



Workshop Session



Reimbursement Considerations for Advanced Therapy Medicinal Products

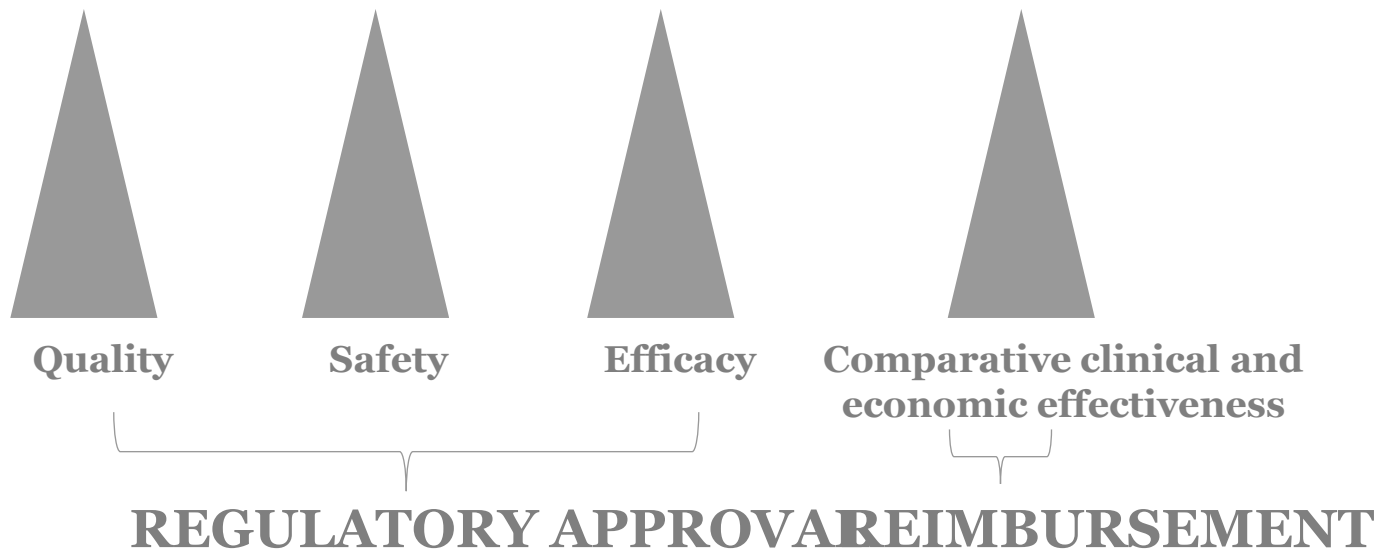
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Reimbursement considerations for ATMPs

May 2019

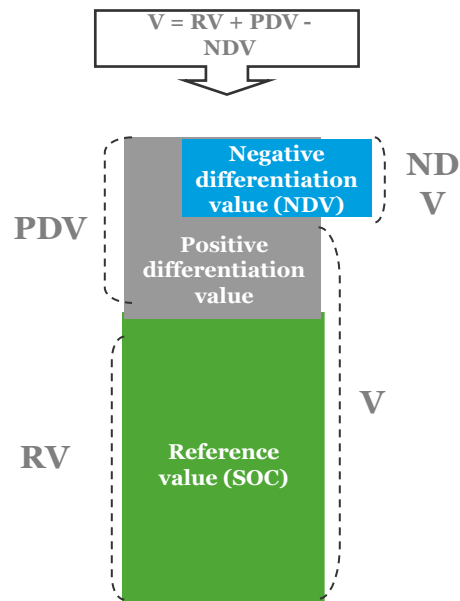
Data requirements for market authorization and reimbursement differ; the latter commands evidence of comparative effectiveness vs SOC*



* SOC: Standard of Care

Value-based assessments are widely used to link price potential to the novel therapy's added-value

