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Absence of comparative survival data in health technology assessment of oncology therapies

A multi-stakeholder perspective on the current challenge, implications and potential solutions

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Introduction

The past two decades have seen unparalleled scientific and therapeutic advances in oncology. Pharmacological treatment of cancer has progressed from chemotherapy and hormonal agents pre-millennium, to the use of targeted treatments, immunotherapies, and chimeric antigen receptor (CAR)-T cell therapies today (Kruger *et al*., 2019; Marshall *et al*., 2018; Saad *et al*., 2012).

Between 2012 and 2021, 169 new active substances were successfully developed for treatment of cancer (IQVIA, 2022a, FDA, 2022). In many oncology indications, patients now have access to multiple lines of therapy before exhausting all available treatment options (ESMO, 2022). With authorisation of the first oncological cell and gene therapies in 2018 (EMA, 2018), another important treatment milestone was passed representing a new chapter in personalised medicine.

Sustained innovation, coupled with earlier diagnosis, has led to considerable improvements in patient survival across several tumour types; in a study examining 1– and 5–year survival rates in nineteen countries from 1995–2014, improvements were seen in each country and across almost all cancers studied (Arnold *et al*., 2019). A significant, sustained decline in cancer mortality rates over the last 30 years has also been recorded by the US NIH SEER database (NIH, 2022).

In some cases, progress has been especially remarkable. For example, it has been estimated that in 2020 alone, 400,000 prostate cancer deaths were averted in the European Union (EU) as a result of downward trends in mortality between 1988 and 2020 (Carioli *et al*., 2020).

Advances in both the number and efficacy of cancer medicines have had important implications for research and development, making it increasingly challenging to quantify overall survival (OS) gains in a clinical trial context. Reasons for this can be divided into three broad categories (described further in Table 1): (i) evolution of cancer from a terminal to a chronic disease (chronicity); (ii) confounding effects of subsequent lines of treatment; and (iii) ethical or feasibility challenges as barriers to conducting randomised-controlled trials (RCTs) (Dima *et al*., 2020; Haslam *et al*., 2018; Knipper *et al*., 2021; Kurzrock *et al*., 2013; Panageas *et al*., 2015; Saad *et al*., 2010). It should be noted that these categories are not mutually exclusive and can apply alone, or in various combinations.

As a consequence, in a number of settings, demonstrating OS benefit with a mature, controlled dataset is now intrinsically difficult or unfeasible – within a reasonable timeframe – ahead of regulatory or health technology assessment (HTA) (Dima *et al*., 2020; Haslam *et al*., 2018; Panageas, 2015; Wilson *et al*., 2015).

Reason	Description	Example	Ref
Chronicity	Situations in which successive treatment innovation has driven substantially increased life expectancy, and thus, time required to demonstrate OS benefit.	In newly diagnosed multiple myeloma, sustained innovation and development of highly effective novel treatment combinations with synergistic mechanisms of action has led to significant improvements in disease progression and response rates and OS. The addition of additional treatments and combinations is anticipated to extend OS even further, and likely beyond a reasonable timeframe of a clinical trial.	Dima *et al.,* 2020
	In certain cancers or disease settings for which disease progression may take many years.	In settings such as localised prostate cancer**,** where the intention of new treatments is to cure patients, the necessary duration of follow-up required can be >10 years.	Knipper *et al*., 2021
	Settings where multiple lines of life-extending therapy can be given following disease progression on the initial treatment.	Due to the growing number of active treatments and associated combinations in advanced breast cancer for example, it has become increasingly difficult to detect an OS benefit for a given drug. In such cases, it is extremely difficult to determine the relative contributions of each component of the therapeutic pathway to any observed gains in OS. Assessment of OS may also erroneously suggest the treatment of interest provides no additional benefit, as patients receive further treatments which also extend life.	Saad *et al*., 2010
Confounding	Situations in which there is substantial crossover during clinical trials.	Incorporation of cross-over in therapeutic trials in oncology can be an ethical requirement in certain settings, or can simply reflect best clinical practice. Patients switching from the control to experimental arm has a confounding effect on study endpoints, including OS.	Haslam *et al*., 2018
Ethical or logistical barriers to conducting RCTs	Settings in which conducting an RCT presents ethical challenges.	When a treatment represents a medical step-change in treatment benefit (e.g., early evidence of an unprecedented objective response rate) in an area of high unmet need, clinical equipoise is lost and it is not considered ethical to conduct a randomised Phase II/III study.	Kurzrock *et al*., 2013
	Settings in which conducting an RCT presents feasibility / technical challenges.	In rare cancers or patient populations stratified according to a highly specific biomarker, conducting an RCT may not be feasible, due to the low numbers of eligible patients.	Panageas *et al*., 2015

