

Health Intelligence



When Precision Meets Decision

It Is Time to Evolve Current Approaches to Health Technology Assessments for the Evaluation of Precision Oncology Therapeutics.

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With small trial sizes, lack of active comparators and limited knowledge of the prognostic value of biomarkers complicating the generation of evidence, precision oncology therapeutics pose a challenge to current HTA approaches.

Scientific advancements over the past two decades have ushered in a new paradigm of precision medicine, which is changing drug development and care delivery. Precision oncology, in particular, is redefining how we approach cancer. We once treated cancer as an organ-specific disease. We now understand it as a disease of the genome, with precision oncology therapeutics targeting smaller and better-defined patient populations based on their molecular profile. With cancer treatment rapidly moving toward stratification based on the molecular makeup of a tumour, drug developers have needed to shift from large, randomized control trials (RCTs) to smaller, single arm clinical trials involving a subset of individuals with a targeted molecular profile. This shift also applies to tumour-agnostic therapies (TATs) that are being developed independently of tumour type with the use of basket trials that involve patients who have different types of cancers that all share the same mutation.

While novel precision oncology therapeutics have been gaining regulatory approval, these technologies face challenges in gaining widespread adoption through reimbursement processes. One reason for this trend are the evidentiary constraints and outcomes uncertainties that arise with single arm or basket trials where patient populations are small and indirect comparators (i.e. standard of care [SoC]) may not be well-defined due to a lack of natural history and testing availability. However, while health technology assessment (HTA) agencies and payers are coming to terms with the clinical and economic constraints that come with evaluating therapies for small populations for rare diseases, the same is not the case for precision oncology. Given the increasing fragmentation of patient populations according to non-tumour-specific genetic mutations, an opportunity may exist to apply learnings from approaches to assessing rare disease therapeutics to cancer.

Recognizing the need for equitable access to innovations that present a favourable benefit-risk proposition for all stakeholders, there is an opportunity to evolve current HTA approaches for the evaluation of precision oncology therapeutics by systematically extending the window for evidence generation and decision-making to the full lifecycle of a technology—from pre-market to market entry to the post market stage. To this end, Shift Health facilitated a series of discussions with an Expert Working Group (see next page) comprised of a patient advocate, a health economist, an oncologist and HTA experts to reflect on key challenges and opportunities and develop some initial thinking on an HTA framework that reflects the unique challenges of precision oncology therapeutics. The following brief explores the key recommendations of this framework (visualized below) and highlights critical considerations for stakeholders looking to prepare health systems for the growing pipeline of precision oncology therapeutics.

Life Cycle HTA Framework



 Indicates an iterative step that may take place more than once during the life cycle.

* Real-World Data (RWD): Data collected during the routine delivery of health care; Real-World Evidence (RWE): Evidence derived from the analysis of real-world data. Source: htglossary.net

This report captures the outputs of discussions with the following Expert Working Group:



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Horizon Scanning and Early Scientific Dialogue

Early planning and deliberate, proactive engagement of all partners during clinical development will be critical to creating awareness of the pipeline of emerging precision oncology innovations, as well as product-specific challenges. Once the developer of a technology recognizes that a therapy presents evidence generation challenges that may be overcome through the collection of post-market data, (potentially using predetermined criteria to help manage the costs associated with a greater emphasis on RWD/E; see Box 1), they should initiate discussions with HTA agencies, regulators, patient groups and clinicians. Key topics to explore during these talks may include: the challenges associated with evidence generation for the therapy; potential strategies and methodologies for addressing uncertainties during trial design and in real-world settings; and perspectives on meaningful clinical endpoints. Ideally, these discussions should occur prior to the finalization of trial protocols, most notably the pivotal trial protocol. A balanced, transparent approach to managing diverse stakeholder interests will be critical to an informed and objective assessment and may promote early and equitable access to promising therapies.

