these trials collected PROs as primary outcome and 85% as secondary. Most trials used generic instruments (like the EQ-5D) or generical cancer instruments (like EORTC-QLQ30) to measure PROs whereas only 27% used disease-specific instruments (like EORTC-QLQ-MY20 or FACT-MM). This was especially evident in phase 3 (Figure 2).

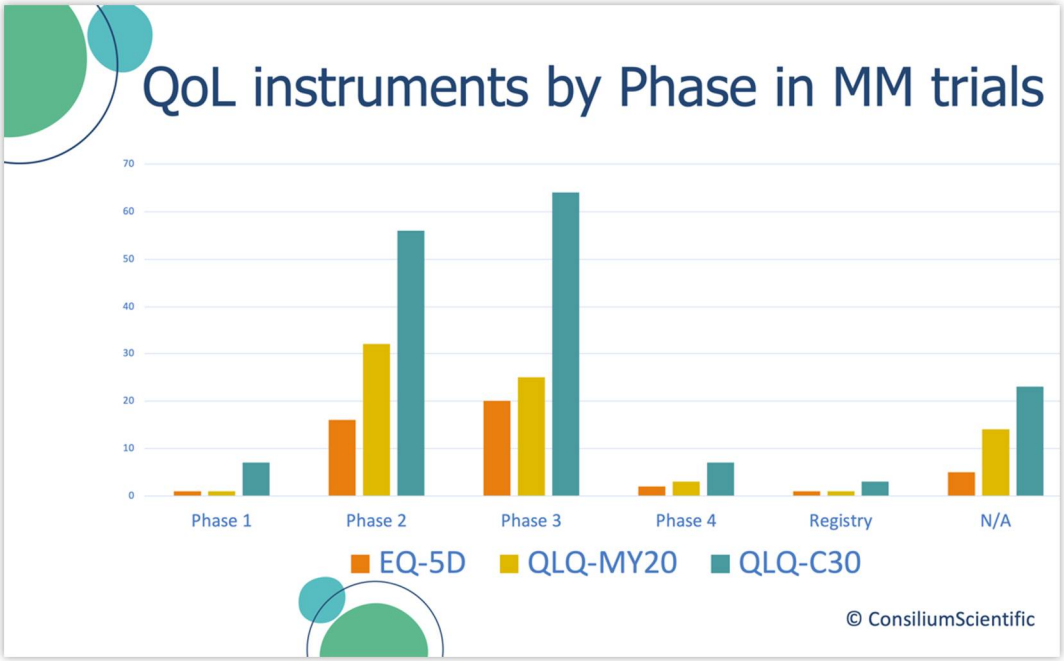

Figure 2: HRQoL instruments used in 382 clinical trials in MM by development phase.

For oncology it is particularly important that patient reported outcomes (PROs) are collected as early as in phase II trials as more and more oncology products enter the market without phase III data. Both generic and disease-specific instruments need to be included into every trial.

The creation of informative and clinically plausible data sets using both general and disease-specific instruments is very important. We are lacking PRO/HRQoL data collection in routine clinical practice. We should strive to:

- Better plan the timing and frequency of data collection
- Avoid overburdening the patients with many QoL instruments
- Improve quality of PRO/HRQoL data
- Ensure that PRO/HRQoL data collected in trials reflect the population for whom the treatment will be intended in clinical practice

Patient relevant outcomes are essential for the HTA process. Patient reported outcomes must be converted into utilities for inclusion into an economic model. Also, the HTA process requires comparative data for decision-making. Often these data are not available from registrational trials (choice of a comparator not relevant to the HTA process, registrational trial is non-comparative, or HRQoL data is of poor quality). In this case, secondary sources need to be used. Published data might not be current or suitable for the HTA decision problem. Thus, additional efforts are needed to ensure collection of PROs in clinical practice and in dedicated QoL studies to generate representative data sets for HTA purposes.

What needs to be done

QoL data collection should be a requirement in every oncology clinical trial

- Phase 2, Phase 3, Phase 4, registries and follow ups

- QoL data collection in clinical practice should become routine

We need to encourage creation of QoL data sets for different population subgroups – patients with co-morbidities, people unable to self-report, etc.

It is important to keep QoL data current as treatments and patient profiles change overtime.

