WHITE PAPER

Improving the understanding, acceptance and use of oncology–relevant endpoints in HTA body / payer decision-making

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This thought piece has been developed as part of an EFPIA project to drive awareness of the use of oncology-relevant endpoints in HTA body / payer decision-making. Oncology-relevant endpoints refer to all endpoints used in oncology clinical trials to measure outcomes relevant to patients. These can include, in addition to overall survival, patient-reported outcomes as well as progression-free survival in some metastatic settings, pathological complete response or event-free survival in early oncology settings. The thought piece was written with the support of L.E.K. Consulting and was informed by a literature review as well as 13 qualitative interviews with clinicians, patient advocates and former HTA bodies / payers to better understand the value of oncology-relevant endpoints and the challenges facing their adoption. The findings were discussed and refined at three roundtables with the project's sounding board.

This report is explicitly endorsed by the following organisations:

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Executive summary

In clinical trials, overall survival (OS), defined as the time from randomisation (assignment of clinical trial participants to treatment groups) until death from any cause, remains a robust measure of the clinical benefit of cancer medicines. Its objectivity, suitability for comparing treatment regimens and relevance to patients have made it the preferred measure of clinical efficacy in regulatory and HTA body / payer decision-making. However, reliance on OS data in regulatory and HTA body / payer decisions has its limitations. Namely, it fails to capture health-related quality of life (HRQoL) outcomes, is more vulnerable to confounding than other endpoints, and may lead to increased cost and delayed patient access to novel medicines as time to measure OS benefit increases in many treatment settings.[1–3]

Oncology-relevant endpoints refer to OS and all endpoints used in oncology clinical trials to measure outcomes beyond survival (e.g., progression-free survival, disease-free survival and pathological complete response) as well as patient-reported outcomes (PROs). Oncology-relevant endpoints beyond OS can help to address some of the challenges with OS in the assessment of novel medicines by HTA bodies / payers to inform the reimbursement and pricing of novel therapies. In some cases, these additional oncology-relevant endpoints (e.g., progression-free survival) can act as surrogates for OS or other target outcomes, providing an earlier measure of medicine efficacy. Furthermore, they can be measures of efficacy in their own right through capturing clinically important outcomes (e.g., disease progression, response to treatment) or other outcomes of high importance to patients, such as time to disease-specific events (e.g., disease recurrence, metastasis) and HRQoL. Finally, OS is generally measured across several lines of therapy, while oncology-relevant endpoints beyond OS can be captured within a single line (e.g., first line only). As such, oncology-relevant endpoints beyond OS are less likely to be influenced by confounding and are thus well suited to provide clear measures of the therapeutic benefit of novel medicines and their relevance to patients. It is critical that the value of all oncology-relevant endpoints is considered per cancer type and stage, taking into account outcomes of importance to patients and clinicians. For example, PRO measures may differ between early-stage cancers in the neoadjuvant and adjuvant setting, where disease may be asymptomatic, and the metastatic stage.

However, uncertainties about their value present barriers to the broader recognition of oncology-relevant endpoints beyond OS in HTA body / payer decision-making. These uncertainties stem from a lack of evidence and from misalignment between clinicians / patients, regulators and HTA bodies / payers on the relative value of specific endpoints within each treatment setting. This is further exacerbated by inconsistency in the types of endpoints collected within a given cancer indication, as well as in the methods used to collect them.

Several actions can be taken to address uncertainties around the use of oncology-relevant endpoints beyond OS in HTA body / payer decision-making. Suggested actions focus on alignment across and within stakeholder groups (patients, clinicians, regulators, HTA bodies / payers and industry) on the value of specific oncology-relevant endpoints in each treatment setting. This will allow for the creation of a portfolio of endpoints that are fit for purpose, by cancer type and stage. Stakeholders should further support evidence generation to demonstrate the standalone or surrogate value of oncology-relevant endpoints. Furthermore, standardisation of the core outcomes collected per treatment setting and methodologies used to collect them will ensure consistency, validity and comparability of oncology-relevant endpoint data.

Introduction and methodology

This research has been conducted to gain a better understanding of the role of overall survival (OS) and other oncology-relevant endpoints in regulatory and HTA body / payer decision-making of novel cancer medicines. The aims are to:

- Identify current challenges and drawbacks related to the use of OS in clinical trials
- Articulate the value of oncology-relevant endpoints in addressing these challenges
- Define the barriers preventing the adoption of oncology-relevant endpoints other than OS, particularly by HTA bodies / payers
- Suggest a set of cross-stakeholder and individual stakeholder actions to help ensure timely access to medicines that provide benefits to patients

Findings from this research have been generated through one-on-one interviews with 13 stakeholders (physicians, patient advocates and former HTA bodies / payers), supplemented by a comprehensive literature review. Outcomes from this research were then presented at three round-table discussions with clinicians, patient advocates, and former HTA bodies / payers, where participants debated the benefits and drawbacks of OS, the value of oncology-relevant endpoints, barriers and potential actions to improve the recognition of these endpoints.

Chapter 1. The value and drawbacks of measuring overall survival

Key messages

- Extending overall survival (OS) remains highly important across cancer types and stages, particularly in cancer settings where survival remains a high unmet need and OS data is more readily available
- However, reliance on OS data presents three key limitations:
  - It doesn't capture outcomes of high importance to patients beyond survival, particularly those that capture health-related quality of life (HRQoL)
  - Time to collect OS data is increasing as cancer prognoses improve, delaying patient access to novel medicines in instances where regulatory / reimbursement processes rely on OS
  - OS is vulnerable to confounding (i.e., the distortion of outcomes caused by factors not related to the medicine being investigated), diluting the impact of medicines being investigated and preventing access to potentially efficacious medicines

OS, defined as the time from randomisation (assignment of clinical trial participants to treatment groups) until death from any cause, quantifies the clinical benefit of a medicine through extended patient survival.[4] OS remains a robust and clinically relevant measure of importance to patients that is universally accepted as evidence of the value of a medicine. Its inherent objectivity and suitability for comparing treatment regimens have made it the preferred measurement of clinical efficacy, especially for HTA bodies / payers.[1]

However, reliance on OS in HTA body / payer decision-making, including HTA assessments, for novel cancer medicines presents three key limitations.

Firstly, although extending OS is highly important, relying solely on OS data does not capture the effect of a treatment on the quality of survival. As innovation in oncology medicine development continues and prognoses improve in some treatment settings, studies show that patients value outcomes beyond survival equally or even more than OS.[1,2] As such, the weighting given to OS in HTA body / payer decision-making should be considered by cancer type and stage in the context of clinicians' and patients' goals in the given treatment setting. For example, in the advanced stages and in cancers with poor prognoses, OS should continue to receive significant weighting in HTA body / payer decisions. However, even in this setting, patients emphasise the importance of HRQoL and may value medicines that lead to fewer side effects or better symptom control over incremental OS gain: in a study conducted on the preferences of 459 advanced cancer patients, 27% of patients stated a preference for HRQoL over length of survival, and a further 55% valued HRQoL and length of survival equally.[5] Patient advocates interviewed as part of the research for this article also highlighted the importance of outcomes beyond survival in early-stage disease. In this setting interviewed patient advocates stated a need to measure a medicine's capability to increase time to disease-specific events such as metastasis or disease progression, due to the increased morbidity related to these events and the burden from the additional treatment required following their occurrence.[2] Achieving complete response to therapy has also been shown to be of high importance to patients, even in the case of eventual relapse. For example, in early breast cancer, a study on patient preferences found pathological complete response to therapy to be the most important outcome to patients, above OS.[6] Furthermore, in both curative and non-curative settings where OS is extended, there is a need to differentiate treatments based on other factors, for example, HRQoL as a measure of treatment burden.[5]

> *By looking only at OS in decision-making, you miss out on subjective improvements, such as symptom reduction, and don't get a full understanding of the treatment burden associated with new medicines.*
>
> Cancer Drug Development Forum

> *Outside of OS, there are other treatment goals that are important to patients and should drive clinical decision-making, such as QoL, disease- and progression-free survival. These additional outcomes are not considered sufficiently through OS-driven decision-making.*
>
> Lung Cancer Europe

Secondly, in cancers with improved prognoses, as well as multiple treatment lines, time to mature OS data (i.e., the availability of median OS data), in order to show OS benefit of a novel medicine, can now reach over a decade.[1,2] Examples of cancers where collecting mature OS data is becoming increasingly challenging include:

