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Future-Proofing HTA: the case for flexibility in assessment frameworks

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Executive Summary

The rapid evolution of healthcare technologies, from gene and cell therapies to tumour-agnostic and personalised treatments, offers unprecedented potential to address unmet medical needs and transform patient outcomes. However, access to these innovations remains variable and often delayed, largely due to the limitations of traditional health technology assessment (HTA) approaches. Conventional evidence hierarchies, rooted in randomized controlled trials (RCTs) and other "gold standard" evidence, can fail to capture the full value of emerging therapies, particularly in contexts where patient populations are small, diseases are rare or rapidly progressive, or long-term outcomes cannot be measured within feasible timeframes.

This paper highlights the concept of unavoidable uncertainty, situations in which uncertainty associated with clinical evidence cannot be fully resolved, not due to a lack of rigor, but because of scientific, ethical, or practical constraints. Recognizing this spectrum of uncertainty is critical for HTA bodies seeking to balance patient access, innovation, and budget sustainability. Uncertainty ranges from fully resolvable, to reasonable uncertainty (where some gaps are tolerated to unlock meaningful benefits), to irreducible uncertainty (which persists despite time or investment).

To address these challenges, we propose a framework that emphasizes two key dimensions:

1. Understanding Uncertainty:
    - Assess the nature, magnitude, and context of uncertainty in clinical evidence.
    - Distinguish between uncertainty that is likely.
    - Consider factors such as patient need, availability of alternatives, ethical considerations, scientific and clinical limitations, and broader societal impact when assessing the likelihood that uncertainty can be resolved over time.

2. Applying Context-Sensitive Flexibility:
    - Implemented principled adaptations throughout the HTA process, spanning evidence requirements, assessments, and decision-making.
    - Without compromising the robustness of the decision process, such flexibility may include accepting surrogate endpoints, adaptive trial designs, alternative analytical methods, or conditional reimbursement approaches.
    - Decision-making should weigh residual uncertainty against potential clinical, ethical, and societal benefits, rather than requiring full resolution of all evidence gaps.

Through a structured review of literature and case studies – particularly in rare diseases, gene therapies, and advanced oncology – we identify core elements of a framework that can guide a consistent and transparent management of uncertainty. Input from stakeholders, including payers, HTA bodies, clinicians, patients, and developers, ensures that this framework reflects real-world trade-offs and evolving evidence needs.

Conclusion

Rigid application of traditional HTA processes risks delaying or denying patient access to highly valuable innovations. By explicitly characterizing uncertainty and embedding context-sensitive flexibility, HTA bodies can better balance timely access, scientific rigor, and healthcare sustainability. This approach enables more equitable, informed, and consistent decisions, ensuring that patients benefit from transformative therapies without unnecessary delays.

Setting the Scene

The rapid evolution of healthcare technologies, from personalized therapies and gene editing to tumor-agnostic cancer treatments, offers unprecedented promise in addressing unmet medical needs and transforming patient outcomes[29]. Access to these innovations, however, depends on health systems' ability and willingness to provide them.

Many systems turn to health technology assessment (HTA) to guide these resource allocation decisions, balancing the value such technologies deliver with the sustainability of healthcare budgets. Yet, despite their potential, patient access often remains variable and delayed[9], partly due to a reliance on traditional evidence assessment approaches, which may fail to fully capture the clinical impact and therapeutic potential of these advances. In certain circumstances, traditional evidence generation may require trials of impractical duration or scale. While uncertainty might be technically avoidable, doing so would delay access to innovation for decades. This is the type of situation we refer to as "unavoidable uncertainty".

This paper outlines the need for adopting more flexible and tailored approaches to evidence assessment in specific circumstances, where traditional methods in HTA may not be sufficient to reflect the full value of innovation, but also demand evidentiary standards that, in some cases, are virtually unattainable and incompatible with timely access.

