Closing the Gap: Early Access and Uncertainty
The Preparation Earmark, The Choice of Analytical Tools, and Data Needs

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Increasing uncertainty with early access

Uncertainty is always part of the drug development process, with limited clinical knowledge and a changing environment in both the treatment and payer landscapes. Delivering a molecule as early as possible to patients further limits the opportunities to collect information, emphasizing the importance of assessing, addressing, and planning for uncertainties. Hence, using the right analytical tools is crucial. These should help identify and assess the importance of these uncertainties, allowing attention to be focused on evidence substantiating the most essential patient benefit.

At the same time, the external environment into which drugs are launched is also changing. Healthcare reforms are initiated and implemented in far less time than it takes to develop a pharmaceutical asset; the emphasis on value is increasing, and competitors are equally seeking an earlier and earlier launch. Thus the discussions on value development plans need to be framed by the limited information of the clinical benefit (e.g., mature data on the outcome of interest, such as overall survival) and the future payer requirements, focusing on a more integrated approach to convey value and differentiation, and to align on a value proposition that can be substantiated to meet potential pricing and reimbursement requirements.

New market access approaches aiming to deliver earlier access, such as conditional marketing authorization as seen in Medicines Adaptive Pathways to Patients (MAPPs), are shifting the focus not only on a more integrated approach of licencing and pricing and reimbursement (P&R), but also on the uncertainties and flexibility in the face of the continuously developing evidence base. Adaptive market access should be based on adaptive evidence development and flexible tools incorporating the changing evidence base.

The need for uncertainty management is not new

When anticipating P&R outcomes in the development process of new pharmaceutical products, the sources of uncertainty can be identified and managed, depending on the complexity of the molecule and the level of incongruity of the environment. Appropriate analytical forecasting tools can be used to identify the best course of action to narrow uncertainty, and actions can be determined, such as missing data can be collected according to existing and anticipated payer requirements.

A critical factor in the management of uncertainty is the time involved in the development of a molecule from Phase 1 to completion of Phase 3. Potential sources for uncertainty can be monitored and assessed during that time. However, if a molecule is developed via an expedited process (e.g., launch and market access at Phase 2 or earlier), it is confronted with a triple challenge in managing uncertainty: less time to identify and plan for uncertainties, new uncertainties due to incomplete data, and the need for new, innovative tools and pathways to manage these uncertainties.

Different situations imply different levels of uncertainty in the development process. In the case of an indication with limited competitors on the market for the targeted population, or line of therapy, and no new competing developments under way, there is limited incentive for earlier access. Thus, the development of the standard clinical plan can be completed. Nevertheless, there may still be uncertainty about the price potential of the molecule, and unexpected changes may still happen in the health policy environment.

In other situations, the molecule may be developed in parallel with competitors, racing for first-in-class status. In this case, reducing the time spent in development and applying for early access opportunities can be crucial. This can result in a shorter development process, potentially less conclusive data on patient relevant endpoints, and a not fully conclusive safety profile, increasing the uncertainty in both clinical and health economic value stories. Since this is increasingly prevalent in advanced oncology, a short example showing the potential sources of uncertainty in the data and the currently used solutions are described below.

Sources of uncertainty

Turning towards early access limits the time and the resources for collecting data. In oncology, this often manifests through the use of Phase 2 trial data, a shorter follow-up period, use of surrogate outcomes, and reduced potential for data collection outside the clinical trial program, leading to immature data, cross-over designs, single arm trials, limited comparators, and lack of quality of life (QoL) data (see Figure 1). This limited data, though increasing uncertainty, does not necessarily affect the decision making.