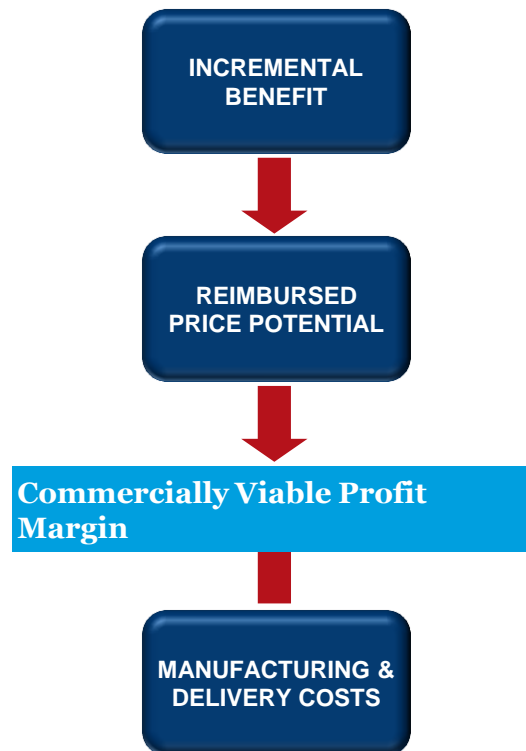
PRINCIPLES OF VALUE-BASED ASSESSMENTS



Differentiating Value

- Added-value defined in terms of clinical and economic terms
- Comparative data against the SOC is required
- For a given indication, “V” varies depending on therapeutic positioning

The high manufacturing and delivery costs of ATMPs present challenges that need to be considered from the early stages of their development



- Levers that help reduce challenges:
 - Incremental benefit maximisation
 - Supporting evidence generation planning
 - Manufacturing cost minimisation
 - Reduction of those healthcare costs (that are additional to therapy acquisition) and associated with the delivery of the novel therapy

To secure ATMP commercial viability, certain market access considerations need to be addressed before starting clinical trials



Shape early ATMP development by identifying:

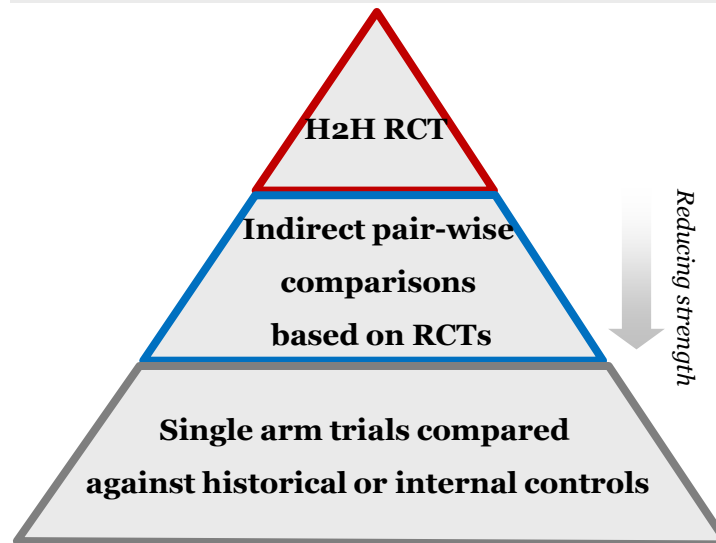
- Headroom for innovation in target indication / therapeutic position
 - Identify whether target indication can accommodate high cost therapies, inform clinical strategy accordingly
- Value maximising clinical and economic outcomes
 - In order to inform development of Target Product Profile and evidence generation plan
- Interrelationship between therapy benefits and reimbursed price potential in order to:
 - Define product performance and manufacturing cost thresholds for commercial viability
 - Inform clinical and manufacturing strategy accordingly

Meeting reimbursement requirements for supporting evidence at launch, can be challenging for ATMPs

Common challenges include:

- Potential for a cure but lack of long-term data at launch
- Weak comparative effectiveness data vs the standard of care (SOC) due to one or more of the following:
 - Head-to head comparative data against the standard of care is not available
 - Randomised controlled trials not feasible (limiting prospect for indirect comparisons)
 - Meaningful comparative data from single arm trials can not be generated due to limitations with historical control data / natural history of disease is not well known/ patient population heterogeneous
 - Small trials limit statistical significance of outcomes measured
 - Only surrogate rather than final/hard clinical outcomes may have been measured (risk for overestimation of benefit)
 - No comparable treatment and measures of outcome may be available

