

Cell and Gene therapy reimbursement: the CGC approach

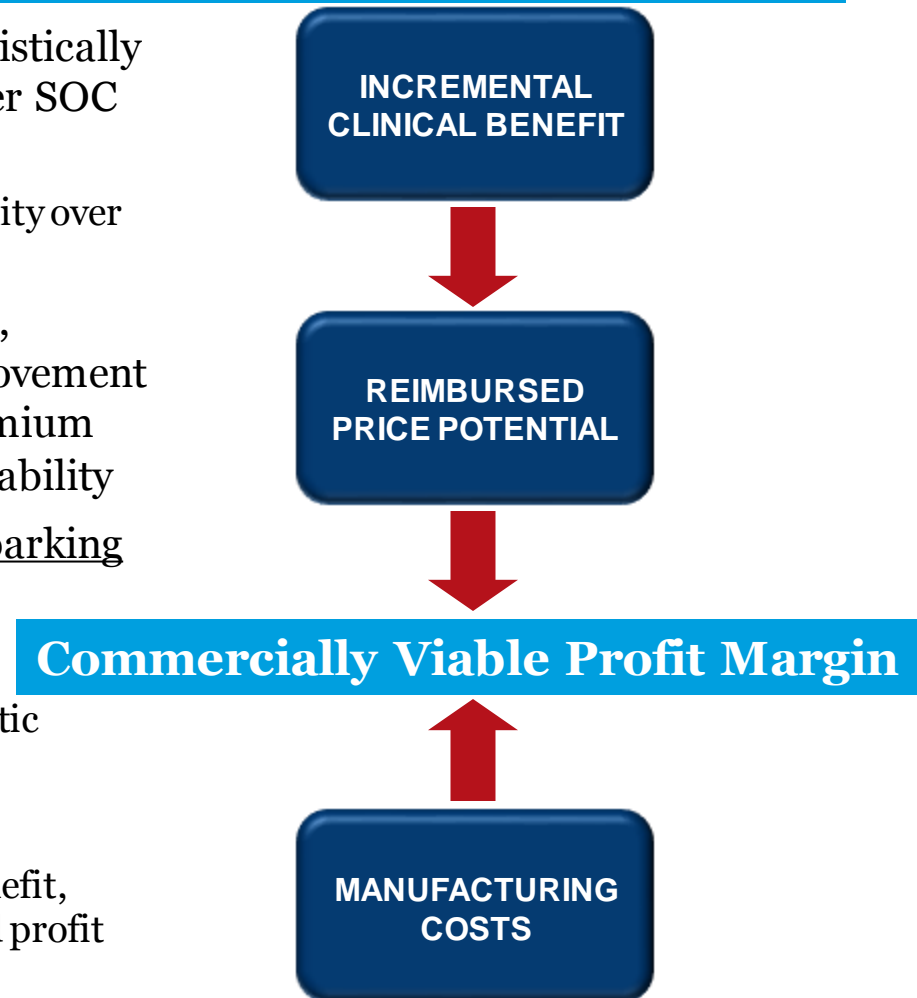
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The considerably higher cost of ATMPs necessitates earlier consideration of reimbursement matters

- For small molecules demonstration of statistically and clinically significant improvement over SOC can often secure commercial viability
 - Lower manufacturing costs provide flexibility over commercially viable price thresholds
- Besides statistical and clinical significance, ATMPs also need to demonstrate an improvement proportionate to the substantial price premium (over the SOC) required for commercial viability
- It is important to understand prior to embarking on clinical development:
 - Room for innovation
 - Value maximising indication and therapeutic positioning
 - Key HE drivers to inform TPP
 - Interrelationship between incremental benefit, reimbursed price, manufacturing costs and profit margins
- Inform clinical and manufacturing strategy
- Ongoing re-assessment as evidence is generated to support go : no go decisions



The CGT approach: incorporation of HE&MA considerations in shaping early development

- Key objectives:
 - Explore novel therapy's reimbursed price and adoption potential across the Big5EU, by reviewing factors relevant to national and local level market access stakeholders
 - Understand key drivers of product value
 - Investigate the interrelationship between reimbursed price potential and the Target Product Profile (TPP) parameters
 - Define product performance and manufacturing cost thresholds for commercial viability
 - Inform TPP
 - Inform clinical and manufacturing strategy
 - Define go: no go decision making criteria

Factors impacting willingness to pay and reimbursed price potential across the Big5EU



