CATAPULT
Cell and Gene Therapy

Developing an Early-Stage Target Product Profile (TPP)

A therapy developers guide to creating an evidence generation plan for successful therapy adoption

Introduction

A target product profile (TPP) is a directional tool that needs to be developed from an early stage of a medicinal product's development; it captures aspirational product attributes at launch in order to steer the evidence generation plan, address regulatory and reimbursement requirements, aid development of strategies that reduce downstream risks and ultimately increase the probability of successful therapy adoption. It is a dynamic, living document that is updated as evidence is generated during development. The document is shared between the different stakeholders involved in development including regulatory, clinical, commercial, and market access teams for responding to emerging data on the medicinal product and changes in the external environment. The document requires regular review of milestones and updates in response to new data, with possible changes in clinical and commercial strategy initiated if the new data is not supportive of the attributes needed for commercial viability.

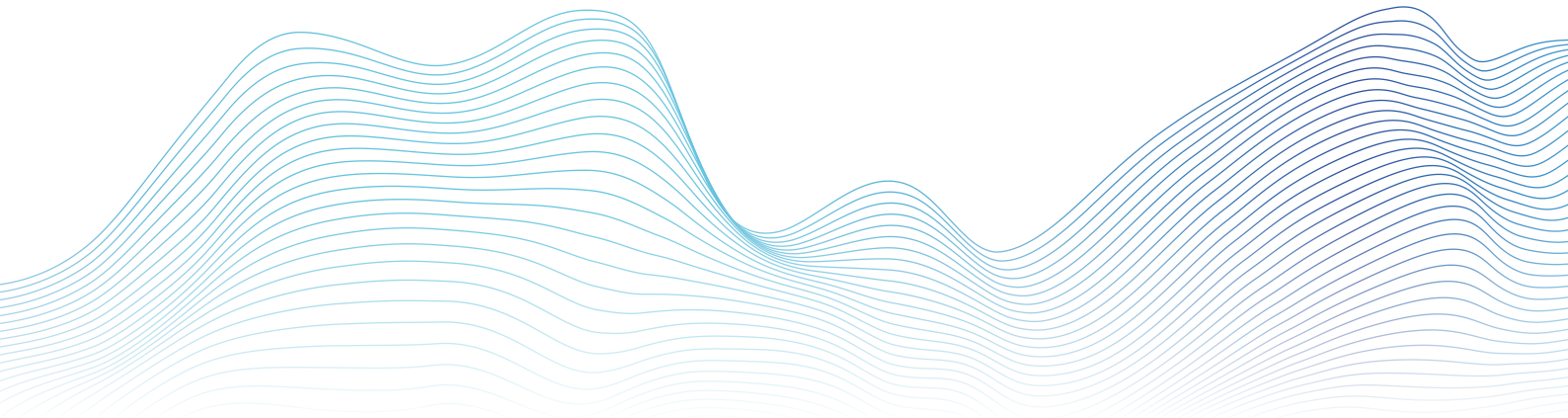
For cell and gene therapies, significant clinical and commercial challenges exist including novel mechanisms of action, one-off administration, often small patient populations and clinical trial sizes, long-term benefits beyond clinical trial duration, and high price required for commercial viability due to the high co st of manufacture and other operational costs. Therefore, the development plan needs to be designed with a vision of the final product from the early stages to guide evidence generation activities and reduce the risk of failure.

It is recommended that a TPP document is developed prior to non-clinical studies, and at the latest before clinical development begins. This ensures that the attributes of the product can be monitored throughout the clinical studies and required thresholds of product performance help inform go/no go decision-making across consecutive stages of development as well as timely corrective action. The product attributes included in the TPP are:

- **Indication –** The target population, taking into consideration subpopulations and therapeutic positioning
- **Administration –** How the product will be delivered to patients
- **Clinical Efficacy –** The outcomes to be measured in the clinical studies and the treatment effect required for commercial viability
- **Clinical Safety –** The safety outcomes and how they impact product value
- **Cost-effectiveness –** How health benefits and cost-savings to healthcare systems, in comparison with existing treatments, impact the commercial viability of the product
- **Competitor Landscape –** How competitors are performing in comparison with the product in terms of the attributes listed above; impact on therapy's unique selling proposition

Generating the information on the ideal characteristics of the product requires multidisciplinary expertise in medical affairs, regulatory, pricing and reimbursement, taking into consideration that there may be geographical variation in the ideal attributes of a product and the supporting evidence required. Key activities include review of applicable clinical and regulatory guidelines, Health Technology Assessments, review of analogous precedents to generate relevant insights, health economic analysis, engagement with clinicians, regulatory and reimbursement bodies. Commercial analysis is also required to inform thresholds of product performance and operational costs for securing viable profit margins and return on investment.