Due to clinical feasibility constraints only lower levels of comparative data may be available at launch



Engagement with market access stakeholders early in clinical development is needed to understand evidence requirements and plan accordingly



- Engagement with key market access stakeholders early in clinical development to understand evidence requirements and how challenges with evidence generation can be addressed; options include:
 - Centralised at national level: parallel EMA and EUnetHTA consultation
 - Decentralised at national level: Engaging with individual HTA bodies across markets
 - Decentralised at national, regional and local level: Key market access stakeholder engagement across individual major markets and their regions

Developers need to establish prior to seeking HTA advise which value story secures commercial viability; the subsequent HTA advise will identify evidence needed to substantiate this value story

Identify the commercially viable target price and population

Develop a value story that supports the target price in the target population

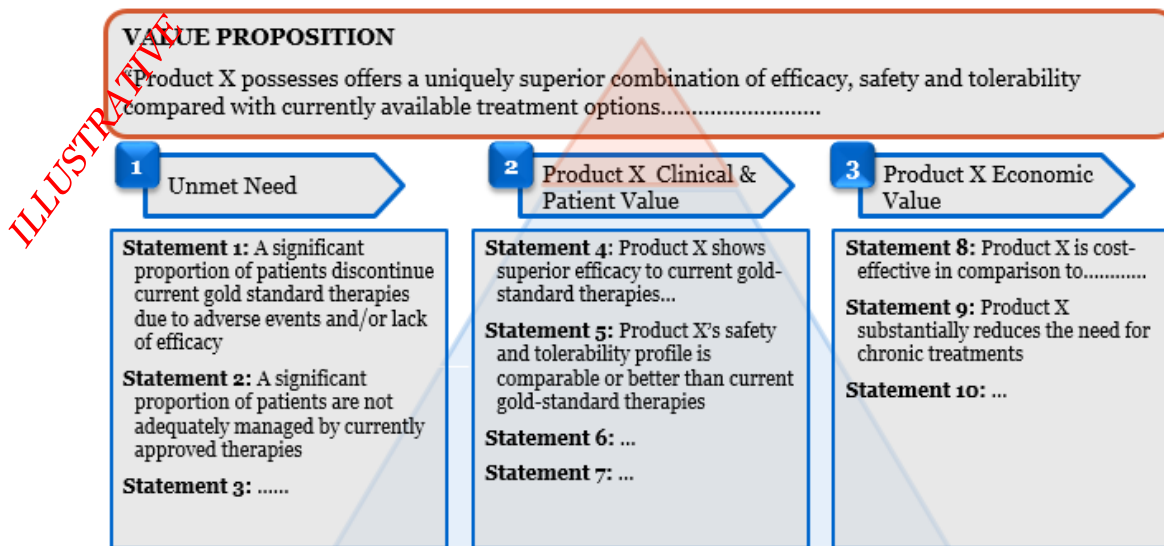
Create an evidence generation plan that provides the best possible support for the value story

HTA/Payer Consultation

Contextualise learnings and revisit evidence generation plan to optimise commercial viability

In order to engage constructively with HTA bodies, it is important to conduct the following activities sequentially:

- Understand value drivers for given therapy and how these can support a commercially viable price and volume; this information forms the basis for the development of the target value story
- Develop the *briefing document* for the consultation, addressing:
 - Unmet need in the target therapy area
 - Product's target value story and how it addresses the unmet need
 - The evidence generation plan, and how it supports the target value story
 - The areas where evidence gaps may exist, and formulate questions for HTA bodies and propose potential solutions
- Explore the HTA bodies' perspective on how best to substantiate the value story; adjust evidence generation plan accordingly



- The value story is typically structured in three domains, with an overarching paragraph that summarizes the value proposition
 - **Value proposition:** Summary of incremental value of novel therapy over existing
 - **Value statements:**
 - Unmet need: it should align with the incremental benefits of the novel therapy
 - Clinical and economic value statements: describe therapy's incremental benefit in clinical and economic terms
 - Value statements should be supported by the proposed clinical and economic evidence to be generated