Figure 1. Trial design situations for early regulatory access create uncertainty and significant challenges for health technology assessment (HTA) and pricing and reimbursement
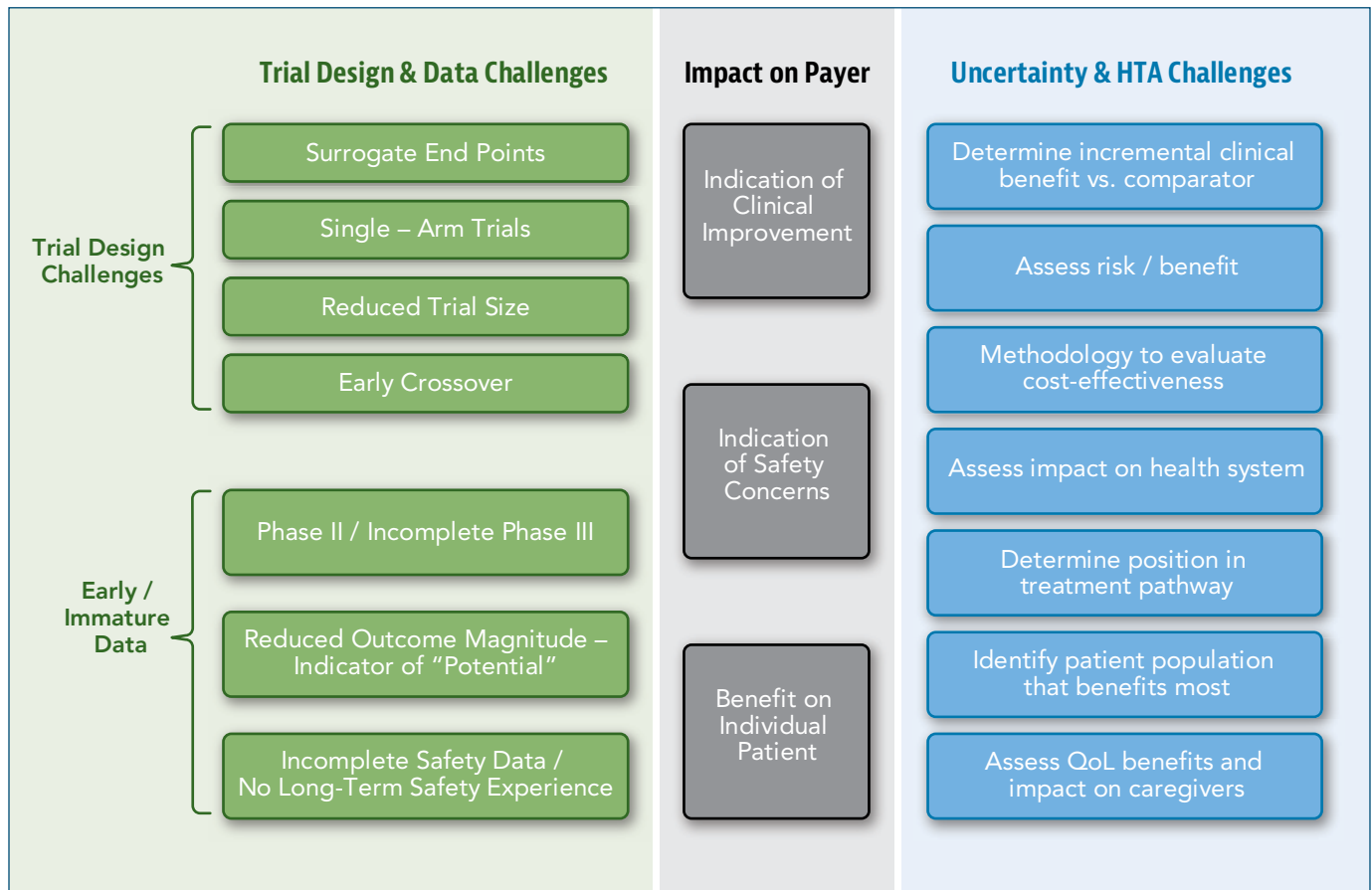
Table 1. Oncology technology appraisals by NICE after conditional marketing authorization

Brand Name	Generic Name	Therapeutic Area	HTA Number	Duration (Months)
Votrient	Pazopanib	Renal Cell Carcinoma	TA215[1]	~10
Xalkori	Crizotinib	Lung Cancer	TA296[2]	~9
Bosulif	Bosutinib	Chronic Myelogenous Leukemia	TA299[3]	~ 8.5
Pixuvri	Pixantrone	Non-Hodgkin's Lymphoma	TA306[4]	~ 27
Pomalyst	Pomalidomide	Multiple Myeloma	TA338[5]	~8.5
Zydelig	Idelalisib	Chronic Lymphocytic Leukemia	TA359[6]	~10

In the UK, the National Institute for Health and Care Excellence (NICE) has evaluated six drugs to date after conditional marketing authorization (see Table 1). As NICE has the most complete documentation of the appraisal submissions and review documents, these were reviewed to assess the sources of uncertainty mentioned in the descriptions of the appraisal and the decision.