How differentiating value is captured and translated to reimbursed price varies by geography

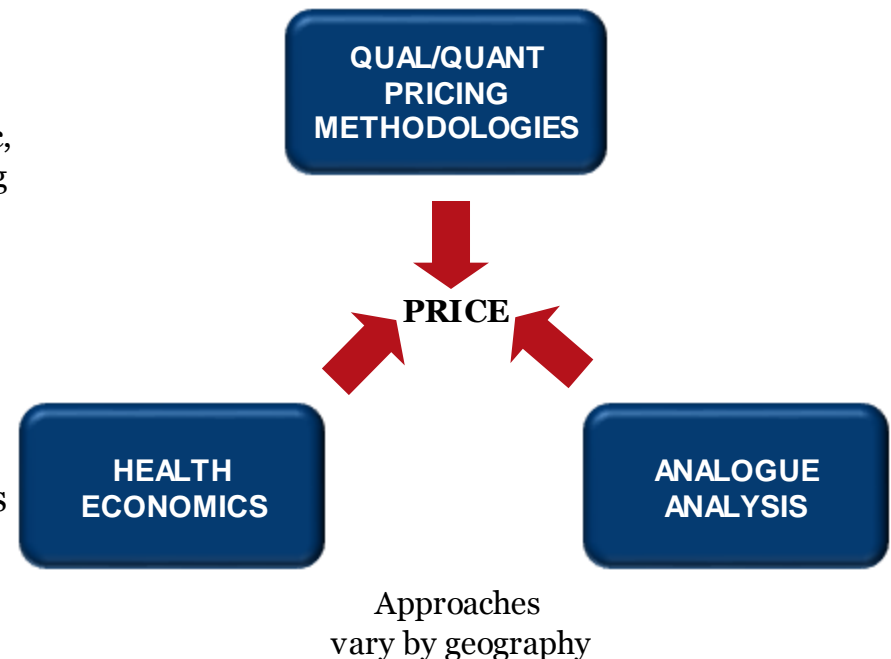
Most commonly used levers by market

Levers	UK	France	Germany	Italy & Spain
1 st order	Comparative clinical effectiveness of the novel therapy vs a relevant comparator in the given market			
2 nd order	Cost-utility	<u>ASMR1-3:</u> International price referencing (EU4) + Cost-utility <u>ASMR4-5:</u> Domestic comparator price Price-volume agreements	<u>With added benefit:</u> Budget impact Efficiency Frontier International price referencing (EU15) <u>No added benefit:</u> Domestic comparator price	Budget Impact + International price referencing (cost-utility: minor lever)

In developing an early stage European pricing & reimbursement strategy for innovative therapies we leverage multiple frameworks