- Chronic lymphocytic leukaemia where life expectancy is now 10 years or more[2]
- Testicular cancer where men diagnosed at 30 have a life expectancy that is only 2 years lower than that of men without the disease
- Cancers with curative potential such as early breast cancer, where the life expectancy of the active treatment group can approach that of the normal population[7]

Despite this, HTA bodies / payers continue to state a preference for demonstrating benefit with mature OS data, in some cases denying, delaying, or restricting reimbursement for patients in its absence.[2] The result of delaying or limiting access to efficacious medicines has a direct impact on patients through potentially increased morbidity and mortality, and might trigger indirect healthcare and socioeconomic costs.[8,9]

> *The cost and time required to gather mature OS data are making OS data increasingly difficult to collect and may delay patient access to potentially efficacious medicines.*
>
> European Haematology Association

Thirdly, the vulnerability of OS to confounding (i.e., the distortion of outcomes caused by factors not related to the medicine being investigated, or by switching between the control and investigation arm in the clinical trial) means that OS benefits may in some cases go undetected, particularly for treatments used in early disease. There are multiple causes of confounding; one key cause highlighted by interviewed stakeholders is patients switching from the control group to the treatment group. Switching can occur in trials where it can be assumed that the efficacy of an investigational drug is not inferior to the control, diluting treatment effect with regards to OS outcomes. Confounding from patient switching has a particular impact on highly efficacious medicines as switching is more likely when strong efficacy is observed.[3] This can create scenarios where the most effective medicines might be unable to demonstrate their true OS benefit in a randomised control trial (RCT). [1,2,10] Although confounding shows the impact of a novel medicine on the whole treatment paradigm, it limits HTA bodies / payers' ability to accurately evaluate new treatments and potentially denies patients access to effective medicines, particularly as some HTA bodies / payers don't accept statistical data adjustment techniques to account for confounding. Additionally, in a small proportion of trials aimed at measuring OS, patient cross-over may be prevented, meaning that participants with life-threatening disease in the control arm may not have the opportunity to access a potentially more effective treatment.[11] This has a particular impact on the investigation of medicines targeting paediatric oncology, where patients may be prevented from accessing potentially more effective treatment.[12,13]

> *Confounding is particularly problematic for effective interventions as patients cross over from the control to the interventional arm; ethical considerations mean that patients shouldn't be prevented from crossing over and that endpoints that are less susceptible to confounding better capture the efficacy of a medicine being developed.*
>
> European Society for Paediatric Oncology

Chapter 2. Introduction to oncology-relevant endpoints

Key messages

- Oncology-relevant endpoints include OS, other clinical endpoints and PROs that capture outcomes of high importance in a given cancer type
- The value of oncology-relevant endpoints should be considered and evaluated per cancer type / stage to ensure they are fit for purpose, measuring outcomes of high importance to patients, collecting core outcome sets per treatment setting and using standardised methodologies to collect them
- Oncology-relevant endpoints can be classified into time-to-event (e.g., progression-free survival), response rate (e.g., overall response rate), and patient-reported (e.g., quality of life measures)
- The value of oncology-relevant endpoints beyond OS includes:
  - The ability to measure outcomes of high clinical importance and of high importance to patients, beyond survival
  - The ability to provide an early indication of efficacy in the absence of OS data
  - Benefits due to lower sensitivity to confounding

2.1 Classification of oncology-relevant endpoints

Endpoints used in clinical trials can be classified according to the outcome types they are intended to measure. They can be broadly considered to measure time to event and response rates. In addition, PROs provide cancer-agnostic, cancer-specific or symptom-specific measures.

Figure 1: Approach to endpoint classification

	Time to event		Response rates		Patient-reported (i.e. PROs)^		
Definition	Time from randomisation until occurrence of a pre-defined, disease-specific event		The proportion of patients who achieve a pre-defined outcome in response to a treatment; can be complete response, partial response or stable disease		Information on the impact of disease, symptoms or treatment on patient's quality of life (QoL); participation in activities of daily living and healthcare resource use		
Segmentation	**Mortality-related**	**Disease-state-related**	**Tumour marker / Biomarker**	**Non-biomarker**	**Cancer agnostic measures**	**Cancer-specific measures**	**Symptom-specific measures**
Examples (non-exhaustive)	• OS	• Progression-free survival (PFS) • Time to progression (TTP) • Disease-free survival (DFS) • Event-free survival (EFS) • Relapse-free survival (RFS) • Metastasis-free survival (MFS) • Time to next treatment (TTNT) • Time to metastasis (TTM) • Duration of response (DoR)	• Minimal / measurable residual disease (MRD)* • ctDNA* • Disease-specific biomarkers (e.g., AFP in hepatocellular carcinoma, beta HCG in non-seminomatous testicular cancer)	• Complete response • Partial response • Overall response rate (ORR) • Pathological complete response (e.g., Breast Ca) • Disease control rate • Clinical benefit rate	• PROMIS • QLQ-C30** • EQ-5D • FACT-G • SF-36 • MD Anderson Symptom Inventory (activities of daily living)	• QLQ-BR23** (breast) • QLQ-CR2** (colorectal) • FACT-C (colorectal) • QLQ-LC13** (lung) • NSCLC-SAQ (lung)	• SBQ** (symptom burden) • KESS (constipation) • IIED / FSFI (sexual function) • PDQ (pain)

Notes:

* Some biomarkers may be used as predictors of event-related outcomes, e.g., MRD for PFS and ctDNA for DFS

** Modules of the EORTC PROs tool

^ PROs can also be measures of time to event, e.g., time to deterioration, or response, e.g., percentage of patients with improved HRQoL

Time to event: a measure of the time from randomisation to the occurrence of a pre-defined event. These endpoints can be classified as mortality-related (OS) and disease-state-related. Disease-state-related endpoints refer to endpoints measuring changes in a patient's disease state pre-mortality, and include disease-free survival (DFS), progression-free survival (PFS) and duration of response (DoR). The relevance of specific endpoints varies according to cancer type and stage, as in some cases specific endpoints may have utility as a surrogate for OS or other target outcomes of interest and / or as a standalone measure of value. For example, in prostate cancer, time to progression (TTP) has been shown to have strong surrogacy for OS in patients with metastatic disease.[24] In the localised disease setting metastasis-free survival (MFS) should be considered, due to its surrogacy for OS and as it measures an outcome of high importance to these patients.[25] Furthermore, other endpoints such as PFS are identified as potential surrogates for OS in relapsed, refractory multiple myeloma; however, no general consensus is reached in this setting and further clinical data is needed.[26,82]

Response rates: a measure of the proportion of patients who respond to treatment. Response rates can be measured using biomarker and non-biomarker approaches. Non-biomarker endpoints look at whether patients achieve complete or partial response and may in some cases use tissue samples to define this (e.g., pathological complete response). Biomarker endpoints measure response at a microscopic level through Minimal / measurable residual disease (MRD) and circulating tumour DNA (ctDNA).

Patient-reported: these outcomes rely on information collected from patients or carers on the impact of a disease, its symptoms or treatments on the quality of patient survival. The tools used to collect these outcomes can either be cancer-agnostic measures that can be used across disease and cancer types (e.g., PROMIS – patient-reported outcomes measurement information system; MD Anderson Symptom Inventory – symptoms affecting a patient's ability to perform activities of daily living; EORTC Quality of Life Questionnaire Core 30); cancer-specific measures, which capture specific outcomes of importance within a disease area (e.g., QLQ-BR23 – breast cancer; FACT-C – colorectal cancer) or symptom-specific measures (e.g., PDQ – pain; IIED / FSF – sexual function).

2.2 Ensuring oncology-relevant endpoints are fit for purpose

Oncology-relevant endpoints refer to OS and all endpoints used in oncology clinical trials to measure outcomes beyond overall survival (e.g., progression-free survival, event-free survival and pathological complete response) including patient-reported outcomes (PROs). Appropriate selection and use of oncology-relevant endpoints is critical to ensure that they capture outcomes of high importance to patients in each treatment setting, minimise uncertainties associated with their use and facilitate adoption in HTA body / payer decision-making. Appropriate oncology-relevant endpoint selection includes choosing those that measure specific symptoms and morbidity experienced by different patient groups. Therefore, their value must be considered per cancer type and stage and measure outcomes related to the natural history of a given disease. In treatment settings where survival outcomes remain poor, emphasis should continue to be placed on OS when assessing the efficacy of novel therapies during HTA body / payer decision-making.