As expected, these highlight that, in the face of limited clinical evidence, the greatest uncertainty in the oncology health technology assessments is presented by the estimation of progression-free survival (PFS), overall survival (OS), and the relative treatment effect. In the assessment documentation, treatment duration was also indicated to have high levels of uncertainty in half of the assessments (3 out of 6) (see Figure 1). In all cases, the uncertainty of relative effectiveness was emphasized as contributing to the decision making, with the uncertainty of PFS/OS estimates following closely behind. In the majority of cases, the decision was driven mostly by these two estimates, balancing the cost-effectiveness by reduction in costs through patient access schemes. Based on the documents, there were no extra stipulations or allowances for early access drugs, allowing the assumption that the same criteria and expectations are used as with drugs with fully executed development programs.

Levels of uncertainty

Even the most uncertain business environments contain a lot of strategically relevant information. First, it is often possible to identify clear trends or learnings from previous assessments of molecules that underwent early access or faced a similar situation that can help identify potential payers' expectations. Second, there

is usually a large amount of information that may not be currently evaluated but can be assessed with the appropriate analyses.[7] Good examples could be the implicit assessment criteria for early access molecules or long-term survival in a disease area where the clinical trials were short-term and terminated early. Appropriate analysis may reveal important insights, and the level of uncertainty may be shifted to a manageable degree.
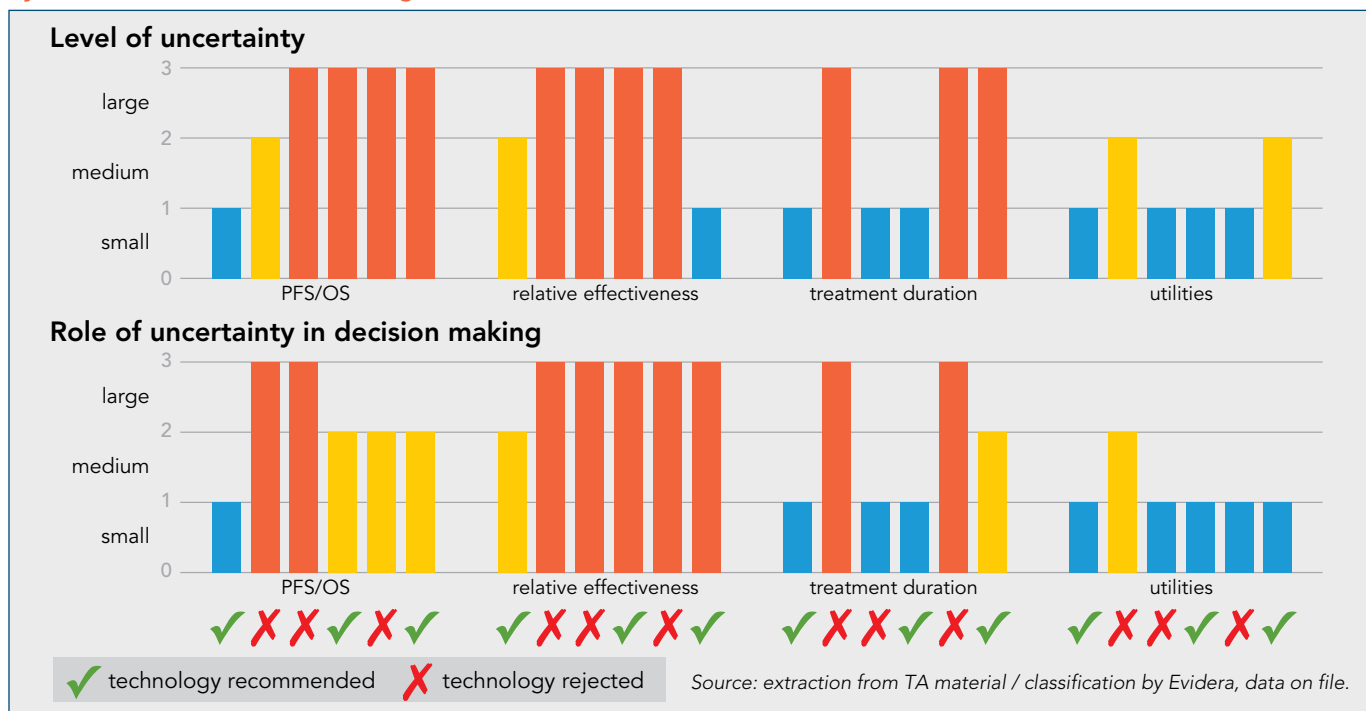
The uncertainty that remains after the best possible analyses have been done is, what Courtney calls, residual uncertainty[7], such as the outcome of an ongoing payer debate on modifying assessment or value criteria. Courtney, et al., argue that even these residual uncertainties are not so uncertain and fall into four broad levels according to their relevance to strategic decision making.