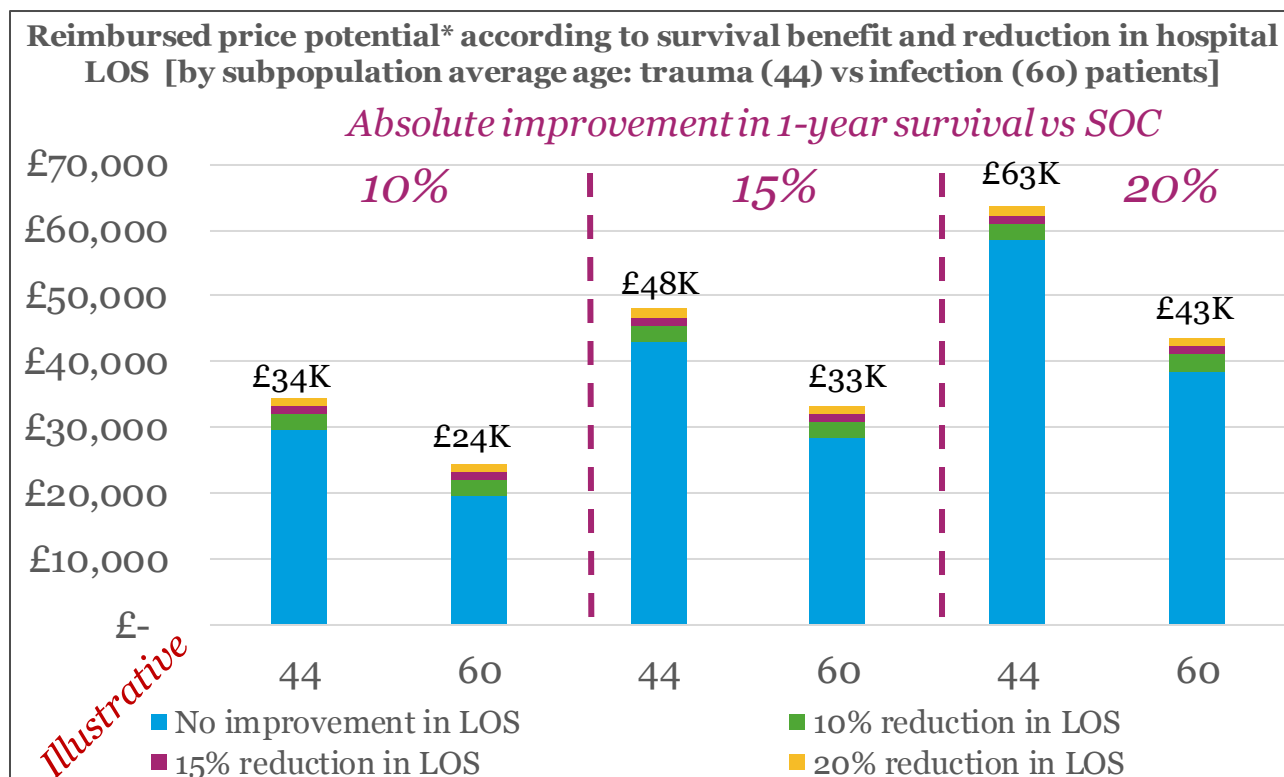
- Stage 1: UK focused
 - Systematic evidence review
 - Advisory board
 - Cost-utility analysis (CUA)
 - Also relevant for Australia, Canada, Nordic, Netherlands (and other markets to varying degrees)
 - Budget impact analysis (BIA)
- Stage 2: Big4EU perspective (GE,FR,IT,SP)
 - Country customisation of Stage 1 findings
 - Analogue analysis
 - Qual./Quant. pricing research
- Stage 3: synthesis of findings and formulation of pricing & reimbursement strategy
- Subsequent stages (pre-launch): Reiteration and refinement as clinical data is generated, value story and dossier development, global optimisation

Methodology Triangulation



***Timelines for stage 1 & 2:
~20 weeks, 3 FTE***

Example 1 (Respiratory disease): Using CUA we assessed reimbursed price potential for a novel therapy across a range of TPP parameters and therapeutic positions / subpopulations



- Key drivers of reimbursed price potential are survival improvement and therapeutic positioning by subpopulation
- Typical age of subpopulation impacts QALY gain from survival benefit
- Reduction in LOS is a weaker value driver

These findings help inform clinical development specifications (e.g. target regulatory label, trial inclusion criteria, comparator, outcome measures, endpoints, trial duration) so that resulting value proposition enables commercial viability