In this resource, we will discuss each of the attributes included in a TPP in detail, to help therapy developers navigate through the process and support the development of successful commercially viable products.



1. Indication

The target indication of the advanced therapy medicinal product (ATMP) should be informed first by biological plausibility and the likelihood of demonstrating a clinically significant treatment effect, as well as the feasibility of clinical development and commercial viability.

Biological plausibility needs to be fully justified early in the non-clinical or pre-clinical development cascade. Decisions on parameters such as pharmacology endpoints and future clinical biomarkers can then be investigated at the R&D stage. Proof of concept (POC) studies are also required in the R&D phase to fully understand how the intended therapeutic product will interact at the in vitro, in vivo (animal model), and clinical levels. Mode of action (MOA) will also need to be exhibited in vitro and in appropriate in vivo animal models with a view to justifying the plausibility of clinical indication selection. Justification of the targeting ability of the ATMP within appropriate tissues along with factors such as tissue latency, clearance, and pharmacodynamic biomarkers can all be used to help justify appropriate clinical indication(s).

Health economics can be used to understand the commercial opportunity in a defined indication, and for the relative prioritisation between indications and therapeutic positions. When reimbursement decisions are made at launch, an economic evaluation determines the value of a new technology compared with currently available treatments; the headroom available to accommodate a high-price therapy (like an ATMP) can be determined by quantifying the unmet need in an indication.

The activities performed to complete this assessment include:

- A literature review of existing treatment guidelines, patient outcomes, economic evaluations of currently available therapies, and pipeline therapies with a high likelihood of entering the market
- Engagement with expert clinicians to gain their insights into unmet need and the feasibility of identifying and treating target patients in existing pathways
- Health economic analysis to quantify the headroom per target indication under consideration, size of target patient population, as well as corresponding thresholds of product performance and operational costs for commercial viability

Clinical feasibility and commercial opportunity vary between indications and therapeutic positions (e.g. 1st vs 2nd line chemotherapy), with later-stage therapeutic positions often having higher price potential but smaller patient numbers and more challenging disease stages for demonstrating benefit.

Once a commercially viable indication has been identified which the technology is likely to have a significant treatment effect, supported by the relevant non-clinical and CMC (Chemistry, Manufacturing, and Controls) considerations, the feasibility of conducting clinical trials in the indication and capturing meaningful clinical benefit must be considered. This requires epidemiological assessment of eligible patient numbers, considering the heterogeneity in the indication and the number of patients needed to capture significant benefit. For feasibility, ethical considerations also need to be assessed regarding the risk-benefit to patients of receiving an experimental therapy (especially when alternative therapies are available). Similarly, the availability of necessary hospital infrastructure at clinical trial sites needs to be assessed. For this feasibility assessment, insights from expert clinicians are valuable as well as engagement with regulators to endorse the proposed clinical trial design, including the minimum number of patients required.

Target Attribute	Considerations

Indication	• **Primary indication:**
	  • Subpopulation
	  • Therapeutic position
	• **Follow-up indications (paediatric)**
	• **Restrictions and exclusions**

Table 1. Key considerations for the target indication of ATMPs.

2. Administration

Advanced therapies can have complex preparation and administration processes, so the clinical and commercial viability of the proposed regimens should be assessed during the clinical trials and pre-launch. This can occur through clinician advisory boards to ensure challenges aligning within the healthcare systems are resolved so that they do not become a barrier to access. The cost of delivering the therapies can also have a significant impact on the reimbursement potential, given the cost to the healthcare system will be incorporated into any cost-effectiveness models at launch.

Target Attribute	Considerations

Administration	• **Patient-level:**
	  • Administration route (IV etc)
	  • Treatment duration (single or repeat dosing)
	  • Monitoring
	  • Procurement of starting material such as leukapheresis
	• **Supply chain:**
	  • Clinical trial; site selection
	  • Starting material and drug product logistics (storage and shipping)
	  • Drug product handling at the clinical site (e.g. pharmacy preparation/in-theatre preparation)
	  • Clinical site infrastructure requirements
	  • Specialised equipment & surgical needs
	  • Hospital capacity

Table 2. Key considerations for the administration process of ATMPs.

3. Clinical Efficacy

The target clinical efficacy of a new technology is determined by the clinical meaningfulness and commercial viability. At the early stages of development, early efficacy signals can be established in non-clinical models. In indications where there are no disease-specific non-clinical models, paper-based approaches can be used, for example, to show that the mechanism of action is comparable to a competitor. The efficacy parameters in the TPP should be updated as clinical development begins and more efficacy data is generated and compared with commercially viable parameters.