The outputs from the activities described so far will inform the development of the target product profile (alongside clinical and regulatory considerations)

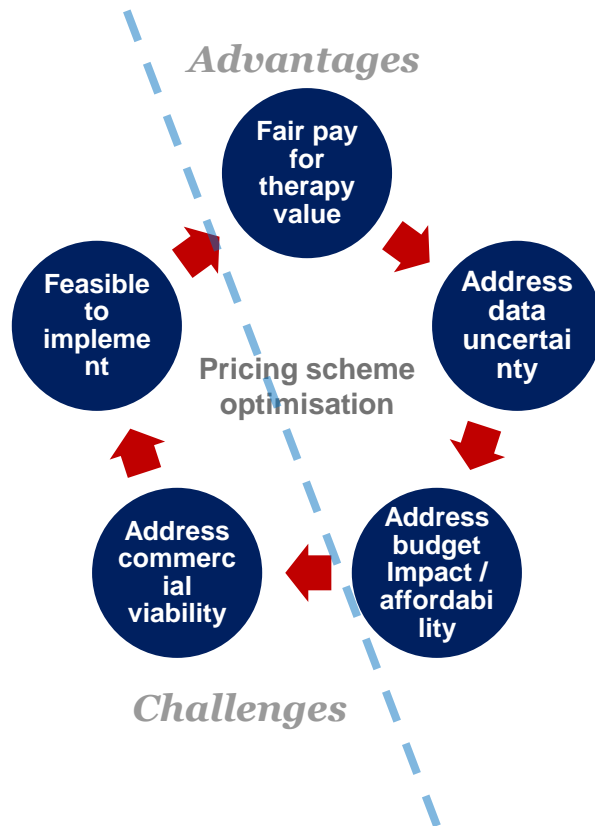
| Objective | Activity | Output |
|-------------------------|---|---|
| Commercial Viability | Room for Innovation | Ensure target indication/ therapeutic position can accommodate a high cost therapy |
| | Pricing research and sensitivity analysis | Incorporate key clinical and economic drivers of product value into TPP |
| | | Define product performance and manufacturing cost thresholds for commercial viability |
| Clinical Considerations | Clinical feasibility | Understand feasibility of undertaking clinical development in target indication / therapeutic position |
| Data Requirements | Engage with regulators | Ensure agreement on therapeutic position with regulators ; Ensure evidence generation plan in line with expectations of regulators and key market access stakeholders |
| | Engage with payers | |

Given that data uncertainty is high, consideration of innovative pricing mechanisms in preparation for launch is key for ATMPs



- Where appropriate, address evidence gaps through modelled data (e.g. extrapolation frameworks to support long-term claims)
- Finalise:
 - Health Economic Models
 - Value Dossier including:
 - Value story and supporting clinical and economic evidence (customised to individual market requirements)
 - Target price for each launch market
 - Geographical launch sequence
- Develop strategies for maximising reimbursement and adoption potential
 - Innovative pricing schemes/Managed Entry Agreements (MEAs)
 - Post-launch evidence generation plans