Challenges with Conventional Approaches to HTA

Conventional approaches to evidence assessment of new treatments are rooted in evidence-based medicine (EBM)[16]. EBM seeks to use the 'best available' evidence to make decisions for patients, forming the basis of the concept that evidence exists in a hierarchy and certain types of evidence represent the 'gold standard'[27]. Guided by these principles, HTA bodies typically prioritize double-blind, closed label, randomized controlled trials (RCT) and often consider other evidence sources, such as real-world data, single-arm trials, or patient-reported outcomes, to be less robust or reliable[17]. While this hierarchy of clinical evidence helps maintain the best possible standards, its rigidity may undervalue other relevant sources of information, which can be particularly necessary in some circumstances. It is therefore important that all forms of evidence are considered, with their quality judged in context and in relation to the specific decision being made[25].

It is clearly important for HTA bodies to use the best available evidence to ensure patients receive access to safe, efficacious treatments, and incorporating EBM principles within HTA supports this objective. At the same time, the nature of healthcare technologies is changing considerably; in some clinical contexts, it becomes clear that the optimal evidence package simply cannot be achieved, not for lack of intent, but due to inherent constraints tied to the disease or technology (e.g., cell and gene therapies, tumour-agnostic cancer therapies, orphan medicines, etc)[2, 23]. In these situations, there is also a strong policy and ethical imperative to provide access to innovation as early as possible, rather than delaying. For example, one-time gene therapies often involve substantial uncertainty at the time of assessment, as reimbursement decisions rely on short-term clinical data while long-term durability of benefit remains unknown, given the novelty of these treatments and the years of data needed for greater certainty. Another example is the case of rare and ultra-rare diseases, where extremely small populations preclude adequately powered studies or standard statistical certainty, making it difficult or impossible to demonstrate significant outcomes[1].

As the nature of healthcare technologies evolves and scientific advances lead to complex and innovative new treatments, an inflexible reliance on more conventional evidence assessment approaches risks undermining sustainable patient access. This can result in delayed or restricted uptake and undervaluation of innovation, which in turn may threaten its long-term sustainability. Moreover, current processes often struggle to manage uncertainty when gold standard evidence is not possible, limiting their capacity to incorporate novel data sources and adapt to evolving scientific realities.

Technical Constraints in Evidence Generation Require Context-Adapted Assessment

In most situations, challenges in evidence development can be mitigated or better anticipated through mechanisms like early scientific advice, joint consultations, and adaptive study designs. There are, however, certain contexts and circumstances where optimal evidence generation is technically constrained and uncertainty around clinical evidence becomes 'unavoidable', not due to lack of intent or rigour from developers, but because no realistic solutions exist, approaches would raise ethical concerns, or the factors involved lie beyond the developer's control. These situations can occur, for instance, for (ultra-)rare diseases, cell and gene therapies, rapidly progressive or life-threatening conditions and tumour-agnostic therapies[3, 7, 15, 30]. Such instances of unavoidable clinical uncertainty demand a deliberate and differentiated response.

Within the EBM framework and amid growing pressure on healthcare budgets, HTA processes are designed to minimise risk, typically favouring 'gold standard' evidence and managing uncertainty through conditional approvals, managed entry agreements, or real-world evidence integration[21]. While these tools can support decision-making in the face of clinical evidence uncertainty, their application is inconsistent across jurisdictions, reflecting differences in reimbursement archetypes, institutional capacities, and legal frameworks for managing post-launch commitments[10]. Moreover, even when such mechanisms are available, they often lack the flexibility needed to address situations where alternative evidence approaches are required and / or evidence gaps cannot feasibly be closed due to the nature of the disease or treatment[13]. For instance, single-arm trials, commonly used when RCTs are infeasible (e.g., in ultra-rare diseases or paediatric oncology), provide only limited comparative evidence, and HTA bodies like the German G-BA accept them only under strict conditions[31](see Case Study 1). Similarly, generating long-term evidence remains challenging: short follow-up times at launch limit extrapolation, while HTA processes often cannot accommodate the delay required for real-world longitudinal data to emerge[8] (see Case Study 2). As a result, patient access to innovative healthcare technologies can be delayed, restricted or denied, not due to hard safety or efficacy concerns, but because of clinical evidence uncertainty that cannot be resolved within the existing practical timeframe (or in other words is "unavoidable"), coupled with conventional evidentiary expectations that cannot be met[12, 18, 35].