Advancements in methodology should be pursued:

- Standardize/ compare instruments and approaches (proxies)
- Develop valuation sets/ mapping algorithms
- Validate PRO instruments

Academic Perspective on Patient-Reported-Outcomes (PRO)

Dr. Corneel Coens
Lead Statistician, European Organisation for Research and Treatment of Cancer, Brussels, Belgium

This presentation gives a study design and statistical analysis perspective on development and implementation of PROs in cancer drug development.

Key points of the presentation

PRO assessment in cancer clinical trial has seen a **strategical shift** in the recent decade to keep up with new drug developments and design implications. With both therapies targeting multiple disease sites and trial designs with more tailored objectives, the use of a single PRO standard questionnaire is increasingly outdated.

PRO development usually begins with what is known of the disease and the treatment and it should be considered that **treatment effects are not singular** and may affect multiple domains. Other practical issues are that PRO is often a secondary endpoint, so design characteristics such as sample size are determined by other factors.. And multiple stakeholders may impose different requirements on the data collection. Figure 1 gives an overview of these complex interactions.

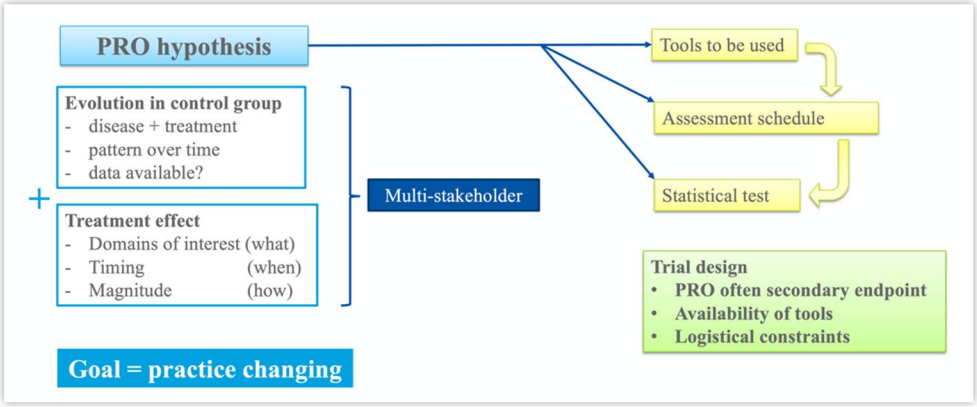

Figure 1: PRO design of a clinical trial

This situation makes it necessary to address the data **requirements from various stakeholders** which has often led to combining several standalone questionnaires or to complement core questionnaires with disease or symptom specific extensions. However, this

"one hypothesis fits all" concept is outdated. It is better to use a tailored approach: measure what matters and create value for patients, clinicians, regulators, HTA, and others.

The more **tailored approach adds complexity** as issues change faster than questionnaires. Treatments and adverse effects evolve (e.g. rash) and PRO hypotheses get more specific and diverse just as clinical trials get more complex. The constant updating or creating new questionnaires is inefficient and a time and resource consuming process. Therefore, multiple questionnaires with broad issues are used which increases the burden for the patient (often negatively impacting data quality) and decreasing sensitivity to detect treatment differences. To address the need for more tailored PRO questionnaires, the use of **item libraries and computer-adaptive-testing** (CAT) have been developed. Item libraries[28] allow the user to identify items and scales that best address the specific issues of interest for a given setting (see Figure 2).

CAT[29] on the other hand facilitates greater measurement precision and reduces questionnaire length by selecting the administered questions based on the already provided answers (Figure 3). This makes CAT an attractive option as the increased measurement precision does not come at a cost of patient burden and allows to skip uninformative questions.

