Defining Unavoidable Uncertainty in HTA:
Towards Flexible and Adapted Approaches for Promising Treatments

HTA 103

Elena Nicod[1], Anna Albiero[1], Lindsay R. Kreill[1], James Albon[1], Raphaelle Boudet[1], Dimitri Pouradier Duteil[2], Nebibe Varol[2], Jose Diaz[2], Marion Bouillon-Pichault[2], Adam Parnaby[2],
[1]Dolon Ltd, London, UK; [2]Bristol Myers Squibb

Background:

Optimal value recognition by HTA becomes increasingly challenging due to an increasing misalignment between generated evidence and HTA requirements:

- Conventional HTA processes rely on traditional evidence hierarchies, prioritizing evidence from double-blind, randomized controlled trials (RCTs), considered as the 'gold standard'.
- New innovative therapies, including cell & gene therapies, orphan drugs and tumor-agnostic oncology therapies, often face inherent scientific, ethical, and logistical constraints that limit the generation of 'gold standard' evidence (Abrams, et al., 2025; Nicod & Kanavos, 2016).
- These constraints are context-specific and can result in clinical uncertainties that are difficult or impossible to avoid. Treating such uncertainty as a weakness, rather than considering what is feasible within the context of the disease or technology, risks delaying, restricting or denying patient access to treatments with high transformative potential.

Objectives:

- To propose a framework that determines when evidence uncertainty is truly unavoidable due to technical constraints that make 'gold standard' evidence unattainable and then define the types of HTA flexibility warranted in such cases.

Methods:

- Conducted a targeted literature review to identify and delve into key areas of evidence uncertainty in HTA and possible reasons for their unavoidability.
- Mapped findings against selected HTA case studies in Germany, France, and the UK, to illustrate and further characterize "unavoidability".
- Leveraging these insights, developed a framework evaluating when gold standard evidence is unattainable and refined the framework with input from a multi-stakeholder advisory board.

Results:

Uncertainty is inherent to evolving healthcare. Examples of diseases or technologies where evidence standards are commonly unattainable:

- **Ultra-rare diseases**, where populations are too small for powered trials,
- **Gene and cell therapies**, where long-term outcomes cannot be measured within a decision-relevant timeframe, or where the bespoke nature of the treatment process makes it impossible to blind trials,
- **Heterogeneous or multi-systemic diseases**, where clear clinical endpoints may be lacking or where outdated comparators are being used if the standard of care evolves trial initiation.

Contextual factors for evaluating clinical uncertainty unavoidability

The inability to generate gold-standard evidence is often linked to several key factors that help determine when uncertainty cannot be resolved, including:

- Urgency of need and availability of alternative treatments: High clinical urgency and unmet need often lead regulators to permit shorter, single arm trials; HTA must show similar flexibility in such situations.
- Scientific or clinical limitations: Generating gold-standard evidence may be infeasible in small or highly stratified populations, in potentially curative treatments where long-term efficacy takes years to confirm, in targeted therapies that require identifying eligible patients, or in dormant or slowly progressing conditions where final outcomes are uncommon and reliance on alternative endpoints is necessary.
- Ethical factors: Ethical reasoning related to equity, fairness, and timely access, especially for underserved groups, may provide justification for moving away from gold-standard evidence; in such cases, flexibility from HTA is needed.
- Economic & societal impact: HTA requirements can be infeasible within reasonable timeframes and investments, leading to unavoidable uncertainty. Delays or denials affect not only patients, but also increase system costs, burden families, and undermine innovation and investment.

Illustrative Example: 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 (Lu & Jiang, 2022).
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 unresolvable at launch. Trial duration represents a reasonable trade-off, enabling timely patient access while maintaining commercial viability. • Reliance on surrogate or alternative endpoints: are 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 challenge	HTA bodies that adhere strictly to conventional hierarchies of evidence may struggle to accommodate single-arm data or accept immature survival endpoints. This has led to restricted or delayed access in some jurisdictions, even where clinical urgency is high and no alternatives exist (Rodrigues, Howard, Akesson, & Brown, 2023). 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 (Pauwels, Huys, Casteels, & Simoens, 2022).

Magnitude of uncertainty

Another dimension to be accounted for when evaluating uncertainty is its magnitude - the extent to which it could influence the HTA decision. Assessing magnitude helps determine proportionate responses, including the appropriate degree of flexibility.

Uncertainty as a spectrum

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. These are cases where scientific or technical constraints make it impossible to generate traditional forms of evidence, often regardless of time or investment.

Fig. 1 – Uncertainty as a spectrum for HTA

Uncertainty spectrum for HTA
Uncertainty exists on a spectrum; the further on the right of the spectrum, the more unavoidable it becomes.