> *The natural history of a disease needs to be considered at each stage and this must directly influence the endpoints that are used. For example, in early prostate cancer, patients want to prolong time to metastasis due to the impact of metastatic pain on their HRQoL, meaning that medicines that can prolong the time to this event will be highly clinically relevant.*
>
> Europa UOMO – Voice of Men with Prostate Cancer

> *Lung cancer patients see overall survival as important, but also consider other endpoints such as PFS, as well as HRQoL. Patient treatment goals determine the importance of individual endpoints; for example, younger patients may be more focused on HRQoL and on being able to continue activities of daily living.*
>
> Lung Cancer Europe

As per U.S. Food and Drug Administration (FDA) the European Medical Association (EMA), and European Network for Health Technology Assessment (EUnetHTA) guidelines, oncology-relevant endpoints used in clinical trials, including OS, should be **fit for purpose**, meaning that they are appropriately evaluated to assess their utility within each cancer type and stage as surrogates for OS or for their ability to capture other outcomes of importance.[14,15] Evaluation of oncology-relevant endpoints is critical; without this, there is a risk of enabling access to medicines that expose patients to treatment-related toxicity without proven therapeutic benefit.

> *Oncology-relevant endpoints must be well defined, meaningful to patients and need to measure outcomes that address unmet needs from current treatment options.*
>
> Health Technology Assessment International

For oncology-relevant endpoints to be used as **surrogates for OS**, they must be validated for the ability to predict OS to ensure appropriate use in clinical trials and in subsequent decision-making. Validation is required per cancer type and stage, and even per mechanism of action in some instances; for example, a systematic review of solid tumours treated with immunotherapies, such as checkpoint inhibitors, demonstrated good predictive value for overall response rate (ORR) of OS, in addition to PFS which is used as a surrogate in other modalities.[16] However, evidence validating the use of ORR as a surrogate in medicines with other mechanisms of action is less well-established. Stakeholder groups, including clinicians, HTA bodies / payers and regulators agree that the most robust method to determine surrogacy is through meta-analysis of patient-level data across multiple RCTs to quantify the correlation between improvements on a specific endpoint and improvements in OS.[17,18] However, the prescriptiveness of guidance on surrogate validation and evidence generation thresholds is variable across HTA bodies / payers.[18–22] To address the variability in guidance available on the use of surrogates, EUnetHTA has advised that a surrogate may be acceptable if there is evidence of a strong association or correlation of effects on the surrogate with effects on the final outcome, in cases where it is not feasible to measure the final outcome.[14]

Evaluation of the **standalone value** of oncology-relevant endpoints is also critical to ensure that they appropriately measure outcomes of the direct antitumour effect of a novel medicine, and a medicine's ability to provide outcomes of high importance to patients and clinicians (e.g., prolongation of metastasis-free survival in prostate cancer). Although best practices are less clear for the assessment of standalone value, clinicians and patient advocates interviewed as part of this research highlight the importance of patient experience data, as collected through preference studies, in assessing which endpoints to measure for each disease area. Furthermore, health economic studies can help identify which disease-specific events carry the highest socio-economic cost.

> *Academic rigor is key when implementing new endpoints into regulatory and HTA body / payer decision-making. Oncology-relevant endpoints must be evaluated for their ability to measure factors of high importance to patients, that translate to socioeconomic benefit to healthcare systems.*
>
> Cancer Drug Development Forum

> *Non-OS endpoints use must be evaluated per disease type and stage. Each disease has specific treatment goals, symptoms and treatment side effects which need to be accounted for.*
>
> European Haematology Association

> *Patient experience data gathered for example through conducting patient preference studies can be very valuable in identifying outcomes of high importance per treatment setting.*
>
> Patvocates

To drive comparability of PROs between studies, it is critical that outcomes collected are in line with **predefined core outcome sets** per treatment setting and use validated **methodologies**.[14,15] Core outcome sets define the minimum outcomes to be measured and reported for a particular condition and aim to provide key domains (e.g., pain, fatigue) that should be collected. These are important for PROs where there is higher variability in domains that can be collected compared to other oncology-relevant endpoints. For example, for PFS, data must be collected and interpreted using validated tools and methodologies as stated by guidelines such as RECIST (response evaluation criteria in solid tumours), whereby a 20% increase in the sum of diameters of a target lesion is required to identify tumour progression.[23] For PROs, there is also greater variability in tools available, for example disease-agnostic instruments such as the FACT instruments and EORTC QLQ-C30 support comparisons of the level of benefit across indications. Further, disease-specific PROs are available to better capture target outcomes within a disease area (e.g., QLQ-B23 in breast cancer, QLQ-C29 in colorectal cancer). Interviews conducted as part of this research identified a preference among clinicians and patients for disease-specific PROs, as they can better identify outcomes of importance within a disease area. However these must be in line with core outcome sets required for the given treatment setting.

> *It is crucial for PROs to be measured in a pre-defined manner to be able to compare these outcomes within a study and between studies.*
>
> EVITA

> *Disease agnostic PROs can be compared across cancer types, however, disease-specific tools have been developed that better capture outcomes of importance within a specific cancer type.*
>
> Patvocates

2.3 Value of oncology-relevant endpoints

Oncology-relevant endpoints can capture a medicine's value both as surrogates for OS, enabling earlier identification of survival benefit, and as standalone measures of outcomes beyond survival.

Value of oncology-relevant endpoints as surrogates

The use of some oncology-relevant endpoints as surrogates for OS or other target outcomes of relevance provides an opportunity for earlier measures of medicine efficacy.[18] This can enable shorter clinical trial durations and potentially facilitate expedited approval of, and patient access to, efficacious treatments. Beyond the benefit to patients, faster access to efficacious innovative medicines can reduce healthcare costs related to disease- / symptom-burden and increase incentives for innovation.[9,27]

> *Using endpoints such as PFS has massive implications as it removes the need to wait for OS. This is an opportunity for medicine developers to accelerate approval and would enable patients to gain access to potentially life-prolonging medicines sooner.*
>
> International Myeloma Foundation

> *The potential for non-OS endpoints to be used as surrogates is meaningful in allowing earlier access to effective medicines. Surrogates should be considered in a disease-specific manner, validated through patient-level meta-analyses of randomised clinical trials.*
>
> European Haematology Association

CASE STUDY EXAMPLE 1: the value of oncology-relevant endpoints in multiple myeloma

CONTEXT:

The treatment paradigm for multiple myeloma has changed significantly over the last decade, leading to improved patient prognoses, and extending the median time to overall survival (OS) to over a decade for some patient groups.[28] Myeloma patients also typically cycle through multiple lines of therapy, making OS data highly susceptible to confounding.[29]

ONCOLOGY-RELEVANT ENDPOINTS WITH POTENTIAL FOR USE IN HTA BODY / PAYER DECISION-MAKING:

Progression-free survival (PFS), minimal residual disease (MRD)

DETAIL:

In myeloma, extending PFS, particularly in early lines of therapy, provides patient benefit as it has been shown that the extent and duration of patient response decreases with successive lines of therapy, while the burden of symptoms and treatment toxicity increases.[29] PFS may also be considered an appropriate surrogate for OS, though evidence is inconclusive and with treatment advances, it can now take 5 years to demonstrate PFS.[30,82]

Measuring minimal residual disease (MRD) can detect patient response to a medicine with greater sensitivity than radiological measures of response and may hold promise as a surrogate for PFS and OS, enabling faster identification of treatment benefits.[31]

Lower likelihood of confounding

In well-managed cancers and early lines of therapy, oncology-relevant endpoints beyond OS are typically less susceptible to confounding than OS and can therefore provide a more reliable and direct measure of treatment efficacy.[32] Firstly, oncology-relevant endpoints beyond OS, such as PFS, are typically measured up to a disease-related event within one line of therapy, reducing the impact of subsequent treatments on outcomes of interest.[32] Oncology-relevant endpoints beyond OS allow for patient switching without diluting efficacy demonstrated by a novel medicine. Secondly, as some oncology-relevant endpoints beyond OS (e.g., MRD, ctDNA) are direct measures of tumour burden, they are less likely to be impacted by confounding as they directly measure anti-tumour activity from treatment, as opposed to death which can be caused by multiple factors. Finally, dropout rates in oncology clinical trials are currently estimated to be c.20%.[33] Reasons for early dropout include forgetting visits, inconvenient trial locations, schedule conflicts, financial constraints, lack of improvement or worsening condition, side effects, or simply a change of mind.[34] The longer the trial, the higher the number of patient dropouts expected, especially as some drivers of dropout are likely to become more prevalent with longer trials (lack of improvement, forgetting visits, side effects). Consequently, measures of efficacy which can be captured earlier than OS, including PFS, DFS, MFS, pathologic complete response (pCR) and MRD, may be less susceptible to confounding from patient dropout, and provide a more robust evidence base.