Table 1: Common reasons for lack of OS data in oncology trials.
OS, overall survival; PFS, progression-free survival; RCT, randomised control trial

Although OS remains the most strongly preferred outcome for both regulatory and HTA in oncology (Sola-Morales *et al*., 2019), regulatory agencies have responded comparatively quickly to the increasing need to assess the benefit of cancer medicines using a broader range of endpoints. Between 2017 and 2020, for example, approximately two in three European Medicines Agency (EMA) marketing authorisations for oncology therapies were granted without data demonstrating controlled, statistically significant OS benefit (Janssen, data on file). In such cases, authorisation was most commonly granted based upon progression-free survival (PFS) or overall response rate (ORR) instead (Kordecka *et al.*, 2019) – metrics typically available in a shorter timeframe than OS. By comparison, such intermediate outcomes are less readily or consistently accepted for use in pricing and reimbursement (P&R) decision-making (Kleijnen *et al*., 2016).

These differing evidence requirements are explained, at least partially, by the fundamentally different sets of questions that the agencies must answer. Whilst regulators are required to provide a binary yes/no decision on the acceptability of the risk versus benefit ratio, HTA agencies must also assess comparative efficacy, cost-effectiveness, and affordability within a wider context of constrained resources. Robust OS data is of clear value to HTA agencies because it is objective, quantifiable, and of unambiguous clinical and patient-relevance. Mature OS evidence enables assessment of the magnitude and certainty of clinical benefit in order to inform reimbursement decisions (Lux *et al*., 2021). Notably, OS data are necessary for the calculation of quality adjusted life years (QALYs), a metric relied upon by some HTA agencies to assess and compare the value offered by medicines within and across disease areas (Whitehead *et al*., 2010).

In the absence of mature OS data from RCTs, negotiations between marketing authorisation holders and payers can be complex and lengthy. This can contribute to substantial delays to patient access (EFPIA, 2020), during which time eligible patients are often unable to gain access to treatments from which they may benefit.

Disparities also exist among European HTA agencies in the rigidity of their requirement for OS data, giving rise to variability in time to reimbursement (EFPIA, 2020; Wilking *et al.,* 2019) and eventual coverage decisions (Adkins *et al*., 2017; Nicod *et al*., 2012) across countries. As a result, inter-country inequalities in access to innovative cancer medicines can be considerable, with implications for patient outcomes (EFPIA, 2020).

This is clearly an important and pressing issue, as illustrated by the wealth of literature published on the topic (Sola-Morales *et al*., 2019; Quinn *et al*., 2015; Wilking *et al*., 2019; Zhuang *et al*., 2009). There is, however, a lack of pragmatic, comprehensive recommendations to address the current challenges.

In this work, a multi-disciplinary panel of expert stakeholders with a range of perspectives on this issue was assembled. The panel was comprised of clinicians, patient representatives, regulatory and HTA experts, drawn from a range of large European healthcare and HTA systems (France, Germany, Italy, Spain, the UK, EU-level patient organisations).

A facilitated roundtable meeting was held in March 2020 in order to: (i) explore OS-related evidential uncertainty in regulatory and HTA decision-making in oncology, and (ii) to make consensus recommendations on how to best ensure timely, equal and affordable access to cancer medicines in Europe. Potential solutions were put forward by the facilitators, and discussions were structured to elicit an assessment of the impact, feasibility, and desirability of each potential solution from the perspective of all stakeholder groups represented, as well as key considerations for their implementation. Meeting outputs were supplemented by a targeted review of the published and grey literature, prior reimbursement submissions and outcomes, and EMA, U.S. Food and Drug Administration (FDA), and pan-European HTA guidance on methodology in cancer therapeutic trials.