Avoidable ← // → *Unavoidable*

Avoidable uncertainty

For many products and disease areas, it is broadly accepted that uncertainty can be avoided, for example:

- Treatments for common diseases with a clear standard of care can be studied in an RCT

Area of reasonable trade-offs

- Many uncertainties exist in an area on the spectrum in which reasonable trade-offs are likely to be accepted
- Reasonable trade-offs involve **accepting a certain level of uncertainty in clinical evidence in exchange for meaningful benefits**, such as addressing high unmet need, quality of life, or enabling earlier access
- Trade-offs are likely to occur when, for example:
  - Smaller or single-arm trial vs RCTs to provide **earlier access** in **high-risk diseases**
  - Surrogate endpoints vs. final outcome measures in **chronic or curative settings**
  - Allowing for cross-overs in trial design vs. not providing a promising alternative if standard of care fails
- **'Reasonableness' depends on context:** E.g., disease severity, lack of alternatives or magnitude of benefit may justify evidence that is below the gold standard, for the benefit of patients

Unavoidable uncertainty (area of necessary trade-offs)

- Unavoidable uncertainty describes **binary situations** where uncertainty cannot be reduced
- Truly unavoidable uncertainty reflects **limitations at scientific or technical level** that create 'black-or-white' constraints, e.g.:
  - Patient populations are small or stratified, so statistical power cannot be reached
  - Transformative or one-time treatments bring uncertainty around long-term efficacy, since benefit durability can only be demonstrated over decades
  - When treatments are highly effective and no clinical events occur for analysis, surrogate endpoints may be required to demonstrate impact
- In unavoidable instances, **no amount of waiting or investment will resolve the uncertainty** within a decision-relevant timeframe

Flexibility in HTA

Flexibility in HTA is the application of corresponding principled, context-specific flexibility at appropriate points in the HTA process when uncertainty is unavoidable. Flexibility can take different forms throughout the HTA process.

- **Evidence** – Adapting evidence requirements by accepting non-traditional data sources, alternative endpoints, and innovative trial designs when conventional approaches are not feasible.
- **Assessment** – Interpreting and valuing evidence using adapted criteria such as accepting broader endpoints, or alternative statistical approaches, to make best use of limited data.
- **Decision-making** – Making context-aware judgements on the plausibility of evidence assumptions, allowing for informed decisions that may tolerate greater uncertainty when justified by greater considerations.

Flexibility should consider stakeholder perspectives, as they provide a fuller understanding of the disease and treatment context, help assess the plausibility of assumptions, and reflect real-world priorities and trade-offs.

Fig. 2 - Framework for assessing "unavoidable" uncertainty and appropriate HTA flexibility

Framework for evaluating "unavoidable" uncertainty

Classification of uncertainty along a spectrum

- Uncertainty exists on a spectrum; the further to the right, the less likely it can be resolved over time or with additional data
- The spectrum frames the entire contextual analysis

Magnitude of uncertainty

The magnitude of uncertainty and its impact on the HTA outcome should be assessed to guide proportionate responses and the appropriate degree of flexibility

Contextual factors impacting uncertainty

Factors to consider when determining when uncertainty cannot be resolved include:

1. Urgency of Patient Need / Availability of Alternatives
2. Scientific or Clinical Limitations
3. Ethical Considerations
4. Economic & Societal Impact

Flexibility in HTA

Flexibility can be introduced at multiple stages of the HTA process, and should incorporate input from all relevant stakeholders

EVIDENCE

ASSESSMENT

DECISION MAKING

+

Stakeholders' Perspective

Patients

Caregivers | Payers

Policymakers | Manufacturers

Conclusion

- Uncertainty exists along a spectrum; some forms are unavoidable, yet current HTA frameworks are not consistently equipped to address these.
- Distinguishing when evidence is truly unavoidable (reasonable given the disease or technology context, or impossible to eliminate), can guide when flexibility is warranted and help prioritize improvements in HTA methods and processes.
- A principled framework that applies flexibility across evidence generation, assessment, and decision-making can enhance transparency, equity, and timely access in situations of reasonable and unavoidable uncertainty.
- Such a framework is needed to better ensure that high-value innovations risk failing to reach patients or becoming infeasible to develop.
- As next steps, the framework will continue to be refined and piloted, proposing specific solutions for flexibility when it is warranted, as well as their mechanism and requirements for implementation of these solutions.

References

- Abrams, K., Aiuti, A., Eichler, H.-G., & Ziegler, A. (2025). Considerations driving the choice in clinical trial design of cell and gene therapy products: weighing convenience vs necessity. Cytotherapy. Advance online publication. https://doi.org/10.1016/j.jcyt.2025.06.001
- Lu, L. & Jiang, G. (2022). The journey of CAR-T therapy in hematological malignancies, Mol Cancer 21, 194 https://doi.org/10.1186/s12943-022-01663-0.
- Nicod, E., & Kanavos, P. (2016). Scientific and social value judgments for orphan drugs in health technology assessment. International Journal of Technology Assessment in Health Care, 32(4), 218–232. https://doi.org/10.1017/S0266462316000330
- Pauwels, Huys, Casteels, & Simoens. (2022). Market access of CAR-T therapies in Europe: a retrospective analysis of reimbursement decisions. Front Pharmacol, 13:850498. doi:10.3389/fphar.2022.850498.
- Rodrigues, T., Howard, R., Brown, S., & Akesson, C. (2023, November). An Evaluation of the Reimbursement Status of CAR-T Cell Therapies in the EU-4 and UK. Presented at ISPOR Europe 2023, Copenhagen, Denmark. Published in Value in Health, 26(11, Suppl. 2)

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