CASE STUDY 1: RARE/ULTRA-RARE DISEASES

Description	Rare and ultra-rare diseases affect small patient populations, limiting the feasibility of large, randomised controlled trials within a reasonable timeframe for patient access. Treatments for these conditions may be the first therapy of their kind, offering hope where no alternatives exist.
Clinical Uncertainty	Uncertainty in rare disease evidence arises from multiple, often overlapping challenges: – **Small sample size:** due to limited patient availability and recruitment challenges that constrain study size and reduce statistical power – **Feasibility of RCTs:** conducting adequately powered RCTs is often impractical due to population rarity, urgency of treatment need, or lack of a standard of care. As a result, single-arm trials are common, sometimes supplemented by indirect treatment comparisons (ITCs), but these approaches introduce uncertainty around the true magnitude of benefit – **Heterogeneity:** rare diseases may vary widely in presentation and progression, making it difficult to demonstrate consistent treatment effects across patients, particularly when same samples are small – **Lack of control arm:** rare diseases often have no available treatment and thus no comparators; attribution of observed outcomes to treatment rather than natural history or background care remains uncertain – **Patient-reported outcomes** (PROs): are increasingly important for capturing what matters to patients (e.g. quality of life, symptom relief), especially when other clinical data is uncertain. However, they are themselves a source of uncertainty, since in rare diseases PROs are often poorly measured, lack validated instruments, or are inconsistently reported
HTA Challenges	When HTA bodies apply rigid evidence hierarchies, the available evidence for rare diseases can be undervalued. Small samples, single-arm data, and PRO-related uncertainty may be dismissed as insufficient, even when they represent the only feasible evidence. Without more flexible approaches, such as contextualising PROs, accepting indirect treatment comparisons, or enabling conditional reimbursement linked to real-world evidence collection, HTA processes risk undervaluing therapies that address urgent unmet needs, resulting in restricted or delayed patient access[3].

CASE STUDY 2: CAR T CELL THERAPIES

Description	Chimeric antigen receptor T-cell (CAR T) therapies are a novel class of personalised immunotherapies that re-engineer a patient's own T cells to recognise and destroy specific cancer cells. They have shown high efficacy in certain haematological malignancies, with some patients achieving complete remission after exhausting all other treatment options[19].
Clinical Uncertainty	The transformative potential of CAR T therapies has been recognised, but there are also key challenges associated with the uncertainties generated by the evidence: – **Uncertain long-term durability:** relapses may occur years after treatment; survival data can take a decade or more to mature, leaving key uncertainties unresolvable at launch. Trial duration represents a reasonable trade-off, enabling timely patient access while maintaining commercial viability – **Reliance on surrogate or alternative endpoints:** often used to address trial feasibility (e.g., overall response rate, event free survival) and disease characteristics (e.g., duration of response, progression-free survival), but may not fully capture long-term or patient-centred benefits – **Cross-over effects:** at the investigator's request, and / or for ethical reasons, control-arm patients are often allowed to cross over to CAR T after progression, introducing bias and confounding overall survival and quality of life outcomes – **Infeasibility of binding:** observable side effects, logistical challenges, and the bespoke manufacturing process make blinding unrealistic
HTA Challenges	HTA bodies that adhere strictly to conventional hierarchies of evidence may struggle to accommodate single-arm data or accept immature survival endpoints[32]. This has led to restricted or delayed access in some jurisdictions, even where clinical urgency is high and no alternatives exist[26]. In several countries, manufacturers have withdrawn CAR T therapies from the market or opted not to launch when negotiated prices failed to reflect their long-term value and high manufacturing costs. Reimbursement analyses across Europe further show that divergent national decisions and HTA assessments have, in some cases, prevented launches altogether[24].

Without adapting assessment processes to better manage situations where uncertainty cannot be resolved within a practical or decision-relevant timeframe, there is a risk that transformative or high-need innovations may fail to reach patients or become infeasible to develop. Addressing this requires a framework that enables: 1) an assessment of the level and nature of uncertainty (for example, whether it is reasonable and expected to diminish with further data, or whether it is effectively irresolvable within the timeframes needed for access), and 2) a corresponding degree of flexibility in how such uncertainty is handled in the assessment process.