Given the complexity of this topic and the diversity of stakeholder perspectives, there can be no single solution to the fundamental trade-off between timely patient access and evidential certainty. Instead, adaptations are needed throughout the development and approval process, designed to better mitigate and manage uncertainty in the absence of mature survival data.

Outlined on the following pages are five key recommendations proposed and collectively refined by our expert panel, presented in chronological order according to the phase of product development, approval, or commercialisation that they are intended to address.

Pre-approval (clinical development)

Establish clearly defined, context-specific expectations regarding acceptable levels of evidence with incorporation of appropriate, patient-relevant endpoints

Consideration of the wider clinical context is critical in regulatory and HTA decision-making, informed by an array of factors including treatment objectives, line of therapy, disease stage, level of unmet need, and target patient population.

For example, in disease settings such as pancreatic cancer, a particularly aggressive and life-threatening malignancy with an average life expectancy of 10–12 months (Principe *et al*., 2021), OS is readily quantifiable in clinical trials and remains of primary relevance (Sola-Morales *et al*., 2019). Accordingly, OS was used as the primary endpoint in all but one of the pivotal trials for approved therapies (Pink Sheet, 2019).

Conversely, in advanced breast cancer, where OS is less readily quantifiable due to the effects of subsequent therapies, PFS is the most frequently used endpoint in Phase II and III trials (Seidman *et al*., 2020; Song *et al*., 2016).

What is missing, among these varied situations is any clear, consensus definition of what constitutes acceptable and relevant evidence within a given disease setting, pre-agreed among all parties concerned and aligned with treatment objectives. As described above, this can result in mismatched expectations, unpredictable or inconsistent decision-making, protracted negotiations, and substantial inter-country variability in patient access.

Resolution of these issues is becoming increasingly pressing; with 'cure' now the next frontier in the treatment of many cancers, agencies will increasingly need to assess cancer medicines with curative intent, including emerging cell and gene therapies.

Well-defined, harmonised evidential expectations between marketing authorisation holders, regulators and payers would act to increase consistency, transparency, and uniformity in the review process, whilst guarding against incentivisation of possible inferior clinical trial design and/or a general lowering of standards.

In accordance with recent EMA guidance (EMA, 2020), proper design and analysis of studies should begin with clear delineation of:

- The clinical question (i.e., what stakeholders need to learn about the effects of a treatment)
- The 'estimand', or treatment effect of interest, which should take into consideration the therapeutic setting (for example, line of therapy, and availability of other treatments that influence patient outcomes) and the therapeutic intent

We would also propose the development of a general framework that captures the essential characteristics of settings in which particular rules or standards would apply. This would have parallels to existing, proposed checklists for gene therapies (Drummond *et al.,* 2019), likewise designed to increase consistency and transparency in HTA.

Framework categories would be centered around settings in which it is challenging or unfeasible to demonstrate OS (outlined in Table 1). Key disease and therapy-related modifiers, including unmet need, treatment objectives, line of therapy, duration, and magnitude of therapeutic effect, would be incorporated. Existing EMA/European Network of HTA (EUnetHTA) parallel consultation procedures could feasibly be harnessed to ensure alignment on output recommendations for endpoints and/or trial design.

Though achieving a consensus across multiple stakeholder groups likely represents a challenge given divergent opinions on this topic, there is precedent for similar initiatives; Tapestry Networks has previously coordinated multi-stakeholder consultations involving regulators, HTAs, patient representatives, clinicians, and pharmaceutical companies from across Europe (Fronsdal *et al*., 2012). Among HTA bodies, EuNetHTA has developed a value framework to enable transparent structures, procedures, and standards for handling evidence and information in HTA across institutions and countries (EuNetHTA, 2016). These wider changes to systems and processes of evaluation would provide an opportunity to standardise and formally incorporate elements of value most important to patients. Such metrics, including quality of life (QoL), are often considered to be undervalued and under-represented in many national P&R decision-making processes (Kleijnen *et al*., 2017). In the case of QoL, this has been ascribed to lack of robustness and/or availability of data (Fiteni et al., 2014; Wilson *et al*., 2015). In any instance, however, pending issues could be addressed and resolved during development of assessment frameworks described above.