Box 1: Potential Criteria for Greater Emphasis on Post-Market Data in HTA Decisions

- ◆ Extent and nature of the uncertainty associated with the value of a new therapy at market launch
- ◆ Potential of the therapy to result in a meaningful clinical outcome that addresses an unmet need
- ◆ Functional impairment and lethality of the disease
- ◆ Degree of innovativeness of the therapy
- ◆ Alignment with healthcare system priorities
- ◆ Ability to address evidence uncertainties through RWD/E collection and reduce risk through risk-sharing agreements

Broader Value Drivers

Beyond clinical endpoints, the inclusion of broader value drivers in the assessment of clinical outcomes and cost-effectiveness could help manage uncertainty, especially when populations are small and diseases are rare, debilitating, and/or lethal. While it will be important to maintain the foundational regulatory principle of a positive benefit-to-risk ratio, broader value drivers could include:

- ◆ Patient and caregiver preferences (understanding what matters most to patients and caregivers, including quality of life)
- ◆ Societal value (e.g. availability and capacity for education, volunteering, caregiving or labour productivity)
- ◆ Contribution to achieving equitable health outcomes (most notably, in populations with the highest unmet needs)
- ◆ Value of hope (i.e. willingness to accept uncertainty and higher risk given a chance for a cure or a meaningful improvement in symptoms and quality of life)¹
- ◆ Value of knowing (i.e. reduction in disease uncertainty through a diagnosis, which can improve patient well-being and healthcare decision-making)¹

Novel methodologies will need to be established to appropriately integrate broader value drivers into the decision-making process. Furthermore, additional research will need to be conducted to better understand the value of individual preferences and find ways to factor them into the decision-making process.

¹ Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report. Value Health, 2018, 21(2).



Conditional Access and Reimbursement

While the use of risk-sharing agreements with conditional criteria, predetermined and meaningful performance targets and exit points, and processes for adjudicating performance are becoming increasingly common, these types of agreements will be particularly important for precision oncology therapeutics, as they help to reduce the uncertainty for all stakeholders, including patients. Providing conditional market access via performance-based agreements should be discussed during early dialogue so that they can be established prior to market entry and help balance risk across stakeholders. Payers have always accepted some degree of risk when introducing and reimbursing a new therapy, no matter how robust the safety, clinical and cost-effectiveness data might appear at the point of adoption. However, in a situation where significant residual uncertainty remains due, for example, to small trial size, lack of a control arm or direct comparator, and insufficient evidence of a meaningful outcome, the risk should be shifted more toward the developer until sufficient evidence has been collected. The development of standardized performance-based agreement templates, and processes for managing the agreements, for precision oncology therapeutics may serve to alleviate the payer burden of establishing and negotiating the details of these arrangements on a case-by-case basis. Furthermore, transparent, user-friendly and honest communication to patients and patient advocacy groups (PAGs) on exit points or stopping rules within the framework of outcomes-based performance schemes will be critical to ensuring that the rationale behind these important decisions are understood by the individuals that will be impacted most directly.



Real World Data and Real World Evidence

The collection of RWD outside a clinical trial setting allows for systematic RWE generation from a larger patient population in real-world settings, potentially involving patients from multiple jurisdictions through cross-border collaboration. Pre-established protocols for collecting RWD and evaluating RWE that are agreed upon by all parties (including industry, HTA agencies, ethics committees, payers, clinicians) should be established prior to market entry. These integrated evidence plans, should outline:

- ◆ Clear expectations of how the data will be used in decision-making
- ◆ The methodology for data collection in real-world settings
- ◆ Responsibility for data collection and reporting
- ◆ Performance targets and a plan for if performance targets are not met
- ◆ Timelines for reassessment and pricing/reimbursement decision-making.

Decisions on data governance and ownership will need to be determined in a way that complies with patient privacy and respects commercial confidentiality. To ensure efficiency, the processes and types of RWD collection and RWE generation should be simplified and incorporated into routine clinical data collection. If possible, RWD should be linked to a patient's genetic sequencing data. Ideally, data sources should be open and accessible to relevant parties to instill transparency, reliability and trust. While industry could help fund and operate the required data collection infrastructure and processes, governments should ultimately oversee these mechanisms, as they represent a public good.



Patient, Caregiver and Clinician Engagement

Systematic engagement of patients, caregivers, PAGs and clinicians will ensure that decisions are informed by the expertise and experience of these critical stakeholders.