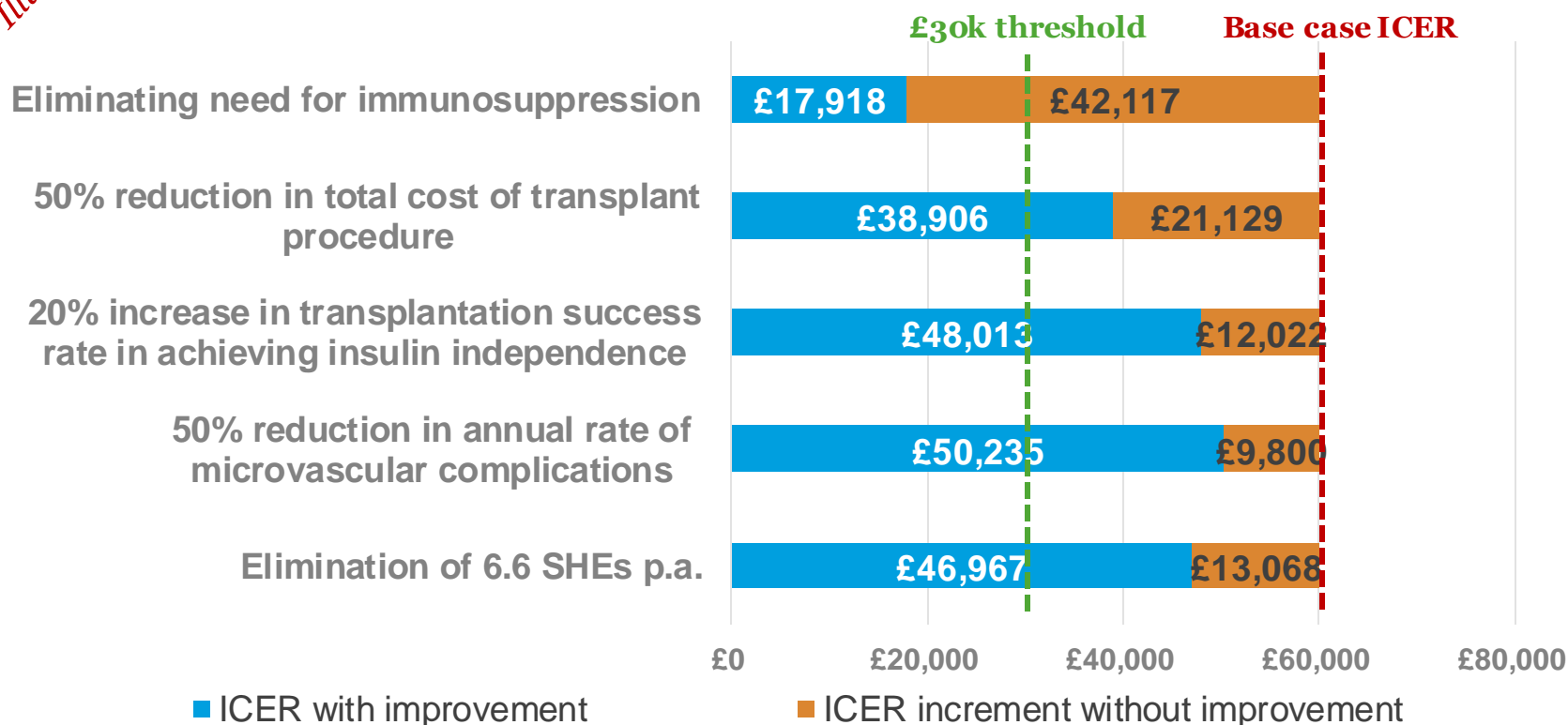
*based on a WTP of £30k per QALY gain

Example 2 (Islet Transplantation in T1D): CUA plus one-way sensitivity analysis helped identify areas for future R&D focus in order to strengthen the cost-effectiveness argument

One-way sensitivity analysis

Impact on ICER of each variable tested

Illustrative



Example 3 (Diabetic Retinopathy): using CUA and multivariate sensitivity analysis we identified efficacy thresholds that support commercially viable target price

- Fixed parameters: Price set at commercially viable level (manufacturer's target price); WTP at £30K per QALY gain
- Variable parameters (clinical outcomes):
 - % patients overcoming macular oedema
 - % patients improving vision significantly (0.1 increase in QoL utility)
 - % reduction in neovascularisation and associated complications
- Table informs on the combinations of the variable parameters necessary given the values of the fixed parameters

% patients not requiring further treatment for MO <i>Illustrative</i>	% Reduction in neovascularisation and associated complications (minimum % of patients improving vision significantly)		
	25%	50%	75%
75%	60%	40%	20%
50%		40%	20%
25%		50%	25%

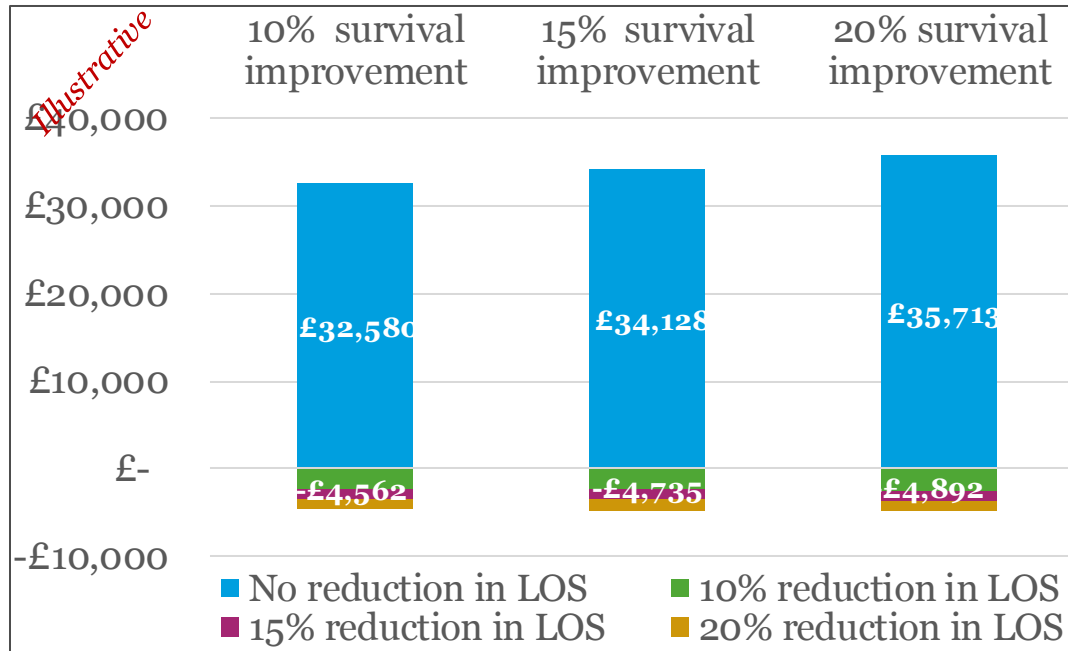
In order to understand local level funding implications and uptake we undertake budget impact analysis