The aim of this work was to identify the essential elements such a framework should contain, using a structured, iterative process designed to capture both theoretical reasoning and real-world practice. A targeted review was used to identify key discussions of uncertainty in clinical evidence in HTA, deliberately broadening the search to capture concepts such as small sample size, rare disease, and trial feasibility. These insights were then mapped against case studies of HTA reports, focusing on rare diseases and advanced gene therapies, where some degree of residual uncertainty is already tolerated. Iteration between the literature and case studies enabled the refinement of an initial set of framework elements, which were subsequently reviewed with input from a multi-stakeholder advisory board, including payers, HTA bodies, clinicians, patients, and developers. This approach ensured that the framework reflects both conceptual reasoning and real-world perspectives on trade-offs.

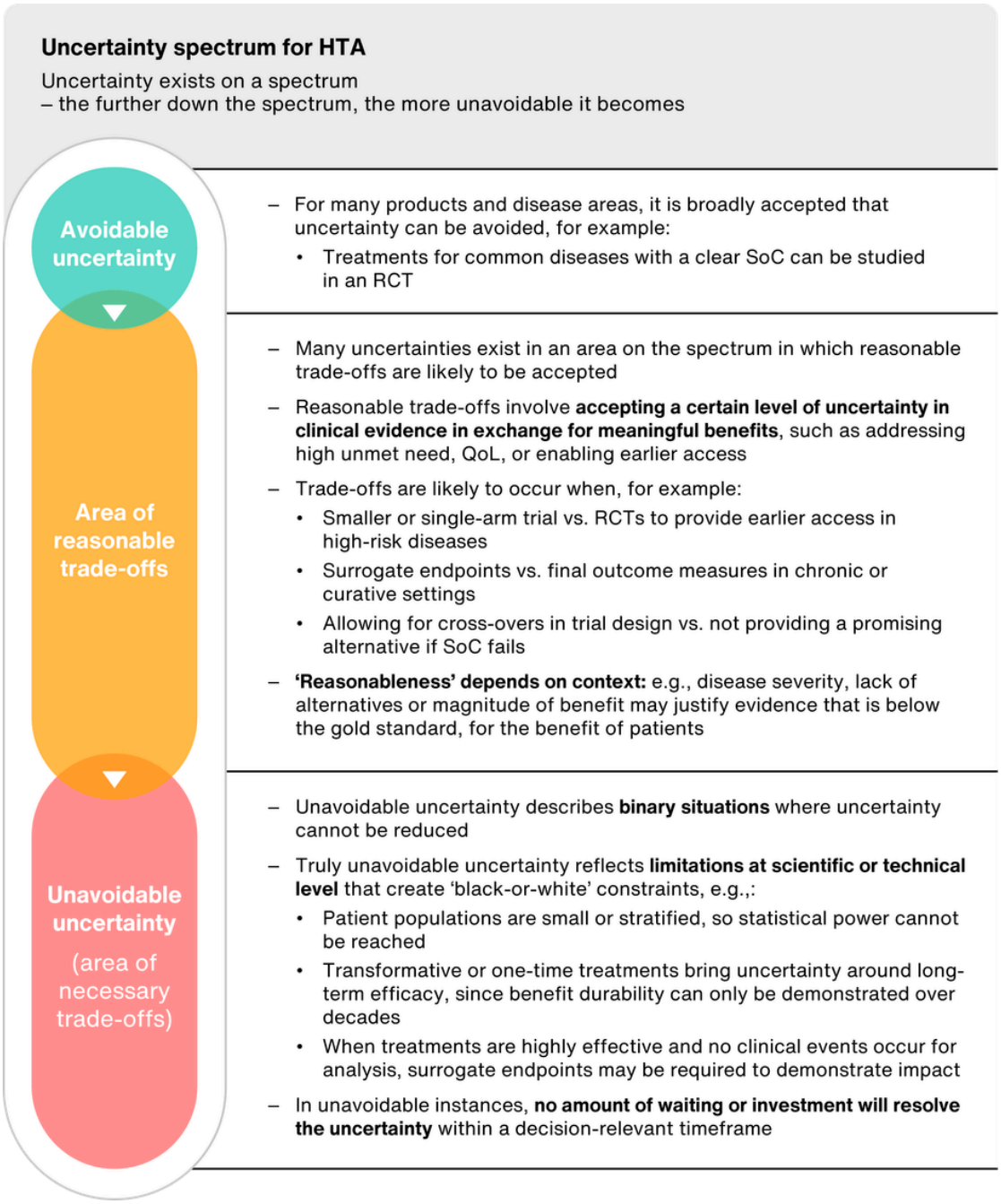
The next sections outline the proposed elements of such a framework within the two broad categories of uncertainty in clinical evidence and corresponding flexibility.