Increase alignment on the validation and weighting of appropriate patient and disease-relevant surrogate and intermediate endpoints

Surrogate and intermediate endpoints – those that measure treatment effects on biological and clinical measures other than OS – are increasingly important in situations where data on the long-term value (survival gains) are pending, or where there is an inability to generate these data (Brooks *et al*., 2017).

However, this is an inherently complex topic, with the appropriate selection and usage of these measures (Kemp *et al*., 2017), and the predictive value of surrogates all representing significant points of contention among payers, regulators, and marketing authorisation holders.

Of note, there is still no uniform, consensus approach to the validation of surrogate endpoints, despite three decades' worth of discussion and debate on this topic (Prentice, 1989; Grigore *et al*., 2020; Zhang *et al*., 2019). Furthermore, where surrogates *are accepted* as valid, this is generally only for a relatively narrow context, specific to the treatment modality and disease setting. This can represent a significant hurdle, especially in the case of new modalities, where it is near-impossible to have OS data. These complexities were well-recognised among the expert panel, from which three key issues were identified:

(i) A binary and narrow statistical approach to endpoint validation ('valid' / 'not valid'), and hence, also to the assessment of clinical benefit ('demonstrated' / 'not demonstrated').

(ii) Lack of consensus among stakeholders on whether, beyond utility as predictors of OS, outcomes such as durable response or delayed progression could be considered patient-relevant in their own right. For example, the EMA does not refer to these endpoints as 'surrogate' or 'intermediate' because in the regulatory process, they are recognised as stand-alone patient-relevant endpoints.

(iii) Variability between HTA agencies in their approaches to surrogate endpoints, resulting in a lack of harmonised policies and guidance among these agencies and regulators.

In order to address these challenges, a series of recommendations were proposed:

- A broad (recognising inherent clinical importance, in addition to predictive power) and non-binary (incorporating both statistical and non-statistical approaches) approach to the assessment of surrogate endpoints:
  - Greater recognition (where relevant) of the innate clinical- and/or patient-relevance of measures that might be considered surrogate endpoints, and thus their value beyond predictive performance alone. For example, though regarded in some instances as a surrogate for OS, discrete choice experiments across a range of cancers indicate PFS and objective response rate are of considerable intrinsic value to patients and caregivers, independently of any relationship with OS (Liu *et al*., 2019; MacEwan *et al*., 2019; McKay *et al*., 2018).
  - A shift away from a binary 'yes/no' approach to validation of surrogate endpoints, towards a probabilistic assessment of predictive validity (Bujkiewicz *et al*., 2019). Rather than determining the acceptability of an endpoint by whether it has met a pre-specified threshold for level of association with OS, validity could be considered in a more holistic manner, weighing the level of association, availability, and quality of evidence to inform that association, effect size on the endpoint, and the overall clinical uncertainty. Where available, real-world evidence (RWE) could provide a valuable additional source of information towards proof-of-concept.
  - Consideration of non-statistical information when assessing whether a surrogate is likely to translate into OS benefit; for example, based upon an understanding of how an intermediate endpoint fits within the underlying disease model.
- Greater patient involvement in the selection, development, validation, and interpretation of endpoints, with particular consideration given to their treatment preferences and expectations.
- Increased effort towards harmonisation of approaches to surrogate endpoint evaluation across HTA agencies, and ultimately also between regulators and HTAs.

Make greater use of biomarkers and diagnostics

Biomarkers and diagnostics could also play a greater role in interpreting the value of new medicines. Used in combination with data provided by other clinical endpoints, well-validated biomarkers or diagnostics tailored to treatment mechanisms of action represent valuable additional sources of information. Specifically, these can aid in understanding whether certain sub-groups of patients respond particularly well to treatment, and reduce overall evidential uncertainty by:

- Increasing the magnitude of treatment effect within pre-selected, biomarker-defined patient populations, potentially including early OS signals. Historically, payers have been more likely to accept uncertainty in evidence if this is offset to some degree by a large treatment effect size. This has been illustrated by the recent positive reimbursement decisions for CAR-T therapies on the basis of very high stringent complete response rates, and in spite of non-comparative trial data (Seimetz *et al*., 2019).