Standalone value of oncology-relevant endpoints

Oncology-relevant endpoints also have standalone value through capturing outcomes of high importance to patients and clinicians. The standalone value of oncology-relevant endpoints beyond OS includes value in guiding clinical treatment decisions and the ability of these endpoints to directly capture antitumour activity of a medicine. There is also growing recognition of their value in assessing a treatment's capability to improve disease- and symptom-related burden through prolonging time to progression and disease-free periods, which can reduce healthcare resource use.[3] For example, a study of 41 patients with early breast cancer identified the importance of pCR as an independent and relevant endpoint in evaluations of clinical utility of neoadjuvant medicines.[6] Furthermore, delaying or preventing disease progression has been shown to have important psychological benefits. As an example, a survey of patients with renal cell carcinoma found that cancer recurrence is a main cause of anxiety in patients.[35] Patient advocates interviewed as part of this analysis identified metastasis development and metastatic bone pain as particularly concerning for prostate cancer patients. A recent systematic review of treatment outcome preferences across 4374 patients found that HRQoL was most frequently prioritised over OS, demonstrating the standalone value of endpoints and PROs that measure outcomes beyond survival.[36] Oncology-relevant endpoints such as pCR are also of value in clinical decision-making. For example, in neoadjuvant breast cancer pCR status is a key driver of patient treatment selection, as patients for whom pCR is not achieved are offered additional lines of chemotherapy.[37,38]

The value of PRO data is already being recognised in HTA body / payer decisions, as demonstrated by a study of PRO inclusion in oncology HTA submissions between 2011-2016 in Germany, France and the UK. This study found that improvements in HRQoL led to higher benefit ratings by the G-BA and HAS and supported clinical benefit assigned by SMC and NICE despite a lack of OS data in some cases.[39] However, the study was less clear on the specific contribution of the PRO data toward the outcome of the benefit assessment and how this was evaluated.

> *For patients, OS is important, but it is also important that medicines have been evaluated for their impact on HRQoL and the level of treatment burden associated with them.*
>
> Lung Cancer Europe

> *PROs are very valuable tools to better understand the patient experience of living with the disease as well as the advantages and disadvantages of a new treatment.*
>
> Cancer Drug Development Forum

CASE STUDY EXAMPLE 2: the value of oncology-relevant endpoints in prostate cancer

CONTEXT:

In early prostate cancer, therapeutic advancements and associated improvements in patient prognosis mean that it can take over a decade to collect meaningful overall survival (OS) data.[40]

ONCOLOGY-RELEVANT ENDPOINTS WITH POTENTIAL FOR USE IN HTA BODY / PAYER DECISION-MAKING:

Metastasis-free survival (MFS).

DETAIL:

There is growing data to support the use of oncology-relevant endpoints as surrogates of OS, using MFS in localised disease and PFS in patients with metastases.[41] Furthermore, event-related oncology-relevant endpoints, such as MFS and castration-free survival, are outcomes that have clinical value, and prolonging time to these events is of high importance to patients and clinicians due to their contribution to symptom- and disease-burden and associated socio-economic impact.[42]

CASE STUDY EXAMPLE 3: the value of oncology-relevant endpoints in breast cancer

CONTEXT:

In early breast cancer, the time to demonstrate overall survival (OS) is increasing, and it can now take over a decade to generate median OS data.[2]

ONCOLOGY-RELEVANT ENDPOINTS WITH POTENTIAL FOR USE IN HTA BODY / PAYER DECISION-MAKING:

Disease-free survival (DFS), pathological complete response (pCR), circulating tumour DNA (ctDNA).

DETAIL:

There is growing evidence supporting DFS as an early predictor of OS. For patients who have undergone first-line neoadjuvant therapies, extending DFS also has standalone value due to being an indicator of avoiding disease recurrence, which has associated symptoms, psychological impact, and need for additional treatment.[1,43] In addition to DFS, there is an increased focus on pCR due to its implications for ongoing treatment decisions. For example, some breast cancer patients are recommended to undergo additional lines of chemotherapy in the neoadjuvant setting if pCR is not achieved. pCR status will also impact the surgical procedures recommended for these patients.[37,38] Finally, although still in its nascency, there is increasing evidence to support the use of ctDNA as a predictor of pCR and potentially of OS in breast cancer.[44]

Chapter 3. Barriers to acceptance of oncology-relevant endpoints

Key messages

- A key barrier preventing broader adoption of oncology-relevant endpoints beyond OS in regulatory and reimbursement decisions is uncertainty that they appropriately quantify the value of new medicines, as well as uncertainty that by meeting these endpoints, there is indeed prolonged benefit to patients and healthcare systems
- There is misalignment between stakeholder groups on the value of oncology-relevant endpoints; for example, regulators are more accepting, whereas many HTA bodies / payers continue to rely predominantly on overall survival (OS)
- There is also misalignment within stakeholder groups; for example, some HTA agencies (e.g., NICE, G-BA) incorporate patient-reported outcome (PRO) measures into their decision-making processes while HTAs in other countries (e.g., Spain and Italy) give less recognition to PRO data
- Inconsistencies in core outcome sets collected and methodologies used to collect them are further driving uncertainties from regulators and HTA bodies / payers and make it more difficult to demonstrate the true value of these endpoints

3.1 Uncertainties about the value of oncology-relevant endpoints beyond OS

Uncertainty around the use of oncology-relevant endpoints beyond OS is a key barrier to their adoption in HTA body / payer decision-making.[14,83] Methodological guidelines from HTA bodies / payers typically express a preference for OS data or limit the use of surrogates to those where validation studies have shown a strong correlation with survival.[19,20] Uncertainty from HTA bodies / payers is exacerbated by examples of medicines that were approved by regulators based on improvements in outcomes on oncology-relevant endpoints, such as PFS, that did not translate into OS benefits.[45]

> *There are multiple examples where PFS and OS aren't linked; this is what drives uncertainties among HTA bodies / payers when considering their use as surrogates for survival outcomes.*
>
> Cancer Drug Development Forum

> *The challenge with oncology-relevant endpoints stems from the uncertainty about their surrogacy to OS and their ability to identify outcomes related to disease- or symptom burden.*
>
> Huntsman Cancer Institute

> *HTA bodies / payers are very aware of the uncertainties that come with the use of oncology-relevant endpoints. HTA bodies / payers are interested in limiting risk which is preventing broader adoption of oncology-relevant endpoints in decision-making processes.*
>
> CZ Health Insurance

Despite the potential value of some oncology-relevant endpoints in capturing outcomes beyond survival, there is concern shared by all stakeholders, particularly HTA bodies / payers, over the ability of oncology-relevant endpoints to accurately and appropriately quantify this value to patients and healthcare systems.[46-48] This is particularly true for endpoints that are not considered to be target outcomes of high importance to patients or those where clear links to patient functioning, HRQoL and the socio-economic impact on healthcare systems cannot be drawn. It has also been argued that in some diseases and / or for some patients, progression events, determined by laboratory measurements of tumour size, may not always be associated with a clinical or functional benefit for the patient and may not be able to measure factors related to patient HRQoL.[46-48] Furthermore, treatments responsible for prolonging PFS or DFS may result in increased treatment-related toxicities that negatively impact HRQoL, which cannot be identified using these oncology-relevant endpoints alone.[46-48]

> *Using endpoints beyond OS increases the risk of additional treatment cost and of exposing patients to treatment burden without additional benefit.*
>
> European Haematology Association

Some concerns are specifically related to PROs as HTA bodies / payers see these outcomes as more subjective and therefore less appropriate for use in isolation compared to more objectively measured outcomes such as PFS and DFS.[49] While interviews with former HTA bodies / payers as part of this research confirmed that the inherent subjectivity of PRO data is viewed negatively in some markets, acceptance of PROs by HTA bodies / payers appears to be increasing. However, the way in which PRO data is reviewed and considered in HTA body / payer decisions differs between countries (e.g., the UK, France and Germany). For example, in Germany, PRO data alone can be used to contribute to benefit assessment outcomes whereas the same data may be rejected in France, if collected as part of an open-label trial.[50] In the UK, NICE most commonly considers EQ-5D through the quality-adjusted life year (QALY) as part of cost-effectiveness analysis, which is an economic measure of health benefit rather than the specific benefit to the patient.[50] These variations on how PRO evidence is reviewed and considered by different HTA bodies / payers lead to confusion on PRO requirements and can act as a barrier to the adoption of these outcomes in clinical trials as well as in regulatory and HTA body / payer decision-making.