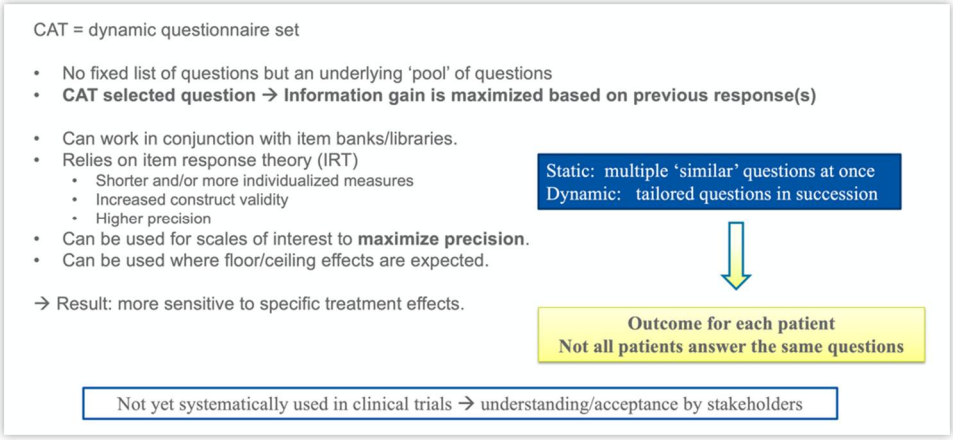

Figure 2: Computerized Adaptive Testing (CAT) of PROs

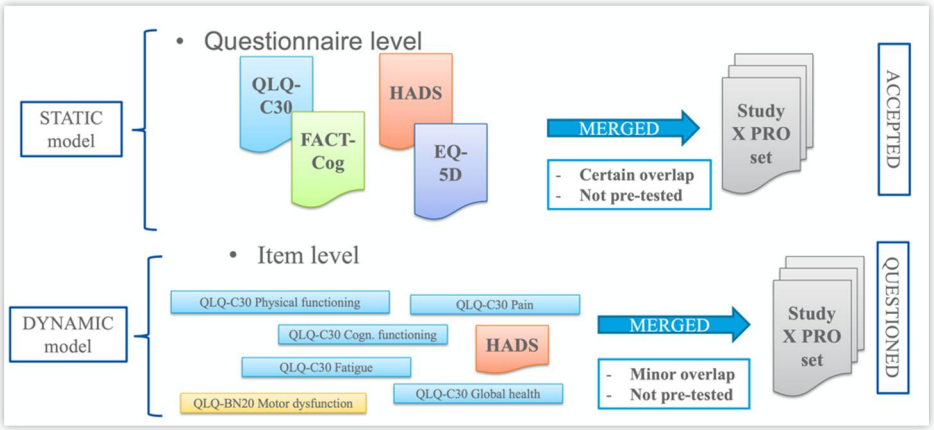

Figure 3: EORTC Item Library: Static and dynamic models of defining the study PRO set

[28] https://www.eortc.be/itemlibrary/
[29] https://qol.eortc.org/cat/

There is a genuine concern that the introduction of these new PRO strategies comes at the cost of **standardization**. Comparisons of trial results across several studies is often crucial for several stakeholders. While 'static' instruments remain valid, their limitations need to be acknowledged. Successful patient-reported trial outcomes will require a balance whereby core questionnaires are augmented with flexible tools allowing trial-specific objectives while contributing to the overall cross-trial body of evidence.

In the future, **PRO guidelines** with an emphasis on tailored PRO hypothesis and assessment are needed. It necessary to allow flexibility to meet the needs of multiple stakeholders and, still, to maintain consistency.

Static questionnaires have advantage of standardization and should address a **core set of HRQoL variables**. One example are the National Cancer Institute's Symptom Management and Health-Related Quality of Life Steering Committee[30] twelve core symptoms — specifically fatigue, insomnia, pain, anorexia (appetite loss), dyspnoea, cognitive problems, anxiety (includes worry), nausea, depression (includes sadness), sensory neuropathy, constipation, and diarrhoea — that should be considered for inclusion in cancer clinical trials where a PRO is measured.

In general, a **compromise between flexibility and standardization** needs to be found. One suggestion[31] has been to combine a core set (that will allow cross-trial comparisons), an extension set (that will allow adequate disease- and treatment-specific coverage) as well as selections from the item list to cover missing trial specific issues.

Summary

- Tailored PRO design is expected to become the norm.
- For successful patient-reported trial outcomes the following is needed:
    - Increased attention to the formulation of a trial-specific PRO hypothesis
    - Make flexible tools more accessible, acceptable, and relevant
    - Ensure adequate analysis, publication, and access to results
- Practice changing trials for all stakeholders would mean:
    - Involvement of stakeholders in the design: directly or indirectly
    - Awareness of the available tools and methods and their advantages and disadvantages.
    - Analysis and reporting: Different stakeholders have different needs; more publications will be needed for each trial to achieve access and understanding of the outcomes.
- Attention should be given to maintain a level of standardization: The 'core + extension + item list' model may be a good solution.

[30] Reeve BB et al., JNCI 2014; 106: dju129
[31] Groenvold M et al., CCR 2016; 22: 5617