- Level 1: A Clear-Enough Future
- Level 2: Alternative Futures
- Level 3: A Range of Futures
- Level 4: True Ambiguity

Market access situations can also be categorized into these four levels, and a potential course of action can be selected according to this categorization. In the following section, we demonstrate each with an example of a potential situation for an early access molecule.

The mitigation strategies for level 2 and 3 uncertainty around the long-term overall survival – not only for the treatment of interest, but also, for relative effectiveness versus the comparator(s) – require extensive statistical analyses of the trial data. Supplementing trial data by

Figure 2. Level of uncertainty of key parameters and their role in decision-making among oncology technology appraisals by NICE after conditional marketing authorization

✓ technology recommended　✗ technology rejected　*Source: extraction from TA material / classification by Evidera, data on file.*

Summary of Approaches: Level 1 – A Clear-Enough Future

"At level 1, managers can develop a single forecast of the future that is precise enough for strategy development. Although it will be inexact to the degree that all business environments are inherently uncertain, the forecast will be sufficiently narrow to point to a single strategic direction. In other words, at level 1, the residual uncertainty is irrelevant to making strategic decisions.[7]"

Clear-Enough Future

Table 2. Example for Level 1 residual uncertainty – A Clear-Enough Future

A hypothetical situation	Molecule performance outcomes and evidence of meeting payer assessment criteria are available; market is well defined with very few competitors; and, therefore, the price potential is predictable within margins and competitor performance. Risk sharing and patient access schemes can be planned.
Analytic tools	Forecast can help determine the price that will maximize the chances of market access
Examples	Orphan molecules (for the time being) with few competitors; later lines in oncology with OS data (excluding non-immuno-oncology molecules)
Applicable to early access molecules	Not really, as it requires sufficient information from full clinical development programs
Payer requirements for P&R known	Yes

Summary of Approaches: Level 2 – Alternative Futures

"At level 2, future can be described as one of a few alternate outcomes, or discrete scenarios. Analysis cannot identify which outcome will occur, although it may help establish probabilities. Most important, some, if not all, elements of the strategy would change if the outcome were predictable. In another common level 2 situation, the value of a strategy depends mainly on competitors' strategies, and those cannot yet be observed or predicted.[7]"