3.2 Misalignment within and between stakeholder groups on the value of oncology-relevant endpoints

Although OS continues to be a priority in some treatment settings, there is growing acknowledgment by clinicians and regulators that survival is not always the most important outcome to the patient; however, HTA bodies / payers continue to put significant weight on OS. For example, EUNetHTA21 guidelines state that while morbidity and HRQoL impact are valued, they are not viewed as final outcomes and are considered below mortality in the outcomes hierarchy.[49] This stance is not aligned with the perceptions of patients and clinicians interviewed for this paper, who state that they value some oncology-relevant endpoints equally if not above OS in some treatment settings and consider them as key drivers in clinical decision-making.[2,5]

> *Currently, there are cases where clinical decision-making on the type of medicines offered is guided using outcomes other than OS, such as PROs. One example of this is the use of Ruxolitinib in Myelofibrosis, to treat splenomegaly and fatigue rather than prolong OS. There is a need for HTA bodies / payers to also recognise the importance of these HRQoL outcomes in their decision-making.*
>
> European Haematology Association

There are also differences in value attributed to oncology-relevant endpoints beyond OS in regulatory versus HTA body / payer decision-making, with regulatory bodies being more open to the use of these oncology-relevant endpoints than HTA bodies / payers.[51,52] In cases where oncology-relevant endpoints beyond OS have been accepted, HTA bodies / payers have required validation of surrogacy, while regulatory bodies have accepted oncology-relevant endpoints that will reasonably likely predict clinical benefit.[51,53,54] Furthermore, interviews with HTA bodies / payers as part of this research indicate a misalignment within this stakeholder group. As an example, some HTA bodies / payers (e.g., NICE in the UK, HAS in France, AIFA in Italy) are open to the use of PFS, to predict treatment duration as part of the economic modelling of cost-effectiveness and for its utility in clinical decision-making, while IQWIG in Germany does not recognise it.[55]

Misalignment can lead to a lack of focused evidence generation to quantify the long-term benefit and patient relevance of disease-related oncology-relevant endpoints, which may in turn prevent HTA bodies / payers from assigning appropriate weighting to these endpoints in their decision-making.

> *In the EU there is a disconnect between the EMA and HTA bodies / payers on which endpoints they use and consider as important; there is also variation between countries in terms of the relative weighting of different endpoints in HTA body / payer decision-making. This needs to be addressed.*
>
> Cancer Drug Development Forum

> *Variation in the types of outcomes used within a disease area is adding to confusion across stakeholders as to which endpoints to focus on for evidence generation, and which are appropriate to use in HTA body / payer decision-making.*
>
> CZ Health Insurance

3.3 Inconsistencies in data collection and reporting of oncology-relevant endpoints beyond OS

Successful incorporation of oncology-relevant endpoints beyond OS relies on measures and definitions being widely understood and implemented across disease areas; however, there are some challenges related to data collection and reporting, which may act as barriers to the adoption of oncology-relevant endpoints. Firstly, tools used for PRO data collection may be considered too generic and may not capture disease-specific outcomes, or outcomes related to medicines with a novel mechanism of action.[56-59] Secondly, selection of PRO domains being collected, as well as data collection methodologies used, might vary within an indication, limiting comparability across studies and thus impacting the general acceptability of these endpoints and PROs.

For emerging biomarker-based endpoints such as MRD and ctDNA, uncertainties around the methodologies used to collect data also need to be addressed.[60-62] For example, with MRD, optimal timing of assessment and a threshold for MRD negativity have not yet been agreed. Furthermore, current measurement techniques vary in sensitivity by over two orders of magnitude.[60,62,63] Detection of ctDNA is less developed than detection of MRD. Outstanding challenges include lack of scientific consensus around the optimal procedures for the extraction of ctDNA, sample volumes required and optimal measurement techniques for ctDNA detection.[64,65] In addition to the lack of standardisation of MRD and ctDNA measurements, stakeholders identify low uptake in clinical trials and in the clinical setting, acting as a barrier for use in HTA body / payer decision-making.[62]

The challenges associated with data collection are most significant for more subjective outcomes, such as PROs. PROs in oncology studies predominantly rely on EORTC-QLQC30, FACT and the economic instrument, the EQ-5D questionnaires.[56] Although these instruments are well understood by different stakeholder groups, they are not specific to the type or stage of disease, and concerns have been raised by clinicians, patients, and academics that they are not sensitive enough to provide clinically meaningful insights into the outcomes that are most relevant to a specific patient population.[56-59] The lack of sensitivity of generic instruments leads to difficulties in generating positive, patient-relevant data, which in turn limits the ability to demonstrate patient impact in regulatory and HTA body / payer decision-making.

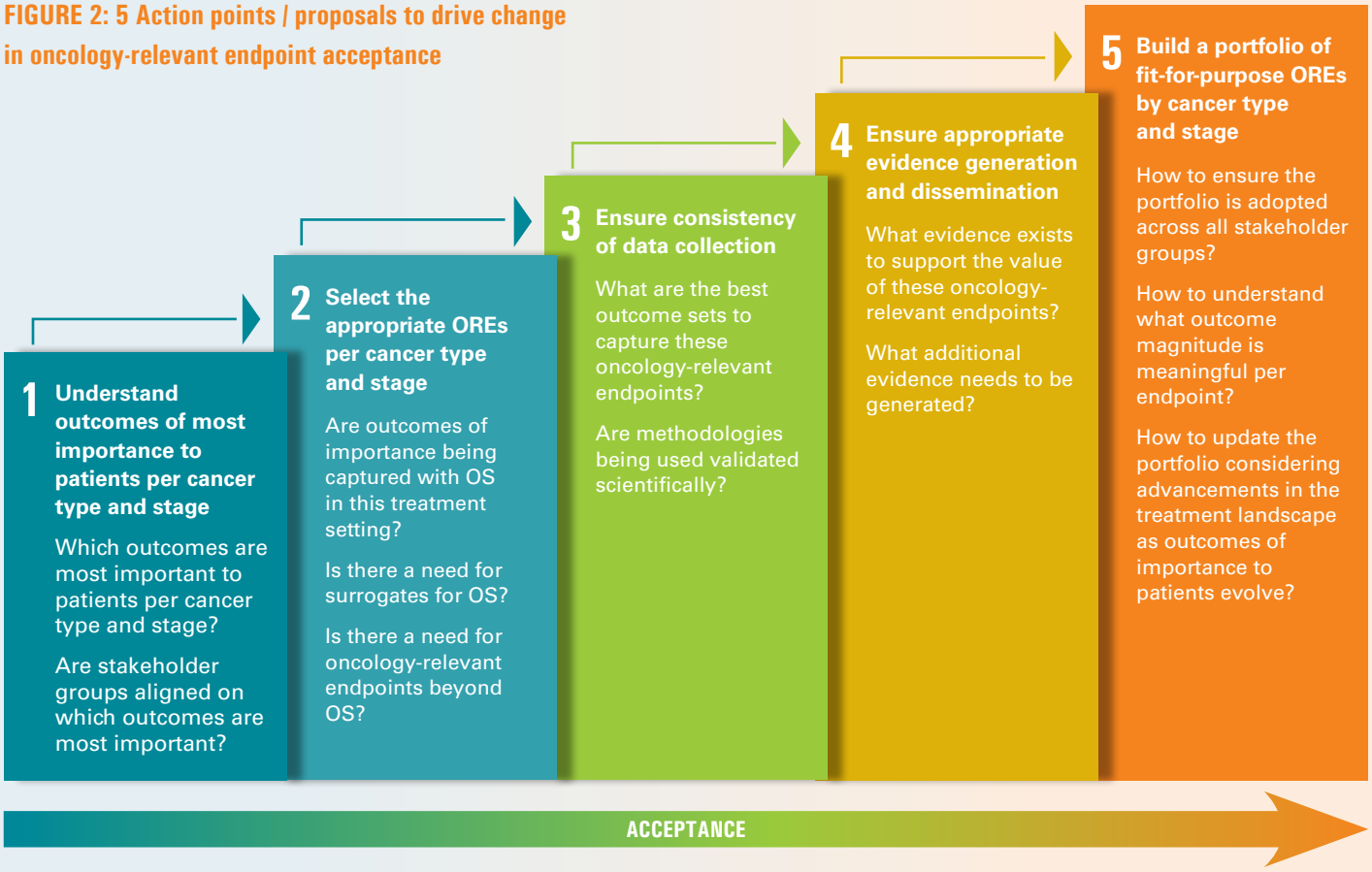
The wide range of available PRO domains (e.g., pain, nausea, fatigue) can drive variations in their use between clinical trials and might decrease awareness of and confidence in PROs by regulators and HTA bodies / payers. For example, a systematic review of PRO collection in metastatic breast cancer identified 17 different PRO domains being used to monitor HRQoL. PROs included both generic and disease-specific measures in breast cancer. The heterogeneity in PRO domains being collected may lead to disaggregation of data due to poor comparability across trials. A more standardised, disease-specific outcome set would improve the interpretation of PROs in clinical trials and to increase their recognition across stakeholder groups.[66] An additional barrier affecting the validity of PRO data is created by high rates of missing data due to poor patient compliance.[67,68] This can lead to difficulties in interpreting results, as well as findings that are skewed towards patient groups who are more cooperative in filling out forms, but not representative of broader patient populations.[69]