Outcomes need to be selected to ensure the benefit of a technology is captured in a way that satisfies regulators as well as provides evidence that can be used in economic evaluations and clinical decision-making, considering that definitions of response to treatment may vary geographically. In some indications, disease-specific guidelines published by regulatory bodies can inform regulatory evidence requirements, for example, the EMA (European Medicines Agency) have issued the draft Guideline on the clinical evaluation of anticancer medicinal products (EMA/CHMP/205/95 Rev.6), and this should be consulted when developing a relevant clinical development plan.

Clinician engagement ensures outcomes are defined in alignment with clinical practice and inform the minimum clinically important differences (MCID), however, the improved magnitude of MCID is often too low to enable the high price that is needed for ATMP commercial viability. Health economic analysis can be used to interrogate the relationship between parameters of product performance and corresponding value-based price potential. This can be used to determine the thresholds of efficacy which need to be demonstrated to ensure a commercially viable product is being developed. The analysis can determine the key drivers of value for a technology (e.g. survival, improved quality of life, displaced costs of current treatments) and therefore the outcomes that need to be prioritised in clinical development. The outcomes that inform health economic analysis are typically patient-centred hard outcomes (such as clinical events, survival, and disease progression); improvements in surrogate outcomes (such as disease biomarkers) must translate to improvements in hard outcomes to be accepted by reimbursement decision-makers. Therefore, a literature review is required to check the surrogate outcomes are validated in the target indication, and validation studies should be considered if there are evidence gaps. Health related quality of life measures can be collected directly from patients, and choice of patient-reported outcome measures (PROMs) need to be carefully selected to ensure the measures will be sensitive to the treatment benefit and can be used to determine health gains at economic evaluation (e.g. deriving the quality-adjusted life year QALY)). Clinician and patient engagement can provide useful insights into the value of different PROMs for clinical development.

When commissioning decisions for new technologies are made, efficacy and value are assessed against existing treatment options. Therefore, the generation of comparative effectiveness evidence is required; achieved through a randomised control arm in the clinical trial and/or using statistical methods. However, the acceptance of the latter by reimbursement decision-makers is variable. Low patient numbers in rare diseases and ethical reasons can sometimes justify single-arm trials, and comparative evidence can be generated against patient baseline characteristics or the natural history of a disease. However, the optimum trial design would be a randomised controlled trial where the control is the current standard of care against which the technology would be assessed at economic evaluation.

For technologies that provide long-term clinical benefits beyond the clinical trial timeframe, it can be challenging to substantiate this benefit in a manner that will satisfy reimbursement bodies, and the uncertainty of long-term value will have a downward impact on the price at which the technology is considered cost-effective.

Potential strategies to address this barrier include:

- Planning for long-term follow-up of early-stage trials
- Generating evidence on the correlation between short and longer-term outcomes, e.g. in oncology indications; literature review can determine if disease registries or other evidence exists on long-term patient outcomes after achieving a complete response
- Biological plausibility of long-term benefit as well as long-term data from therapies with analogous cellular and/or genetic mechanism of action can also be used as an argument to justify long-term claims; this requires a review of outcomes of existing products that work in the same indication, or the same mechanism of action, as well as expert clinician insight on feasibility of the long-term claims
- In certain cases, animal studies with long-term follow-up can provide supplementary evidence on the sustainability of effect

The acceptability of the trial designs in terms of population criteria, outcomes, randomisation, and duration should be discussed with clinicians, regulators, and reimbursement bodies as early as possible (e.g. parallel consultations provided by the MHRA/NICE and EMA/EUnetHTA). However, where advice may be sought on the acceptability of the proposed trial design, the commercial viability of the investigational product is not an aspect that would be covered in these engagements and requires internal decision-making utilising regulatory, medical affairs, and market access expertise.

Target Attribute	Considerations

Clinical Efficacy	• **Endpoints:**
	  • Primary
	  • Secondary
	  • Exploratory
	• **How efficacy outcomes translate to minimum clinically meaningful outcomes (i.e. clinical events):**
	  • Surrogate outcomes
	  • Hard outcomes
	• **Patient-centred outcomes (clinical events, quality of life, PROMs, economic)**
	• **Choice of comparator (may be country-specific)**
	• **How comparative effectiveness will be demonstrated (trial design, indirect comparisons, observational datasets)**
	• **Outcome requirements of national physician bodies, regulators, payers (pre-first in human (FiH))**
	• **Key value drivers (pre-FiH)**
	• **Long term sustainability of effect**
	  • Availability of a registry to monitor long term outcomes
	• **Accounting for heterogeneity, variation in treatment effect & subpopulations to inform:**
	  • Clinical trial design
	  • Impact on cost-effectiveness

Table 3. Key considerations to demonstrate clinical efficacy of ATMPs.