- Providing additional mechanistic evidence to support and supplement a proposed 'endpoint model' of how disease or drug mechanism of action works, and hence instilling confidence in the likely downstream benefit. For example, via serial measurement of biomarker(s) that reflect underlying changes in the status, processes, or extent of disease (a category known as monitoring biomarkers), such as minimal residual disease (MRD).

- Reducing the risk of adverse events (AEs) by selecting only patients who are likely to benefit, therefore further enhancing the overall benefit-risk profile for both payers and regulators, and increasing the willingness and likelihood of reimbursement whilst further data is collected for all patients.

As a further consideration, prospective identification of patients who are most or least likely to benefit from a therapy or who might suffer adverse events, may also serve an important purpose in mitigating budget impact and improving patient outcomes, with likely implications for payers' inclination to reimburse.

There is undoubtedly momentum in this direction, with the use of biomarkers to stratify likely responders to therapy now featuring in 39% of oncology trials, up from 25% in 2010, reflecting a more widespread use of precision medicine approaches (IQVIA, 2019).

To caveat, however, it is important to consider that in practice the situation is unlikely to be as simplistic as a single biomarker to unfailingly predict (non)response. Similarly, it is unlikely that we will be able to identify biomarkers for all cancers or treatments, and the utility of these is also shaped by the mechanism of action of the treatment, and heterogeneity in disease and patient responses.

While increased use of biomarkers or diagnostics require robust validation and may involve added expenses in additional studies and clinical trials, their accurate application may prove beneficial for interpreting the value of new medicines.

Regulatory and HTA approval

Pursue an iterative (adaptive) approach to HTA, incorporating outcomes-based reimbursement

The EMA and FDA have several tools at their disposal to revisit and reappraise decisions after approval, once additional data have been generated. These include Accelerated Approval and Conditional Marketing Authorisation (CMA).

Amongst HTA agencies, however, analogous mechanisms are generally less well-developed. Some European countries conduct mandatory price re-assessments at specific time points, but these are typically not designed to review the evolving evidence base in a systematic fashion. For example, in France, price is renegotiated at 5-year intervals, but re-appraisal of clinical benefit is not necessarily a major part of this process (Emanuel *et al.,* 2020).

Recently, there has been movement in the direction of more adaptive P&R processes. The Cancer Drugs Fund, originally introduced in England in 2011, was later reformed to enable NICE to provide conditional funding for new oncology medicines in situations where: (i) significant clinical uncertainty exists; and (ii) this could potentially be addressed by further data collection or clinical studies (Sabry-Grant *et al*., 2019). In Germany, the recent law 'for greater safety in the pharmaceutical supply' gave the Gemeinsame Bundesausschuss (G-BA) the power to require further studies after initial Arzneimittelmarkt-Neuordnungsgesetz (AMNOG) assessment, with a re-assessment after two years (EUCOPE, 2019). In France, the Haute Autorité de Santé (HAS) has proposed greater use of conditional evaluations in which data collection is mandated alongside frequent re-assessment. Similar processes have also been introduced in Spain and the Netherlands (HAS, 2020).

A continuation and expansion of this trend could help to resolve some of the current issues surrounding OS uncertainty in HTA. Where appropriate, wider adoption of adaptive methods would afford payers greater flexibility in decision-making, providing valuable additional mechanisms to deal with uncertainty in clinical- or cost-effectiveness. Financial risks associated with early access, and funding of higher cost therapies on the basis of immature and uncertain OS benefit, would be more evenly shared between payers and marketing authorisation holders, with opportunities to reappraise value or terminate agreements if longer-term benefit is not as expected. However, there are some important considerations for effective implementation, as outlined in the following paragraphs.

The need for an iterative approach via adaptive approval pathways would not be warranted in all cases, and several factors should be weighed when considering whether this would be appropriate. These include: (i) the level of clinical and economic uncertainty; (ii) the expected magnitude of the treatment effect; and (iii) the resources required to implement the evidence generation program. For example, in situations where clinical and/or economic uncertainty is low, significant efforts from marketing authorisation holders and payers are unlikely to be justified. By contrast, where uncertainty is higher, yet the potential benefit of expedited patient access is also high, it may justify additional investment.

Frameworks designed to gauge the suitability of alternative approval pathways within a given context already exist (Walker *et al*., 2012). These could readily be applied here in order to ensure transparency and objectivity when making these decisions.