> *PROs have the most potential for improvement, particularly through more structured methods and standardised tools for collecting these data points. Currently, variability in methodologies prevents comparison across trials and is a barrier to wider adoption.*
>
> European Haematology Association

Chapter 4. Action points

This chapter suggests some individual stakeholder and cross-stakeholder actions derived from discussions including clinicians, patient advocates and former HTA bodies / payers. These action points are aimed at addressing the need for an early cross-stakeholder dialogue to ensure that appropriate oncology-relevant endpoints are selected for use in pivotal trials. This will help to address the uncertainties preventing greater use of oncology-relevant endpoints in HTA body / payer decision-making in oncology, to ensure future HTA body / payer assessments result in improved outcomes for patients.

FIGURE 2: 5 Action points / proposals to drive change in oncology-relevant endpoint acceptance



ORE: oncology-relevant endpoint

4.1 Understand outcomes that are most important to patients per cancer type and stage

As a first step, it is important for stakeholders to align on which outcomes are most important to patients per cancer type and stage. For instance, in treatment settings with poor prognoses, improving survival outcomes may be of greatest importance to patients and OS data is typically more readily available, whereas in settings where prognosis is improving, outcomes beyond survival (such as progression, metastasis, and HRQoL-related outcomes such as pain and participation in activities of daily living) may have more value.[83] However, priorities can vary between individuals irrespective of cancer type and stage. Outcomes beyond OS are gaining momentum in children and young people, where increased emphasis is being placed on outcomes related to long-term toxicity in survivors and to the mental health of patients and their families, and in outcomes that measure their ability to participate in and progress through education.[70] Across cancer types, the core outcomes to be collected should be aligned with those identified in the core outcomes measures in effectiveness trials (COMET) initiative.[71] The COMET initiative highlights a standardised set of outcomes, representing the minimum that should be measured and reported in all clinical trials of a specific condition.[71]

Early cross-stakeholder involvement is required to identify outcomes that should be measured per treatment setting, and to establish under which circumstances they would be accepted in regulator and HTA body / payer decision-making. Patients and patient advocates will be central to defining patient experience data and outcomes that are most important, but alignment across stakeholder groups is a necessary step to ensure that regulatory, HTA body / payer and clinical decision-making reflect this. There is a particular need for alignment, where appropriate, between regulators and HTA bodies / payers on how these outcomes can be used in decision-making processes to make them more comparable, incorporating the views of clinicians and patients. Furthermore, HTA bodies / payers should consider how oncology-relevant endpoints are important downstream in the patient access pathway, e.g. in clinical decision-making.

Patient advocates interviewed for this paper highlighted that they are often included in regulatory discussions around how to better capture their treatment goals, but that there have been fewer opportunities for engagement with HTA bodies / payers. This might be a key driver of differences in levels of acceptance of oncology-relevant endpoints beyond OS between regulators and HTA bodies / payers.[2] Interviewed patient advocates also stressed that while they may be part of discussions with HTA bodies / payers, insufficient weight was applied to their perspectives.

> *"There are more opportunities for patient advocates to be included in discussions with regulators. These opportunities are less common with HTA body / payers, and this might be one of the reasons for misalignment in the use of oncology-relevant endpoints beyond OS in regulatory versus HTA body / payer decision-making.."*
>
> Europa UOMO – Voice of Men with Prostate Cancer

Figure 3: Action points / proposals to drive understanding of outcomes that are important to patients

Clinicians / academics	• Collaborate with patient organisations on the definition of important treatment goals and outcomes per cancer type and stage; this can be done through patient preference studies, robust surveys or other methodologies to collect patient experience data
Patient advocacy groups	• Advocate for the generation and use of robust evidence on treatment goals, outcome measures and patient experience data (patient preferences and PROs) of high patient relevance per cancer type and stage • Conduct, co-design and contribute to patient preference studies to help define which outcomes are most important per cancer type and stage (e.g., length vs quality of life)
Regulators	• Identify areas where survival continues to be a high unmet need, warranting continued use of OS in regulatory decision-making • Align with other stakeholders on treatment settings where there is a need to measure outcomes beyond survival, and how these should be used • Provide guidance and early scientific advice on the methodologies that stakeholders should use to generate robust evidence on oncology-relevant endpoints that will be acceptable in regulatory decision-making later
HTA bodies / payers	• Align with regulators on areas where significant weighting should continue to be put on OS in reimbursement decision-making • Align with regulators and across HTA agencies on treatment settings where there is need for outcomes beyond survival, and how these should be implemented in decision-making • Join early discussions to provide guidance and early scientific advice on the evidence required to support the use of oncology-relevant endpoints and commit to assessing this data upon submission
Industry	• Engage with clinicians and patient organisations on the generation of patient experience data (patient preferences, patient reported outcomes, real-world evidence) to identify and measure treatment goals and outcomes of high patient relevance

4.2 Select the appropriate oncology-relevant endpoints per cancer type and stage

Once stakeholders have aligned on which outcomes are most important to patients per cancer type and stage, the appropriate endpoints and / or PROs that capture these need to be selected. In instances where survival is most important, stakeholders need to assess whether OS is sufficient, or whether there is a need to identify surrogates to OS to capture survival data in a timely manner without risk of confounding. Stakeholders should also identify and implement endpoints that show ongoing benefit to patients and are more indicative of OS benefit such as time to second disease progression (PFS2).[72] By contrast, in cancer types and stages where outcomes beyond survival are most important, stakeholders need to identify which oncology-relevant endpoints best capture this value. Patient advocates and clinicians interviewed as part of this research highlighted the potential for composite endpoints, combining endpoints and PROs, as a method of improving surrogacy and to measure outcomes beyond survival to better identify the true value of a novel medicine. This benefit has recently been highlighted in prostate cancer, where studies have shown that composite endpoints, combining PROs with PFS, improved surrogacy for OS.[73] Another example of a composite endpoint used is invasive disease-free survival (iDFS) in early breast cancer adjuvant trials, which has been used in recent clinical trials and to support regulatory approval.[74,75]

> *When comparing a new medicine in a clinical trial, the investigational medicine might improve PFS but might hamper HRQoL through medicine side effects and could lead to comparable OS due to treatment burden. If PROs were used alongside PFS in this instance, this could be picked up much earlier and reduce the uncertainty about the surrogacy of this composite endpoint of OS.*
>
> European Haematology Association

> *Composite endpoints would be particularly valuable in assessing multi-medicine regimes, as using two medicines might improve PFS but lead to decreased QoL. Looking at both would allow this to be identified.*
>
> European Association of Urology

> *Collecting QoL alongside event-related endpoints is key in showing not only medicines that prolong life but those that give prolonged QoL.*
>
> Patvocates

The clinical community has a key role to play in identifying and selecting appropriate oncology-relevant endpoints due to their clinical and scientific experience. They also have a key role in explaining this scientific rationale to regulators, HTA bodies / payers and industry to ensure all stakeholders are aligned on why certain oncology-relevant endpoints are best suited to measure a certain outcome. There is a need for early involvement across stakeholders to select the appropriate oncology-relevant endpoints that should be collected per treatment setting, with a commitment from regulators and HTA bodies / payers to review data collected in accordance with these recommendations.