Mapping the Landscape of Uncertainty in HTA Decision-Making

A More Granular Understanding of Uncertainty in Clinical Evidence

Addressing the issue of uncertainty in clinical evidence requires an understanding of its nature. Uncertainty in clinical evidence exists along a spectrum: while some levels of uncertainty can be resolved over time or with additional data, others may not be resolvable, depending on the characteristics of the product or the disease in question.

Figure 1 Clinical Uncertainty Spectrum



At the top of the spectrum lies uncertainty that can be resolved, as is often the case in many therapeutic areas. Treatments for prevalent conditions with an established standard of care can typically be evaluated via an RCT with the appropriate comparator. Likewise, trials in disease areas with low survival rates can more easily include a hard primary endpoint like overall survival.

The central point on the uncertainty spectrum refers to situations where some degree of evidential uncertainty must be tolerated to unlock meaningful treatment benefits, therefore referred to as 'reasonable uncertainty'. This is often the case for severe diseases, where the urgency of care and potential clinical impact take precedence over achieving full evidentiary certainty. For example, a single-arm trial may be accepted to secure early access to a highly promising treatment in areas of high unmet need, such as severe and fast-progressing diseases with limited treatment options. In such cases, although a Phase III RCT may be feasible, the clinical and ethical considerations about expediting patient access could take precedence over resolving all uncertainty. Similarly, cross-over trial designs may be used to ease recruitment in rare or severe conditions with poor standard of care. Allowing patients in the control arm to cross over to the experimental arm, can help address recruitment challenges particularly when withholding an effective treatment would be unethical.

At the bottom of the spectrum lies 'unavoidable uncertainty': these are cases where scientific or technical constraints make it impossible to generate traditional forms of evidence, often regardless of time or investment. This includes ultra-rare diseases, where populations are too small for powered trials, or gene therapies, where long-term outcomes cannot be measured within a decision-relevant timeframe. Heterogeneous or multi-systemic diseases may also lack clear clinical endpoints or require outdated comparators if the standard of care (SoC) evolves after the trial begins.

The understanding that uncertainty in clinical evidence exists along a spectrum helps determine the level of evidential uncertainty present in a certain context. Another dimension that needs to be understood to determine the level of uncertainty is the magnitude, that is, the degree to which the uncertainty could influence the HTA decision. Considering uncertainty magnitude and context helps determine whether additional evidence requirements are feasible and proportionate. Accounting for the magnitude and context of uncertainty in HTA processes is necessary to ensure a fair evaluation of new medicines, enabling equitable and timely access to promising new treatments and limiting costs of foregone health when valuable technologies are rejected.

Characterising Uncertainty: Assessing Its Magnitude, Impact, and Resolvability

To enable a principled and consistent adaptation within HTA processes, it is critical to first understand the level of uncertainty and its impact on decision making, in other words, how significant is the uncertainty, and how does it influence the ability to make a sound reimbursement decision. This is the basis for developing elements of a framework that can identify situations and guide the type of flexibility that should be applied in such cases.

With this understanding, the context of the problem can be considered through the resolvability of the uncertainty, helping to distinguish between uncertainty that might eventually be reduced, and that which will persist despite time or investment.