- Unlike cost-utility analysis, budget impact analysis:
 - Does not reward for gains in life years and QoL
 - Covers a short time horizon (up to 5 years)
- Typically operational by local level payers
- Key drivers:
 - costs / savings arising from the displacement of existing therapies by the novel therapy
 - usually healthcare budget only
 - Number of treated patients
 - Horizon

Model Settings				
Setting	Value	Results Options	Index	
Total Population of England	50,542,505	Cost results selection :	1	
	14,106	Total Annual Costs	1	
		Per-Member-Per-Month Costs	2	

Budget Impact: Tabular Results					
Outcome	Current Year	Year 2	Year 3	Year 4	Year 5
Cost Outcomes					
Drug Costs	£6,447,553	£7,046,901	£7,274,208	£7,728,821	£8,183,434
Clopidogrel	£6,447,553	£4,849,271	£4,243,112	£3,030,794	£1,818,477
Prasugrel	£0	£2,197,631	£3,031,096	£4,698,027	£6,364,958
Rehospitalization Costs	£28,424,710	£28,264,360	£28,200,220	£28,077,285	£27,954,350
Total Costs	£34,872,263	£35,311,261	£35,474,428	£35,806,106	£36,137,784
Change in Costs					
Drug Costs		£599,348	£826,655	£1,281,268	£1,735,881
Rehospitalization Costs		£-160,350	£-224,490	£-347,421	£-470,360
Total Costs		£438,998	£602,165	£933,843	£1,265,521
Health Outcomes					
Number of Rehospitalizations	5,318	5,288	5,276	5,253	5,230
Rehospitalizations Avoided		30	42	65	88

Example 4; based on the cost-effective price potential identified through CUA, we used BIA to quantify additional NHS budget required per patient treated in year 1, across various scenarios



- **In our example large budget impact in year one is driven by:**

- High adoption costs due to the high reimbursed price potential of the cell therapy
- Increase in healthcare costs due to more patients surviving (and incurring additional treatment costs) compared to the SOC
- Cost savings from reducing hospital length of stay is not large enough to offset the previous two

Substantial budget impact can limit speed of uptake, despite therapy being cost-effective

When HTA guidance is not binding, Rx decision subject to individual clinician and patient preference