Key considerations in selecting a Managed Entry Agreement



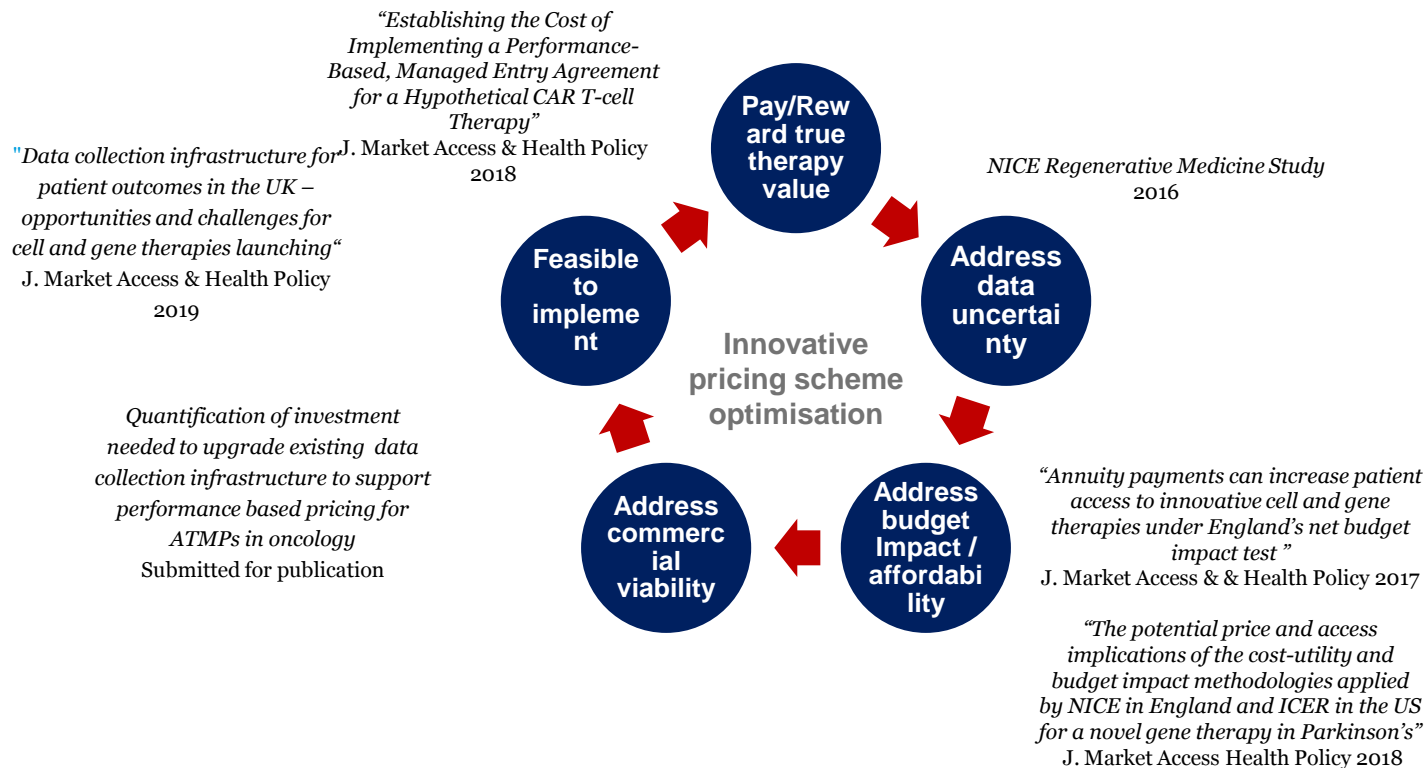
Each MEA can have a different impact on price, volume, cash-flow and margins

Choosing between MEAs with similar effect on uncertainty

| | | Manufacturer | |
|----------------------------------|------------------|--|---|
| | | Pros | Cons |
| Performance-linked reimbursement | Discount | Faster revenue generation | Large Budget Impact (BI) may limit access* |
| | Rebates | | |
| | Annuities | Small BI could enable wider access | Slow revenue generation; is it commercially viable? <i>third party finance?</i> |
| | | High implementation costs; Accountancy practices within the NHS do not support annuities; Revenue recognition challenges within pharma | |

*£20M annual (years 1-3) net BI trigger-point for commercial negotiations with NHS England

Our environmental shaping activities and deliverables so far: focus on innovative pricing mechanisms to support ATMP adoption



Recommendations on cost-utility analysis metrics to identify the pricing scheme that minimises data uncertainty:

“Exploring the assessment and appraisal of regenerative medicines and cell therapy products”, NICE, March 2016

Illustrative

| Scenario (per patient) | ICER | Incremental NHE (QALY*) | Probability Cost Effective | Consequences of decision uncertainty (QALY*) | Adoption potential |
|---|---------|-------------------------|----------------------------|--|--------------------|
| £100,000 one-off acquisition cost | £50,000 | -55 | 50% | 300 | Very low |
| 10% discount | £45,000 | 200 | 65% | 250 | Low |
| Pay-for-performance: <i>i.e. for patients with remission by day 30</i> | £40,000 | 250 | 70% | 100 | Possible |
| Lifetime leasing: <i>payment pcm for surviving patients (£2,000 pcm)</i> | £35,000 | 1000 | 99.5% | 2 | High |