The key factors to consider in determining when uncertainty cannot be resolved include:

- **Urgency of patient need and availability of alternatives**: There is broad consensus that urgency may justify a greater degree of flexibility. Regulatory frameworks such as PRIME, Accelerated Assessment, and Conditional Marketing Authorization reflect this by expediting approval where treatment need is high[28]. Similarly, HTA bodies are beginning to adapt their processes to ensure patient access to medicines in areas of high urgency. A review of 21 HTA bodies found that 'adaptive' HTA methods prioritizing speed (e.g., rapid reviews, rapid cost-effectiveness analyses) were triggered most often by high clinical urgency[22].

- **Scientific or clinical limitations**: In some cases, the generation of 'gold standard' evidence is simply not feasible. This can be the case in different situations:

    - **Small or highly stratified populations**: Rare diseases and personalised therapies often involve very small or fragmented populations, biological heterogeneity, or urgent clinical needs which make traditional trial designs impractical. These aspects may lead to unresolvable uncertainty, necessitating alternative approaches to evidence evaluation.
    - **Unknown long-term efficacy**: For therapies with potentially transformative or curative effects, such as gene therapies, the initial clinical benefit may be high, but durability of effect can only be confirmed over many years. This creates substantial long-term uncertainty that cannot be resolved at the time of assessment. In addition, highly effective treatments may yield very few events for analysis, necessitating reliance on surrogate endpoints.
    - **Precision medicine challenges**: Targeted therapies require biological testing to identify eligible patients, but testing availability, mutation rarity, or new mechanisms of action may constrain trial feasibility.
    - **Dormant or slowly progressing conditions**: Dormant or slowly progressing conditions (e.g., Huntington's disease), where clinical onset is delayed, may have opportunities for preventative treatment. In such contexts, reliance on surrogate endpoints or strong biological rationale may be necessary.

- **Ethical considerations**: The integration of ethical reasoning, particularly relating to equity, fairness and timely access, is increasingly recognised as central to HTA decisions. While inclusion of ethics into formal HTA process is complex, there is recognition that it can lead to more inclusive decision-making[14]. There is increasing interest in embedding contextual normative reasoning and value judgements into HTA, especially for populations that are underserved or face structural barrier to care [4].

- **Economic impact and broader societal considerations**: Delayed, restricted or denied access to effective therapies can result in substantial economic consequences – not only in terms of health system costs, but also in lost productivity, increased caregiver burden, and worsened long-term health outcomes. Inflexible HTA processes can also undermine the value of medical innovation, particularly if high clinical potential is lost due to rigid evidentiary demands. Additionally, these requirements can threaten the financial viability of clinical development and reduce the competitiveness and attractiveness of a country's healthcare system for investment. Prolonged or infeasible trial requirements may introduce substantial time and cost burdens, potentially leading to market withdraw or no launch altogether.

Flexibility in HTA: A Context-Sensitive Approach to Managing Uncertainty

Defining Flexibility

The second element of the framework builds on the contextual analysis of uncertainty by identifying where, and under what conditions, flexibility in evidence requirements and assessment may be justified. Once the nature of the uncertainty has been assessed, it becomes possible to determine the circumstances under which a more adaptive approach could be warranted, and to pinpoint the stages in the HTA process where such flexibility would be most effective.

In this context, flexibility refers to the intentional, structured adaptation of evidence standards, assessment criteria, and decision rules to address situations where traditional approaches are not feasible or appropriate. The intent is not to lower standards, but to apply principled, context-specific flexibility to specifically manage unresolvable uncertainty.

Flexibility can be introduced at multiple points in the HTA process to address such uncertainties:

Flexibility applied to Evidence. In some HTA contexts, conventional evidence requirements (e.g., large, fully powered RCT with long-term follow up and hard clinical endpoints) may not be feasible, for example due to small patient populations. These situations can lead to gaps or biases in the data that cannot be resolved within a practical timeframe or through feasible trial designs when assessed against standard criteria. TGreater flexibility can be achieved by incorporating non-traditional data sources (e.g., real-world evidence), surrogate endpoints, or adaptive trial designs that can generate timely, relevant insights despite such constraints.