FIGURE 4: Action points / proposals to help selection of appropriate oncology-relevant endpoints

Clinicians / academics	• In collaboration with patient organisation, identify the most appropriate oncology-relevant endpoints that measure outcomes of high value to patients based on clinical experience • Explain the scientific rationale behind why certain oncology-relevant endpoints are best suited to measure a certain outcome to regulators, HTA bodies / payers and industry to ensure alignment
Patient advocacy groups	• Identify and communicate the patient value of specific oncology-relevant endpoints to other stakeholders • Engage with industry and clinicians at the time of study design about the selection of patient-relevant endpoints
Regulators	• Assess current evidence supporting the use of oncology-relevant endpoints suggested by clinicians and patient organisations, and align with other stakeholders (e.g., HTA bodies / payers) on those with uncertainties that need further evaluation
HTA bodies / payers	• Assess current evidence supporting the use of oncology-relevant endpoints suggested by clinicians, and align with other stakeholders (e.g., regulators) on those with uncertainties that need further evaluation
Industry	• Support clinicians in understanding the scientific basis of why certain oncology-relevant endpoints might be appropriate to measure certain outcomes

4.3 Ensure consistency of data collection

Once appropriate oncology-relevant endpoints have been identified, it is important to ensure they are measured using pre-defined and validated methodologies, taking into account the clinical and disease context. This will provide consistency in data collection and also address concerns around data reliability driven partially by high rates of missing data.[59,67] The need for consistency in methodologies has been recognised by EUnetHTA guidelines as a key driver to increase robustness and address uncertainties from HTA bodies / payers.[14]

The need to standardise the methodologies used will vary according to oncology-relevant endpoint maturity. For example, more mature endpoints like PFS are already standardised and should be collected according to RECIST guidelines.[23] For PROs, the need to standardise collection methods for specific outcomes per disease area is greater, driven by the variability of methods currently used. Additionally, there is a need for standardisation of analysis and interpretation of PRO data, as per SISAQOL (Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials) guidelines. These provide a framework to ensure that PRO data is collected in a methodologically sound way, analysed in a statistically adequate manner, and appropriately presented to ensure a high study quality and better comparability of results across clinical trials.[76] Adherence to such guidelines during clinical trials, and alignment of stakeholders on tools and methodologies per cancer type, can help to reduce uncertainties around the use of PROs and drive their adoption.

FIGURE 5: Action points / proposals to ensure consistency in data collection

Regulators	• Provide clarity on appropriate core outcomes that must be collected and methodologies to be used within a cancer type and on validation requirements for these to support approval
HTA bodies / payers	• Provide clarity on appropriate core outcomes that must be collected and methodologies to be used within a cancer type and on validation requirements for these to support reimbursement
Industry	• Ensure consistency across trials by adhering to the most current recommendations for defining and measuring specific oncology-relevant endpoints • Engage with all stakeholder groups to design fit-for-purpose instruments to collect oncology-relevant endpoints that accurately reflect patient needs and preferences
Clinicians / academics	• Advance scientific understanding of data collection methodologies for specific endpoints and PROs, and disseminate findings • Increase the adoption and standardisation of PROs used in clinical practice and document use in clinical decision-making
Patient advocacy groups	• Identify and communicate current challenges around patient experience data (patient preferences, PROs, real-world evidence) collection and how these can be addressed

4.4 Ensure appropriate evidence generation and dissemination

Once the appropriate oncology-relevant endpoints of importance have been identified and the core outcomes and methodologies for their collection defined, the evidence base supporting their surrogate or standalone value needs to be evaluated. Clinicians and industry must work with regulators and HTA bodies / payers to identify feasible degrees of correlation for surrogates and acceptable levels of uncertainty when using oncology-relevant endpoints. Where additional evaluation is required, all stakeholders should work to develop a strategy to address these uncertainties through evidence generation. It is crucial to generate evidence on the surrogate value of oncology-relevant endpoints for OS and other target outcomes, and on the standalone value of oncology-relevant endpoints beyond OS. There have been concerted efforts among patient advocacy groups, academia, oncologists, and industry to achieve this.[77,78] However, the involvement of HTA bodies / payers and regulators is needed to provide clarity on acceptable methodologies (e.g., the number of RCTs and patients required), and to agree on thresholds for correlation (e.g., by tumour type, indication, line of therapy) for these endpoints to be used in regulatory and HTA body / payer decision-making. Furthermore, there is a need for improved tools to account for confounding in analysis (e.g., multistate modelling, techniques to handle treatment switching) in order to enable a more accurate assessment of surrogacy. Such guidance on adjustment methods to account for confounding from treatment switching has been

provided by the NICE decision support unit.[79] For industry, conducting studies to better quantify the standalone value of disease-related endpoints can address uncertainties, either by formally linking endpoints to HRQoL measures, the use of real-world evidence or through collaboration with HEOR experts to assess the long-term clinical and economic benefits of improved disease control. HTA bodies / payers then also play a role in assessing the relationship between surrogate outcomes and long-term health outcomes as related to health-care service use and downstream budget implications. An initiative led by NICE, in collaboration with other HTA agencies, is working to put together guidance on the use of surrogate outcomes when analysing cost-effectiveness of novel medicines.[80]

> *Novel medicines are becoming more expensive. Further evidence linking improvements in oncology-relevant endpoints to socio-economic impact that is quantifiable will help support positive HTA body / payer decisions."*
>
> HTAi

> *It is crucial that investments are made into evidence generation to identify the value of oncology-relevant endpoints in terms of their ability to show improvements for patients, through HRQoL benefits, and more broadly through reducing cost to healthcare services.*
>
> CZ Health Insurance

Given the costs of evidence generation, upfront engagement with regulators and HTA bodies / payers and buy-in to proposed studies are recommended. Finally, stakeholders should identify appropriate conduits to disseminate findings in order to drive awareness of oncology-relevant endpoints beyond OS where evidence generation has identified and substantiated their value.

Examples of successful cross-stakeholder collaboration to address uncertainties associated with oncology-relevant endpoints beyond OS can be found in a project initiated in 2019 by Friends of Cancer Research, which brought together multiple stakeholders (industry, government, academia and patient advocacy groups) to harmonise the collection and analysis of ctDNA presence across clinical trials and to identify evidence requirements to further support the validation of ctDNA levels as a surrogate endpoint.[78] Similarly the I2TEAMM, a group consisting of oncologists, statisticians, and industry, has been set up to collect and build upon evidence for MRD surrogacy to the FDA.[77]

FIGURE 6: Action points / proposals to ensure appropriate evidence generation and dissemination

Regulators	• Increase transparency on the evidence requirements and thresholds to support regulatory approval per cancer type and stage
HTA bodies / payers	• Increase transparency on the evidence requirements to support reimbursement per cancer type/stage • Using findings from HEOR research, quantify the socioeconomic impact of improving outcomes beyond mortality and the downstream budget implications (e.g., reduced service utilisation due to reduction in pain) • Enable opportunities for risk-sharing initiatives with industry, whereby access is granted for promising medicines with a requirement for additional / long-term endpoint collection from industry
Clinicians / academics	• Generate evidence on therapy-independent patient preferences to inform the generation of evidence on oncology- and patient-relevant endpoints • Generate evidence supporting/disproving surrogacy of oncology-relevant endpoints for OS, and educate stakeholders on how and when surrogates can be used, to increase confidence in their validity
Patient advocacy groups	• Increase awareness with HTA agencies of new and effective oncology-relevant endpoints that have been scientifically validated
Industry	• Communicate with HTA bodies / payers to determine evidence generation requirements for specific endpoints • Participate in evidence dissemination, demonstrating the value of oncology-relevant endpoints as surrogates and in capturing outcomes beyond mortality • Participate in studies that quantify the long-term clinical/economic benefit of improving outcomes beyond mortality, both to patients and to the broader healthcare system • Participate in risk-sharing initiatives with HTA bodies / payers (e.g., industry-funded access to increase evidence generation) with a commitment to long-term evidence generation on the value of medicines approved based on oncology-relevant endpoints

4.5 Build a portfolio of fit-for-purpose oncology-relevant endpoints by cancer type and stage

Once the appropriate oncology-relevant endpoints per cancer type / stage have been selected, the methodologies by which to collect them have been defined, and the evidence to validate their standalone or surrogacy value has been generated, a portfolio of fit-for-purpose endpoints per treatment setting can be built. This portfolio can serve as a centralised resource, built in collaboration between regulators and HTA bodies / payers, to provide guidance on endpoints that are accepted in their decision-making processes, and under which circumstances. Stakeholders should also work to understand and define the magnitude of treatment benefit required from these endpoints for outcomes to be considered as meaningful by patients, clinicians, HTA bodies / payers and regulators. As an example, the FDA has published a table of surrogate endpoints for OS which aims to provide information to medicine developers on endpoints that may be considered and those that need to be discussed per treatment setting.[81] The proposed portfolio should include oncology-relevant endpoints that have been agreed upon by both regulators and HTA bodies / payers, both as surrogates as well as standalone measures for outcomes of high importance to patients.