Maximise (pointing to 1000 and 99.5%)
Minimise (pointing to 2)

Metrics are sensitive to the discount rate used i.e. 3.5% vs 1.5%

*Based on end-of-life ICER threshold: £50,000

We created a methodological framework that quantifies the administrative burden of innovative pricing schemes

Deliverables

- A. Building on the NICE Regenerative Medicine study, we quantified the administrative burden of introducing an outcomes-based pricing scheme for the exemplar CAR T-cell therapy for late-stage ALL, using a staged payment approach over a 10-year time horizon
- B. Provided a methodological framework for exploring the costs associated with setting up and implementing an outcomes-based pricing scheme

Incremental administrative burden per patient of introducing the CAR T-cell therapy with an outcomes-based annuity

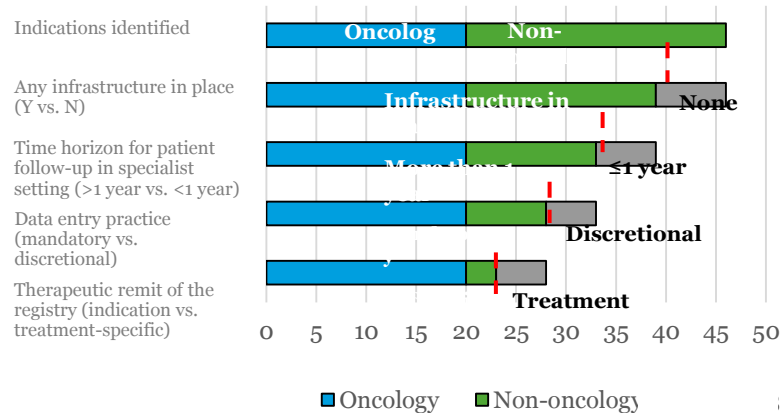
| Comparator | Incremental cost per patient (total over 10 years) | | Incremental cost per patient (per year) | |
|----------------------------|--|-----------------|---|------------------|
| | Cost | Time | Cost | Time |
| CAR T-cell therapy w/o MEA | £2,403 | 15 working days | £240 | 1.5 working days |

Establishing the Cost of Implementing a Performance-Based, Managed Entry Agreement for a Hypothetical CAR T-cell Therapy

J. Market Access & Health Policy 2018

We explored the suitability of existing data collection infrastructure for operating PBRs* in therapy areas relevant for upcoming ATMP launches

- We identified 58 ATMPs at a mature trial stage, in 47 target indications across 12 therapy areas
 - 20 target indications in oncology (being targeted by 23 ATMPs)
- In therapy areas where data collection infrastructure exists it is suboptimal for PBRs
 - Oncology infrastructure most advanced
 - Among non-oncology indications, ~ 2/3 have a data collection infrastructure



"Data collection infrastructure for patient outcomes in the UK – Opportunities and challenges for cell and gene therapies launching"
J. Market Access & Health Policy 2019

We have also explored the investment needed for developing and operating the data collection infrastructure needed for PBPS

- A. The feasibility of upgrading existing therapy area specific infrastructure (starting with oncology and blood disorders due to imminence of launches)

| Therapy Area | Current data collection infrastructure |
|-------------------|--|
| Oncology (x23) | Systemic Anti-Cancer Treatment (SACT) database and the European Bone Marrow Transplant (EBMT) registry |
| Beta thalassaemia | The National Haemoglobinopathy registry and EBMT |

Submitted for publication

- B. The feasibility of a cross-therapy area data collection infrastructure (as per AIFA-web based tool)
- C. An information system that integrates information from multiple sources like disease specific registries, non-disease specific databases, electronic patient records etc, to generate the information needed for PBPS

- This provides flexibility to work with registries that have primarily being developed for other purposes e.g. regulatory, and to have minimal impact on current data entry practices.

Need for cross-border multi-stakeholder (industry / healthcare systems) initiatives to strengthen infrastructure

CATAPULT

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