4. Clinical Safety

If available in the target indication, disease specific regulatory guidelines give guidance on the safety outcomes required. Before clinical development, biological plausibility and non-clinical studies can inform the safety endpoints for the clinical trials. The non-clinical studies required depend on the indication, the mechanism of action of the technology, duration of the clinical trials, and include:

- Toxicology
- Safety Pharmacology
- Immunogenicity
- Tumorigenicity
- Genetic toxicology/genome integration
- Correct animal models
- ISO medical device considerations where appropriate

Once clinical development has been initiated, the safety data from the clinical studies will complement or replace the non-clinical data in the TPP. If adverse events are expected, then expert clinician input is required pre-launch to understand the impact on service delivery and costs from patient management.

Target Attribute	Considerations
Clinical Safety	• **Outcomes** • **Endpoints** • **Warnings** • **Contraindications** • **Expected events/reactions:** • Precautions

Table 4. Key considerations for the clinical safety of ATMPs.

5. Cost-effectiveness

The cost-effectiveness of the product to healthcare systems depends on the health benefits to patients and cost-savings from displacing existing treatments as well as the methodological framework applicable to a given country. However, universally across all geographies, the costs of existing/comparator treatments are taken into consideration. If currently available treatments are low-cost, the new technology will have to provide substantial health benefits in order to be considered cost-effective.

The prices of analogue therapies can also be useful to understand how much a healthcare system is willing to pay for a similar technology. This assessment of the market access landscape should occur before clinical development to ensure there is a commercial opportunity, and a more in-depth health economic analysis can be performed if greater clarity is needed over the value of the technology.

A limitation of early health economic and market access analyses is that there is uncertainty over what comparators will be on the market at the time of launch, so an assessment of pipeline products is also useful, however, the failure rate during early-stage clinical development is high. The market analysis can give valuable insights into the willingness to pay for a new technology and this can be validated with payer engagement.

An early health economic model can determine the maximum cost-effective price potential for key geographies based on the potential to address disease burden in target indications and the use of value-based frameworks. The willingness to pay for a new technology is also affected by the size of the population as healthcare systems are concerned with affordability at the population level. Budget impact analyses can be performed for this purpose. Pricing insights derived from the cost-effectiveness and budget impact analyses can be compared with the anticipated operational costs to inform commercial viability. As clinical data is generated during development, health economic models are updated accordingly, and these updates subsequently feed into the TPP.

Target Attribute	Considerations

Cost-effectiveness	• **Impact of data uncertainty**
	• **Current costs to the healthcare system of:**
	  • Comparator therapies or best supportive care
	• **Anticipated costs to the healthcare system by novel therapies likely to be adopted**
	• **Willingness to pay by healthcare systems considering:**
	  • Variation in pricing frameworks across launch geographies
	  • Launch sequence and impact of cross-border pricing
	• **Product price required for commercial viability vs value-based price; corresponding commercial risks**
	  • Corresponding value-based price
	• **Anticipated incidence/prevalence and budget impact, affordability mechanisms available**

Table 5. Key considerations for the cost-effectiveness of ATMPs.

6. Competitor Landscape

Where the information is available, current and emerging competition should be considered against all aspects of the TPP. This section of the document should be updated regularly; progress made with the new technology should be compared against competitors to inform added value propositions and corresponding evidence generation plans. Predicted time to launch is also important; being the first-to-market could be advantageous, as is reducing the time to launch in general through accelerated regulatory and reimbursement pathways. However, not being first-to-market is not always a disadvantage as it provides the opportunity for barriers to adoption to be reduced by the first-to-market (e.g. reduction of long-term uncertainty around a particular MoA, implementation of suitable commissioning policies, improvement of NHS readiness for adoption of a particular type of therapy etc). Furthermore, if a high-cost treatment enters the market then this increases the opportunity for subsequent entrants to leverage the high pricing benchmark and provides robust health economic justification of added value through displacing costs.

Target Attribute	Considerations

Competitor Landscape	• **Considerations on how the value proposition compared with existing/pipeline products is impacted by:**
	  • MoA
	  • Orphan Drug Designation (ODD)
	  • Clinical Efficacy
	  • Clinical Safety
	  • Administration route
	  • Price
	  • Time to patent expiry
	  • Predicted time to market
	  • First launch country
	  • Requirement for acceleration if a competitor is closer to launch (depending on whether the competitor increases or reduces value proposition)

Table 6. Key considerations for the competitor landscape of ATMPs.

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If you are looking for support in building a robust TPP that maximises the chances of your therapy overcoming commercial and clinical barriers, please contact us: **ct.catapult.org.uk/contact**

Learn more about our Health Economics and Market Access (HEMA) capabilities **here**

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