Flexibility applied to Assessment. Flexibility can also be applied in how evidence is analysed, interpreted, and valued. In contexts such as ultra-rare diseases or rapidly progressive conditions, conventional statistical standards may be unattainable, for example due to extremely small sample sizes or limited follow-up time. In these cases, assessment criteria can be adapted to accept a broader set of endpoints, shorter trial durations, or alternative analytical approaches that make the best use of the available data. For instance, in rare disease trials where patient numbers are inherently limited, applying different thresholds for statistical significance or confidence intervals, supported by methodological guidance, can help ensure that promising treatments are not dismissed solely due to sample size constraints[20]. This approach recognises that while uncertainty may remain, the available evidence can still be robust enough to support reasoned decision-making when interpreted in context. In trial cross-over for example, survival estimates may be biased due to treatment switching between arms. Statistical methods such as the accelerated failure time (AFT) model or the Branson and Whitehead method[6], can help correct for these biases and provide more accurate estimates of treatment benefit. Broader acceptance and consistent application of these methods can help ensure more balanced assessments in contexts where crossover is ethically necessary and its confounding effects cannot be removed by longer follow-up, but must instead be adjusted for analytically.

Flexibility applied to Decision-making. At the final stage, decision-makers may decide to tolerate greater uncertainty when justified by broader clinical, ethical, or societal considerations. This may be done through managed access agreements, conditional reimbursement decisions, or coverage with evidence development. However, in practice, these approaches do not always lead to the resolution of uncertainty over time. Reasons include the difficulty of collecting high-quality follow-up data in real-world settings, the long timelines required to observe relevant outcomes, and the potential for methodological limitations to persist despite additional evidence collection. As a result, decision-makers can find themselves facing the same unresolved questions in other assessments.

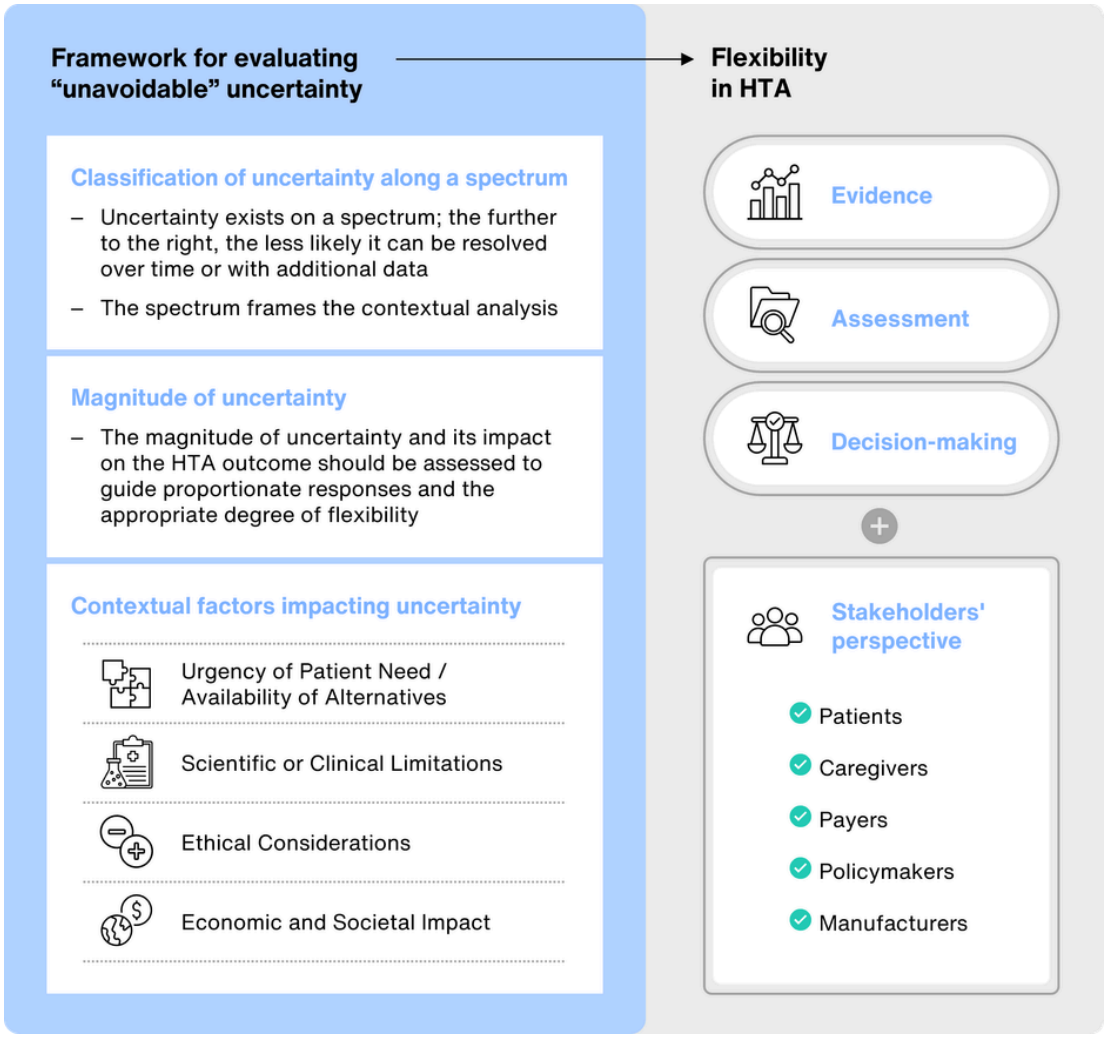
An alternative approach is to base decision-making flexibility not solely on the expectation that uncertainty will be reduced, but on an analysis of the type of uncertainty, its context, and its likely impact - elements explored earlier. This would allow decision-makers to assess the plausibility of the assumptions underpinning the evidence in light of these factors and make a reasoned judgement, even if some uncertainty remains irreducible[11]. In certain cases, this could mean accepting, for example, less robust evidence such as surrogate endpoints where the underlying assumptions are robust and the potential benefits substantial, as in the example of the German G-BA occasionally deeming surrogates ‘patient-relevant’ despite contrary IQWiG assessments.