Alternative Futures

Value Rating A, Price A

Value Rating A, Price B

Value Rating B, Price C

Table 3. Example for Level 2 residual uncertainty – Alternative Futures

A hypothetical situation	Early regulatory approval; conditional marketing authorization (CMA). Molecule performance outcomes at Phase 2 are insufficient; further data collection is required to be correlated to payer assessment criteria; therefore, depending on the expectation on the future data, price potential can include several options. Contracting, risk sharing and patient access schemes can be planned for if performance outcomes do not meet payer requirements or thresholds.
Analytic tools and mitigation options	**Decision tools** • Decision analysis / decision trees, per and across markets • Option valuation • Game theory **Data tools** Aim is to align existing data to payer requirements and concentrate on patient benefit evidence gaps using one of the following: • Clinical trial simulations • Adaptive trial design • Analyses of existing databases • PFS can be supported by other patient relevant endpoints, e.g., by demonstrating causality of patient benefits to adverse event (AE) improvement, QoL, etc. • Enriched populations Time-limited HTA decision / pricing needs to be aligned to assess future performance evidence and price potential. Table 4 provides examples used in the NICE appraisals of drugs after CMA.
Examples	Oncology molecules with PFS or objective response rate (ORR) endpoints with immature or no OS data, or molecules using other surrogate endpoints where correlation with final outcome has not been established; here further long term OS data is required to be collected. Market access is achievable, price is in question.
Applicable to early access molecules	Yes
Payer requirements for P&R known	Not clear, however can be assessed and some information collated based on available evidence.

Table 4. Examples of molecules with CMA that present "Level 2 and 3 uncertainty"

Oncology domain	Indication	Orphan	Year	Primary Endpoints	Source of Uncertainty	Mitigation strategy in UK HTA submission and result
Haematology	Treatment of CML in patients previously treated with ≥1 TKI	YES	2013	Cytogenic Response	No head-to-head data; long term OS benefit, both the treatment and the comparators; therefore relative effectiveness too. PFS and OS were very immature (25.0%, 19%) – while the duration of the extrapolation was 48 years	Attempt was made to use surrogate outcome, but was not successful. Assumption on post-treatment gain was not accepted.
	Lymphoma (Hodgkin's, CD30-positive)	YES	2014	Survival	N/A	N/A
	Non-Hodgkin's lymphoma when other treatments are no longer working	NO	2012	Response Rate (Complete Remission)	Long-term OS. Only 61% dead at end of trial, extrapolation need is 18 years.	Extensive statistical analyses of the data; conservative assumption on post-progression OS gain. Arguments accepted after appeal.
Thyroid cancer	Progressive, unresectable, locally advanced, or metastatic medullary thyroid carcinoma	YES	2014	Progression Free Survival	N/A	N/A
	Advanced medullary thyroid cancer	NO	2012	Progression Free Survival	N/A	N/A
Lung Cancer	Non-small-cell lung carcinoma	NO	2012	Progression Free Survival	Long-term OS uncertain for comparator due to cross-over. Extrapolation was for 13.1 years, with 65%, 28% progressed or dead.	Mitigation was done using external data, KOLs, cross-over adjustment, and network meta-analyses.
Skin Cancer	Advanced basal-cell carcinoma	NO	2013	Response Rate (CR - Complete Response, PR – Partial Response)	N/A	N/A

(Resources used for content in this table are available upon request.)
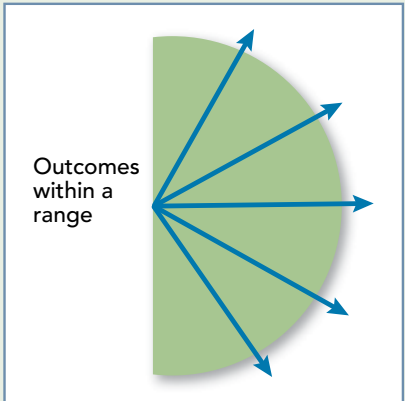
Summary of Approaches: Level 3 – A Range of Futures

"At level 3, a range of potential futures can be identified. That range is defined by a limited number of key variables, but the actual outcome may lie anywhere along a continuum bounded by that range. There are no natural discrete scenarios. As in level 2, some, and possibly all, elements of the strategy would change if the outcomes were predictable.[7]"