Clinician



- ◆ Share insights on natural history of the disease, unmet need, current standard of care and potential place of a new therapy in the treatment paradigm
- ◆ Advise on meaningful clinical endpoints and their metrics and the feasibility of data collection methodologies
- ◆ Collect RWD and report on RWE
- ◆ Share ongoing learning of risks and benefits of new therapies

Patient/Caregiver/PAGs



- ◆ Share insights on experience with the disease, current treatments, unmet need, and perceived inequities in access to treatment
- ◆ Advise on patient and caregiver preferences and meaningful therapeutic value regarding outcomes of importance, quality of life, and willingness to accept risk
- ◆ Create tumor-agnostic patient group consortia/collaborations to support the development of patient group expertise and capacity to serve as co-collectors of RWD and co-creators of RWE

Collaboration and Harmonization

Enhanced collaboration between stakeholders will be needed to improve transparency, enable joint and parallel assessments, harmonize procedures and share information.

Industry



- ◆ Inform all stakeholders on the emerging technology pipeline
- ◆ Engage in early discussions to share insights on new therapies, trial design and evidence challenges
- ◆ Work with payers/health systems to provide funding and training for the collection of RWD and the generation of RWE

HTA Agency



- ◆ Harmonize processes and methods with other HTA agencies and align on timelines with regulators
- ◆ Develop criteria for RWD collection and RWE generation
- ◆ Maintain oversight of newly adopted technologies to inform decisions on extending use as new evidence emerges

Regulator



- ◆ Align processes and methods with regulators from other regions, as well as HTA agencies, to optimize timelines
- ◆ Collaborate with HTA agencies and payers/health systems on parallel clinical assessments
- ◆ Develop guidelines for patient engagement and for the collection of RWD and the generation of RWE
- ◆ Advise on adaptive pathways as more data is collected

Payer/ Health System



- ◆ Co-fund the establishment and maintenance of RWD/E infrastructure, including patient registries
- ◆ Lead discussions on establishing performance-based agreements and innovative pricing models
- ◆ Advise on health and spending priorities
- ◆ Collect and report on real world value of adopted technologies
- ◆ Share ongoing learning of risks and benefits of new therapies
- ◆ Ensure awareness of regional industrial and innovation policies



Reassessment

Post-market collection, review and reporting of therapeutic performance will be needed to update reimbursement status, pricing decisions and clinical guidelines, or support a disinvestment decision if value cannot be demonstrated. If a product does not deliver sufficient benefits, a plan will need to be developed to reposition or disinvest in product use. Alternatively, if benefits are different from those anticipated at first adoption, there may be a need to renegotiate price. Patients already receiving the therapy should be permitted to consult with their physician to decide whether they should continue treatment. An independent third party (e.g. academic centre of excellence, consulting firm) could collect, review and report on meaningful and easy-to-measure outcomes to reduce the administrative burden on HTA agencies.

Conclusion

Our Expert Working Group aimed to explore ways to improve existing HTA approaches to precision oncology therapeutics and to outline a preliminary vision for a life cycle approach to better manage the uncertainties and reduce the risks associated with these technologies. The emerging framework is characterized by the:

- ◆ Application of criteria to determine which therapies would benefit from a greater emphasis on post-market data to overcome uncertainties that exist at market launch
- ◆ Early and broad engagement with all partners through a process that recognizes diverse stakeholder interests
- ◆ Use of broader value drivers in the assessment to reveal the full value of the technology and help manage uncertainty
- ◆ Establishment of performance-based agreements with predetermined performance targets and processes to adjudicate performance; this process could be supported by an independent third party to minimize payer burden, reduce bias, and balance competing interests
- ◆ Development of frameworks, processes, policies and infrastructure for real-world data collection to enable post-market reassessment
- ◆ Harmonization and collaboration across all stakeholders contributing to a life cycle approach to assess precision oncology therapies and enable sustainable healthcare systems and equitable access for patients.

It is important to note that while the framework is rooted in discussions focused on precision oncology therapeutics, it could also be more broadly applied to other advanced therapies. Furthermore, while many of the components of the framework may already be employed by some countries/HTA agencies, there is a perceived need to formalize and optimize the systematic use of these practices as a comprehensive life cycle approach. While HTA agencies will play a critical role in every aspect of the framework, these central stakeholders will require broad support from other partners to advance this intrinsically multi-stakeholder approach to health technology assessment.

Health systems around the world will need to find a way to assess the increasing number of precision oncology therapeutics under development to effectively prioritize the most promising of these technologies and provide patients with equitable access to potentially life-saving innovations. The life cycle HTA framework emerging from our Expert Working Group sessions provides some initial recommendations to overcome the key challenges associated with evidence generation and guide the evolution of HTAs for a future defined by precision medicine.