Implementing Context-Sensitive Flexibility in Practice. Ultimately, managing reasonable or unresolvable uncertainty requires more than methodological innovation but also applying context-sensitive flexibility, at the right moments, in the right ways. By identifying key points in the HTA process where flexibility can be responsibly applied, systems can better accommodate the realities of emerging healthcare technologies without compromising scientific rigor or patient safety.

The broad elements outlined above (summarized in Figure 2 below) could support defining the contextual factors that are important for evaluating uncertainty and the corresponding flexibility that could be introduced to manage it. The development of a framework based on these elements must dive deeper into them to identify sub-elements and build comprehensive guidance.

Crucially, it should include all relevant voices (patients, clinicians, developers, HTA bodies and payers) to ensure it reflects the real-world situation and the different perspectives on trade-offs. Additionally, what is considered reasonable or unresolvable uncertainty may evolve over time, and must also be interpreted in light of the overarching goal to ensure patient access to innovation within a reasonable timeframe while safeguarding evidentiary standards. It will therefore be important to consider the moment in time that uncertainty occurs, or evidence decisions are made.

Figure 2 Proposed Elements for a Framework to Manage Clinical Evidence Uncertainty in HTA



Call to Action

Protecting patient access to effective, innovative medicines requires acknowledging that uncertainty exists on a spectrum and, in certain contexts, cannot be eliminated regardless of time or resources invested. In these cases, rigid application of conventional HTA processes risks delaying or denying access to treatments with substantial clinical, societal, and economic value.

This paper outlines the key elements of a potential framework for characterising uncertainty, assessing its magnitude and context, and identifying where principled flexibility could be applied. Further refinement of these elements into a clear framework would enhance the transparency, consistency, and equity of HTA decisions by explicitly defining when flexibility is justified.

In current practice, HTA bodies and payers rarely reject applications outright; instead, they assign lower benefit ratings or equivalent assessments, which can translate into reduced pricing. This approach effectively determines how the cost of uncertainty is distributed, and today that burden often falls on developers. Recognising that the role of HTA is to balance timely access, budget sustainability, and incentives for innovation, greater flexibility could help preserve this balance is maintained without overburdening any one stakeholder.

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