FIGURE 7: Action points / proposals to help build a portfolio of fit-for-purpose oncology-relevant endpoints per cancer type and stage

Clinicians / academics	• Continually review portfolio to ensure validated oncology-relevant endpoints are updated as the treatment landscape advances
Patient advocacy groups	• Educate patient organisations, clinicians, industry HTA bodies / payers and regulators on oncology-relevant endpoints and meaningful measures to ensure alignment during discussions with other stakeholders • Continually review the portfolio to make sure it reflects outcomes of high importance to patients as the treatment landscape advances
Regulators	• Advise other stakeholders on appropriateness of oncology-relevant endpoints included in the portfolio, including how these would be considered in regulatory decisions
HTA bodies / payers	• Participate in building the portfolio per cancer type and stage, and provide clarity on how these oncology-relevant endpoints would be considered in HTA decision-making • Build awareness across stakeholders of the appropriate use case for endpoints and PROs included in the portfolio, where evidence generation supports their use
Industry	• As treatments and technologies advance, highlight to regulators and HTA bodies / payers additional oncology-relevant endpoints that have been validated and should be incorporated in the portfolio • Appropriately adopt fit-for-purpose oncology-relevant endpoints in pivotal studies

Conclusion

OS remains a robust measure of the clinical benefit of cancer medicines and continues to play an important role in regulatory, HTA body / payer and clinical decisions. However, in certain treatment settings, there is a need for measures beyond OS.

This thought piece has summarised the current challenges facing the adoption of oncology-relevant endpoints beyond OS in HTA body / payer decision-making and identified steps that can be taken to address uncertainties and ensure greater adoption. Stakeholders should align on the outcomes which are most important per cancer type / stage and identify appropriate oncology-relevant endpoints to capture those. Once identified, these oncology-relevant endpoints need to be collected via consistent tools and methodologies and evidence should be generated to address uncertainties and support their adoption. This will help to build a portfolio of fit-for-purpose oncology-relevant endpoints per cancer type and stage.

Patients need to be at the forefront when defining the outcomes of most importance per cancer type / stage. Clinicians and patient organisations will play a pivotal role in identifying the right oncology-relevant endpoints to measure patient experience and outcomes of importance based on their scientific and clinical understanding as well as on patient community insights. Regulators and HTA bodies / payers should provide guidance on acceptable methodologies to measure oncology-relevant endpoints and work collaboratively with clinicians, patient organisations and industry to agree on the evidence requirements and thresholds to support decision-making per cancer type and stage. Industry should take into consideration the endpoints and methodologies stipulated, whilst participating in and driving evidence-generation activities to identify additional oncology-relevant endpoints that better capture the value of novel medicines.

Across settings, increased adoption of oncology-relevant endpoints beyond OS in HTA body / payer decision-making can improve timely access to life-improving or life-prolonging medicines, ensure optimal outcomes for patients and reduce the potential cost to healthcare systems. Continued progress in incorporating oncology-relevant endpoints depends on the collaboration of all stakeholders to overcome barriers and to ensure that HTA body / payer decision-making can result in the best outcomes for patients.

Glossary of terms

AFP	Alfa fetoprotein, a biomarker in some cancers such as subtypes of testicular cancer and hepatocellular carcinoma
AML	Acute myeloid leukaemia
CRR	Complete response rate
CTDNA	Circulating tumour DNA
DFS	Disease-free survival
DoR	Duration of response
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFS	Event-free survival
EMA	European Medicines Agency
EORTC	European Organization for the Research and Treatment of Cancer
EQ-5D	EuroQol five-dimension scale questionnaire
EUnetHTA	European Network for Health Technology Assessment
FACT-C	Functional Assessment of Cancer Therapy-Colorectal
FACT-G	The functional assessment of cancer therapy questionnaire
FDA	Food and Drug Administration
FSFI	Female sexual function index
G-BA	Gemeinsamer Bundesausschuss (The Federal Joint Committee)
HAS	Haute Autorité de Santé (French National Authority for Health)
HCC	Hepatocellular carcinoma
HRQoL	Health related quality of life: quality of life related to disease / treatment of disease
HTA	Health technology assessment
I2TEAMM	International Independent Team for Endpoint Approval of Myeloma MRD
IIED	The international index of erectile function
IQWIG	Institute for Quality and Efficiency in Health Care, Germany
KESS	Knowles Eccersley Scott symptom score for constipation
Mature OS data	Maturity in OS is often defined by median OS, the time at which the Kaplan–Meier survival curve crosses the 50% cumulative survival probability
MFS	Metastasis-free survival
MRD	Minimal residual disease
NICE	The National Institute for Health and Care Excellence
NSCLC-SAQ	Non-small cell lung cancer symptom assessment questionnaire
ORR	Overall response rate
OS	Overall survival
pCR	Pathological complete response
PDQ	Perceived deficits questionnaire
PFS	Progression-free survival
PRO	Patient-reported outcome
PROMIS	Patient-reported outcomes measurement information system
QLQ-BR23	European organization for the research and treatment of cancer quality of life questionnaire - breast cancer specific questionnaire
QLQ-C30	European organization for the research and treatment of cancer quality of life questionnaire
QLQ-CR2	European organization for the research and treatment of cancer quality of life questionnaire - colorectal cancer specific questionnaire
QLQ-LC13	European organization for the research and treatment of cancer quality of life questionnaire - lung cancer specific questionnaire
QoL	Quality of life
RCT	Randomised control trial
RECIST	Response Evaluation Criteria in Solid Tumours: criteria acting as framework for evaluating response to a therapeutic
RFS	Relapse-free survival
SBQ	Symptom burden questionnaire
SF-36	36-item short form survey for patient-reported outcomes
SISAQOL	Setting international standards in analysing patient-reported outcomes and quality of life endpoints in cancer clinical trials
SMC	Scottish Medicines Consortium
TTM	Time to metastasis
TTNT	Time to next treatment
TTP	Time to progression

List of contributors

Interview and roundtable participants

Note: Roundtable 1 conducted in September 2022; roundtables 2&3 conducted in February 2023

Organisations	Date
Melanoma Patient Network Europe	December 2022
Lung Cancer Europe	January 2023
Cancer Drug Development Forum (CDDF)	January 2023
EVITA – Cancro Hereditário	January 2023
European Haematology Association	January 2023
Huntsman Cancer Institute	January 2023
International Myeloma Foundation	January 2023
Health Technology Assessment International	January 2023
European Association of Urology	January 2023
Europa UOMO – Voice of Men with Prostate Cancer	January 2023
CZ Health Insurance	January 2023
Patvocates	February 2023
Association of European Cancer Leagues	February 2023

Organisations	Roundtable no.
Myeloma Patients Europe	1 & 2
Lymphoma Coalition	1 & 2
Health Technology Assessment international	1 & 2
Europa UOMO	1 & 2
European Haematology Association	1 & 3
European Association of Urology	1 & 3
European Society for Paediatric Oncology	2
International Myeloma Foundation	2
Lung Cancer Europe	2
Patvocates	3

EFPIA members

Name	Organisation
Barbara Mclaughlan	Astellas
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Disclaimer: this publication is the result of a multi-stakeholder collaboration but does not necessarily reflect the views of individual organisations or people involved.

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