Range of Futures

Outcomes within a range

Table 5. Example for Level 3 residual uncertainty – Range of Futures

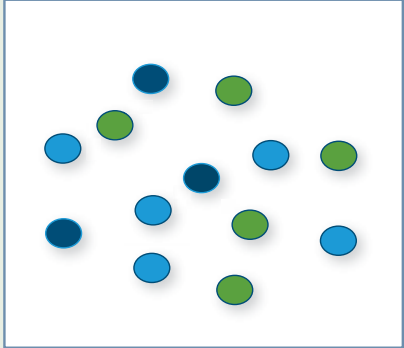|	
A hypothetical situation	Adaptive Pathways. Molecule performance outcomes at Phase 2 are available but do not - or only partially - meet payer expectations, due to the limitations in data (such as surrogate outcome and early cross-over), substantial post-hoc analyses and various assumptions are required; therefore price potential can be aligned to a range of possible value assessment outcomes and strongly aligned to competitor developments. Contracting, risk sharing, and patient access schemes can be planned only with difficulty because of data uncertainty.
Analytic tools and mitigation options	**Decision tools** • Scenario planning across markets • Latent demand research – repeated over time with payers **Data tools** Aim is to align existing data to payer requirements and concentrate on patient benefit evidence gaps. • Validation of surrogate outcomes • Use of external data to support patient benefit and relative effectiveness • Enriched populations • Analyses of existing databases • PFS can be supported by other patient relevant endpoints, e.g., by demonstrating causality of patient benefits to AE improvement, QoL, etc. Time-limited HTA decision / pricing has to be aligned to assess future performance evidence and price potential.
Examples	Oncology molecules launched with adaptive pathways and with limited data due to, for example, PFS or ORR as primary endpoints, cross-over design or incomplete trials. Market access may be thwarted by lack of mature data.
Applicable to early access molecules	Yes
Payer requirements for P&R known	Not clear, however can be assessed and some information collated based on available evidence

"At level 4, multiple dimensions of uncertainty interact to create an environment that is virtually impossible to predict. Unlike in level 3 situations, the range of potential outcomes cannot be identified, let alone scenarios within that range. It might not even be possible to identify, much less predict, all the relevant variables that will define the future.

Level 4 situations are quite rare and they tend to migrate toward one of the other levels over time.[7]"

True Ambiguity

Table 6. Example for Level 4 residual uncertainty – True Ambiguity

A hypothetical situation	No basis to forecast any outcome
Analytic tools	Pattern recognition
Examples	Potentially gene therapies or completely new mechanisms / technologies that may require specific evidence substantiation
Applicable to early access molecules	Not really, but may apply to other new developments such as cure in gene therapy
Payer requirements for P&R known	Yes, as current requirements for "regular" molecules are known, but difficult to apply to gene therapies.

obtaining and analyzing external data (see Table 4 for examples) is a very important, additional mitigation option.

However, the different techniques / methods not only help to reduce the uncertainty, they also bring their own inherent uncertainty. For example, extrapolation of trial data can quantify the alternative results and can determine the most likely ones, but it can be an important source of uncertainty and will point to a very wide range of alternative results, some of which may not be favourable. This uncertainty increases with larger time period without data. For molecules with early access options, due to the limited data, long-term outcomes such as OS, can be the main source of uncertainty. This can be seen in two cases among the NICE assessments with CMA (see Table 4).

Lack of information on the relative effectiveness is another main source of uncertainty (see Figure 2). Some of the mitigation techniques include conducting network meta-analyses, or simulated treatment comparisons, or matching adjusted indirect comparisons.[8] Depending on the level and type of information in the public domain about competitors, level of uncertainty can result in either a few alternative scenarios or a wide range of options.

Summary

Early development molecules face a range of uncertainties. These can be driven by uncertainty of the data, the clinical and payer environments, such as unrevealed expectations from payers on how to assess and manage patient benefit expectations, and competitor developments. To consider and move forward with early access, it is critical that companies understand:

1 which uncertainty factors can in fact be known at least to some extent (such as payer expectations and application of HTA requirements),

2 which factors are influential in the decision making process, and

3 the techniques that can be used to mitigate this uncertainty.

For example, in oncology, critical data on which to focus include long-term clinical outcomes, relative treatment effects, and relative benefits in health related-quality of life, as well as information such as length of treatment, that helps assessment of true costs associated with a new molecule. Choice of the appropriate analytical tools and their systematic alignment with a broad-based set of data can greatly support early access.

This can act as part of the foundation of early formulation of the potential value messages. As most uncertainties require complex strategies that focus on both the data and the clinical and payer environments, it is equally critical to align all members of the development team to the early clinical value and patient benefit of a molecule that aims to launch with early, such as Phase 2, data.

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