For marketing authorisation holders – who are often required to generate new evidence – clarity on the likely requirement for adaptive processes is necessary early on, as new studies have long lead times. Such requirements are context-specific, but it might be valuable to create an agreed basic framework that could provide guidance on the suitability of adaptive pathways in certain circumstances, depending upon the balance of these factors.

Adaptive pathways also raise a fundamental question about the initial allocation of value and risk between payers and marketing authorisation holders. If the ultimate benefit of treatment is not yet definitively known at the time of first appraisal, and instead sits within a spectrum of possible value, whether P&R negotiations should assume the best case, worst case or somewhere in between is an unresolved and potentially contentious question. Marketing authorisation holders would clearly like the initial price to reflect the best-case potential outcomes; payers the opposite. Existing approaches also tend to involve risk being shifted entirely to the health system or to the company (Thanimalai *et al*., 2021). Work is therefore needed to move towards a system which ensures more appropriate sharing of risks and rewards.

Further development and clarity around risk-sharing agreements would provide greater confidence and trust between both parties on the size and direction of future adjustments. Success of adaptive processes would also rest heavily on the robustness of systems in place for additional long-term data capture, described on the following pages.

Post-approval

Engage in long-term data capture (including real world evidence), with clarity and accord on appropriate and acceptable methodology and data collection requirements

Though in some cases OS may not be a feasible or practical primary endpoint in a clinical trial setting, this is not to suggest that these data are not of interest or relevance to HTA decision-making.

Data capture over an extended time horizon – including RWE – would provide more information on the longer-term relative value of a new treatment once these data become available i.e., once sufficient morbidity and mortality events have been observed. Equally, in situations where RCTs are not feasible, long-term data would present a potential solution to uncertainties associated with the lack of comparative data. This could include, for example, rare cancers or biomarker-stratified populations where the pool of potential clinical trial participants is very limited. In the presence of confounding due to cross-over in clinical trials, RWE could also have a role in informing OS analysis. Coupled with adaptive HTA processes, this would enable more informed decision making than any attempt to estimate and extrapolate likely morbidity and mortality outcomes based on very limited absolute observations at the time of the initial relative efficacy assessment (REA).

Critical to the success of this initiative would be an advance agreement on a robust methodology to ensure real-world data are unbiased, of high quality and address a well-defined research question. Beyond data capture alone, it will also be important to clarify exactly how data will be used to derive reliable, unbiased estimates of treatment effect that can be used in P&R decision-making. This is likely to be challenging, and post-marketing studies for vaccines represent a possible blueprint for this approach (Enerly *et al*., 2020). In addition, given the pivotal role for physicians in this process, their willingness and ability to provide ongoing feedback into the system would be vital if this approach is to be successful.

Variability also exists across Europe in the infrastructure to enable data collection; this has been cited as one of the main barriers to implementation of outcomes-based reimbursement of cancer medicines (Michelsen *et al*., 2020). Many local systems remain insufficiently equipped to track drug use by indication and patient, and to link this to response and other longer-term treatment outcomes. Identification of reliable data sources that can systematically capture and report information, and which can be trusted by healthcare providers, HTA agencies, and payers is urgently required.

There is also a need to improve the consistency of data collection requirements between countries and – ideally – to collect data at the cross-country level. Such collaboration increases the efficiency of data collection and quality of the evidence that is generated. However, to date, countries have usually stipulated independent (and often substantially different) evidential needs. Multi-stakeholder guidelines on best practice for generating RWE and pooling data between countries (and between payers and regulators) may help payers to become more comfortable incorporating these data into adaptive processes.

Finally, there must be a willingness among HTA agencies to accept the type of information generated from RWE, including data from cross-over adjusted analysis. Agencies must also be able to interpret and incorporate RWE in their processes and approaches. Non-RCT data currently have only a relatively minor impact on P&R decision-making in some European systems. For example, in Germany, IQWIG and G-BA have traditionally taken a conservative approach to evidence from non-RCTs, preventing attainment of the highest benefit rating in the absence of RCT data (Ivandic, 2014).