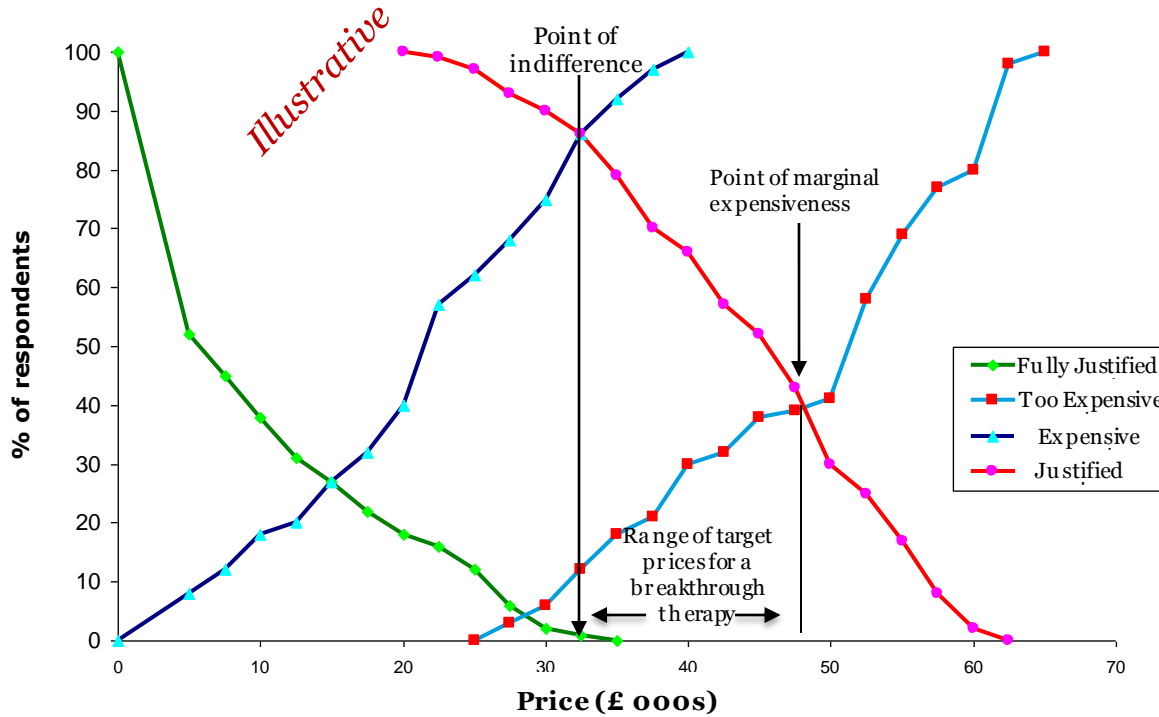
At hospital level, selective use in those patients expected to benefit the most from the therapy (at physician's discretion) is possible at launch and until:

- Supplementary funding to the DRG tariffs is formally introduced
- Real world effectiveness is established and clinical guideline inclusion is secured

Where uncertainty over WTP exists, we leverage additional frameworks to assess reimbursed price potential

Research methodology is tailored to explore the interrelationship between price potential, reimbursement restrictions and supporting data requirements; this can help identify the price-volume trade off and the revenue-maximising prices

Van Westendorp pricing sensitivity meter



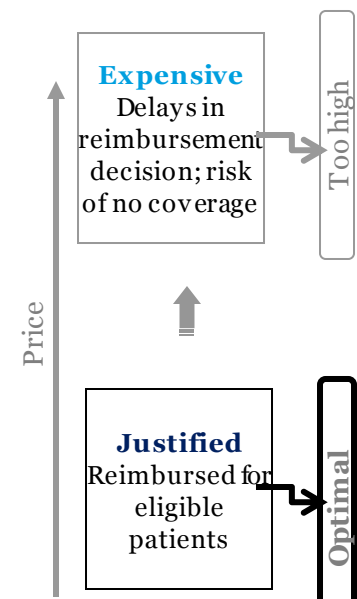
- Semi-quantitative pricing research methodologies are useful for assessing WTP of EU market access stakeholders; fully quant approaches are feasible with US payers

Requirements for favourable access

- Highly restricted use only
 - Subject to subpopulation specific data demonstrating incremental benefit
- Additional Rx controls imposed e.g.
 - Prior-authorization
 - Specialist-center only
- Managed entry agreements linked to real world evidence generation
- Substantial discounts from list price at hospital level

Optimal

- Reimbursement in line with product label
- Real-world evidence (RWE) generation to optimize lifecycle management



To secure commercial viability, robust value optimisation and market access strategies need to be developed; preparations should start prior to clinical development and continue in parallel



Planning for Reimbursement

- Early HE analysis
 - Identification of clinical and HE value drivers
 - Room for Innovation
 - Indication & therapeutic position prioritisation
- Identify incremental benefit and manufacturing cost thresholds
- Define TPP; plan evidence generation to substantiate claims
- go: no go criteria for the “Stage-Gate” process
- Engagement with key market access stakeholders to explore:
 - Key value drivers
 - Likely positioning, pricing, & reimbursement
 - Supporting data requirements
- Develop Value Story
 - Test credibility and impact
- Address evidence gap between RCT data and value proposition
 - Modelled data
- Finalise HE models
- Develop Value Dossier
- Identify price corridor:
 - Revenue maximising price per market
 - International price referencing
 - Launch sequence
- Contingency planning and risk-sharing schemes
- Planning for post-launch evidence generation



For more info visit:
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