However, as an example of recent progress in this direction, recent updates to the methods guidance by NICE will consider a broader range of data, including RWE and electronic health records (NICE, 2020, 2022). Draft guidance on the use of RWE in regulatory decision making was also published by the FDA in December 2021 (FDA, 2021), reflecting growing interest in the integration of real-world data and RWE into clinical research, authorisation and post-approval monitoring of new medicines.

Ongoing advances in the statistical literature, coupled with EU-level initiatives, such as the Innovative Medicines Initiative (IMI) GetReal (IMI, 2021), have the potential to further drive the adoption of tools, methodologies, and training necessary for more widespread, uniform use of RWE in regulatory and reimbursement decision-making.

Where do we go from here?

With parallels to prior advances in the treatment of haemophilia (Mannucci, 2020) and Human Immunodeficiency Virus (HIV) (Deeks *et al*., 2013), certain types of cancer may one day be viewed as chronic conditions. Improved and expanded treatment options could allow patients to remain stable for prolonged periods, possibly even amounting to a functional 'cure'. In this scenario, OS may not be a relevant parameter for the purposes of regulatory or HTA assessment.

Alongside this, we are also likely to see a continuation of efforts by regulators to accelerate access to innovative treatments in certain settings; for example, where unmet need and disease severity are high. This is signposted, for instance, by a steady growth in the number of oncology therapies granted conditional marketing authorisation by EMA (Martinalbo *et al*., 2016) and/or approval on the basis of evidence other than OS (Janssen, data on file).

As a result, it is probable that a steady or growing number of oncology therapies will be approved with only limited mature survival data and/or a lack of comparative trial data. Altogether, the challenges we outline in this article will become only more pressing over the coming years, with a growing need to find practical, and feasible solutions such as those we describe.

In considering implications of these trends for HTA agencies and marketing authorisation holders, their potential responses and likely outcomes, the recent reimbursement of oncological CAR-T therapies in Europe represents an interesting case; in spite of relatively limited evidence packages, including single-arm data, small trial sizes, immature OS data and the use of response rate endpoints (Jorgensen *et al*., 2020; Cerrano *et al.,* 2020), solutions were found between parties to make these therapies available to patients as rapidly as possible (Jorgensen *et al*., 2020).

The way in which this was achieved could serve as a blueprint for subsequent negotiations and reimbursement terms (where appropriate). For example, though agencies arguably showed a greater flexibility in interpretation of evidence (e.g. a willingness to accept evidence from well-conducted indirect treatment comparisons (Jorgensen *et al*., 2020)), crucially this flexibility was matched by marketing authorisation holders in their approaches to pricing and risk-sharing (Reuters, 2017). Outcomes-based agreements could also pioneer greater use of similar deal structures, RWE and/or more iterative approaches to HTA in future.

However, whether precedents set by CAR-T therapies (and a small number of other specific instances) will translate to a more general expansion in the use of these methods and approaches remains to be seen. This will depend, at least to an extent, on how successful and viable they ultimately prove to be for all parties involved.

Nonetheless, recent policy developments in the UK (Adler *et al.,* 2018), Germany (Evidera, 2019), France (HAS, 2020), Italy (Xoxi *et al*., 2012) and Spain (MSCBS, 2019) would suggest a trajectory towards greater use of innovative payment schemes and/or RWE systems across Europe.

Finally, in terms of likely trends in the usage of biomarkers, diagnostics, surrogate and intermediate endpoints as supplementary sources of information to reduce evidential uncertainty in the absence of mature OS data, there is clear evidence of the growing interest of marketing authorisation holders and investment in this area (IQVIA 2022b). Nonetheless, development of infrastructure for data capture, analysis or bioinformatics could prove to be rate-limiting. Whilst promising increases in the use of biomarker-informed care have been seen (Wilson *et al.,* 2018), current evidence in terms of clinical utility (Parkinson *et al*., 2014) and value for money (Scott*,* 2010) also remains variable.

This is a complex topic, with no simple solution and broad implications for drug development and assessment. Through appropriate dialogue, collaboration and joint problem-solving among stakeholders, progress towards timely and sustainable patient access to the most effective cancer medicines should be possible across Europe. This will require concerted activity from all parties, but given the promise of the technologies now coming to market and the remaining unmet need in cancer, such efforts are both worthwhile and necessary.

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